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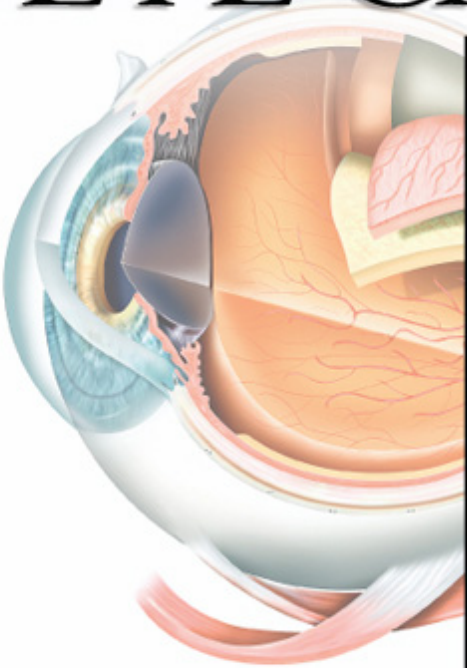
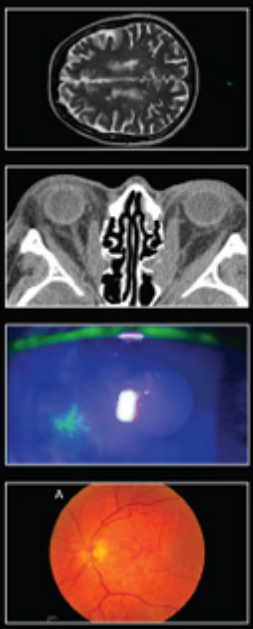
PETER J. KERTES
T. MARK JOHNSON

EVIDENCE-BASED EYE CARE

Second Edition





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EVIDENCE-BASED EYE CARE

Second Edition

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THIS BOOK IS DEDICATED TO THE MEMORY OF MY PARENTS, HILDA AND PAUL, WHOSE LIVES AND LOVE WERE AN INSPIRATION TO ME AND SUSTAIN ME EVEN NOW.

–PETER J. KERTES

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FOREWORD

The first edition of *Evidence-Based Eye Care* offered an important and comprehensive compilation of clinical studies of eye diseases, including cornea and external disease, glaucoma, neuro-ophthalmology, oculoplastics, ocular oncology, and retinal diseases like diabetic retinopathy, retinal vein occlusion, and macular degeneration. As practicing clinicians, we all strive to provide our patients with evidence-based medicine, utilizing clinical trial results and clinical observations. Depending on the disease, questions about management may be addressed using double-masked, controlled clinical trials—the "gold standard"—but not every question can be studied in this way. It is important for clinicians to understand the level of evidence for their approach to patient care and recognize that new technologies and experimental medicine may change their understanding of disease and choice of therapy. The first edition of *Evidence-Based Eye Care* provided an important foundation for clinicians, describing the different methodologies of clinical research and the skills required for critical reading of the literature. In the second edition, the editors and authors have provided updates on clinical epidemiology and health economics. They have added a valuable chapter on statistics, recognizing that today's clinicians must have a basic understanding of statistical analyses in order to evaluate published trials. Moreover, the second edition offers important new information for early age-related macular degeneration and retinal artery occlusion. This edition provides a truly broad scope of clinical trials across all subspecialties of ophthalmology. The text is relevant for all practicing ophthalmologists and students of ophthalmology and is an essential resource given the emerging importance of recertification. Congratulations to the authors and editors for such a wonderful addition to the ophthalmologist's reference library.

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PREFACE

Since the beginning of clinical medicine, physicians have been charged with the task of providing their patients with the best diagnostic and therapeutic skills available. The goal has always been to optimize the outcome and minimize the risk. The practice of medicine was initially, and remains to a much lesser extent even today, based heavily upon the wisdom and experience of certain experts. Over time, physicians and their patients have demanded increasing validation of diagnostic and therapeutic interventions.

Over the past quarter century, evidence-based medicine has come to the forefront of clinical medicine. The underlying principle of evidence-based medicine is the application of the best basic science and clinical research available to a specific patient complaint. The randomized controlled trial (RCT) has become the most revered component of evidence-based medicine. It represents the ideal model for hypothesis testing in clinical medicine. The RCT has been an important part of ophthalmology since the Diabetic Retinopathy Study validated the role of panretinal laser photocoagulation for high-risk proliferative diabetic retinopathy. The RCT continues to play a vital role in all subspecialties in ophthalmology.

Clinical trials in ophthalmology face unique challenges. RCTs have limitations. RCTs are generally able to answer a single research question. The costs and time involved in answering that single question can be significant. It is not always ethical or practical to do an RCT. For example, to be sufficiently powered, RCTs typically require large sample sizes. Ophthalmology is a specialty of relatively rare diseases. Other than glaucoma, cataract, myopia, diabetic retinopathy, and macular degeneration, most ophthalmic conditions are relatively rare from a population point of view. Thus, conducting RCTs on many ophthalmic conditions can be difficult from a recruitment perspective. In addition, RCTs, by their very nature, risk being a little behind the times. From the time a question is formulated, and a study funded, carried out, and analyzed, often some new questions have been asked and new or modified therapies introduced. Therefore, in ophthalmology we must frequently look to sources other than the clinical trials to case–control studies, small controlled trials, and case series for evidence upon which to base our treatment decisions.

The goal of this text is therefore twofold. First, we aim to summarize the major clinical trials in ophthalmology, those RCTs that form the foundation of how we practice ophthalmology. The authors were charged with the task of summarizing the trials in a manner that would allow easy understanding and ready application to clinical practice. The summaries include the specific populations under investigation so that clinicians know to which patients to best apply the findings. The interventions and their results are also summarized and clearly laid out. Finally, the limitations of the studies are reviewed. While a clinical trial answers one question, inevitably, there are many questions about a given condition or therapy that remain. The second goal is to highlight the questions that remain after the clinical trial and to provide the reader with a sense of where the field of ophthalmology is headed and the body of evidence that exists to support heading off in another direction.

The book is multi-authored. Each author has an academic and clinical interest in his or her particular subspecialty. The authors are practicing clinicians and have written the chapters from the perspective of how the results of these clinical trials are applied within the context of patient care. An attempt has been made to provide some uniformity to the chapters, but each has its own unique style.

The genesis of this book lies in the discussions of a junior resident (TMJ) and a senior

resident (PJK) on the underlying principles of patient care in ophthalmology. The first edition was the result. It is remarkable to note how many significant changes have occurred in the last 6 years in the field of ophthalmology as a result of well-designed and executed clinical trials. In many chapters of the first edition, entire sections have been replaced with small summary paragraphs. While many studies have stood the test of time and remain relevant, today there are many "gold standard" treatments that have been replaced by newer therapies. Even in the last few weeks of finalizing the text for this edition some studies have reported results that will further change our treatment paradigms.

The editors sincerely hope that this book will provide clinicians, residents, and students with a foundation in the therapeutic principles of ophthalmic care and serve as a basis for going beyond our current clinical trials in the future.

Peter J. Kertes, MD, CM, FRCSC
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Dr. Kertes thanks his wife, Eve, and daughters, Zoe and Talia, who fill his life with joy and laughter; his brother Joe for teaching him to aim higher and write better; the many medical students, residents, and fellows with whom he has had the privilege of working with who ask the questions that make the practice of ophthalmology stimulating and gratifying; the investigators—the contributing authors chief among them—and the brave patients who have tested the bounds of scientific exploration and allowed our field to progress to its present and future heights.

Dr. Johnson thanks his wife Joanne for her endless love and support, Connor and Dylan for reminding him of the sheer joy of intellectual curiosity, his mother for teaching him to write, and his father for fostering an interest in science. He also thanks the contributing authors for their enthusiasm, dedication, intellect, and insight that they brought to each chapter. In addition, he thanks Dr. Kertes for the coffee and the fundamental training in ophthalmology and clinical trials provided in the café of the Ottawa Civic Hospital.

CONTENTS

1 Clinical Epidemiology

Hussein Hollands MD, FRCSC, MSc (Epid), Simon Hollands MD, MSc (Epid) and Sanjay Sharma MD, MS (Epid), FRCSC, MBA

Introduction

It is now commonplace for physicians and patients to expect that clinical decisions made by physicians—especially when related to therapy or prevention of disease—are based on sound scientific evidence. The efficacy and effectiveness of new treatments, whether aimed at reducing symptoms, curing disease, or reducing the risk of disease or disease symptoms, must be established with results from a randomized controlled trial (RCT) to be considered for government approval. In addition, patients are becoming more likely to demand scientific reasoning in the form of valid clinical studies before undertaking therapy.

Clinical epidemiology can be thought of as the science of making predictions regarding individual patients using a sound scientific method.[1] To accurately assess the evidence available for a particular therapy or preventative measure, it is necessary to understand the fundamentals of clinical study design. Depending on the strengths and inherent biases of different study designs, epidemiological evidence varies greatly in value when applied to clinical decision making. Evidence is classified from Class I through V, from the strongest to the weakest, respectively.[1,2] Table 1.1 summarizes the various classes of evidence as described previously.[2]

In this chapter, we present a review of the common study designs, focusing specifically on the important issues in critical appraisal, interpretation of clinical research, and application to patient care. For each study design, basic measures of effect size and statistical tests will be cited. A more detailed review of biostatistics is provided in Chapter 2.

Observational Study Designs

Results from observational study designs are often frowned upon as evidence to support decision making in medicine, but in many situations experimental evidence is not available and an observational study provides important information to support clinical decisions. For instance, observational studies are usually the only possible study design to investigate environmental or dietary risk factors for disease. They are also useful after a treatment becomes commonplace in medicine and it becomes unethical to randomize a patient to not receive that standard treatment. Finally, although clinical trials are ideal, they are expensive and time consuming and are simply not performed in large numbers. In a typical year, 87% of clinical articles published in the *Archives of Ophthalmology*, *Ophthalmology*, *British Journal of Ophthalmology*, and *Canadian Journal of Ophthalmology* are observational study designs.[3] Consequently, clinical decisions in ophthalmology are being made using evidence from both clinical trials and observational studies.

Case Reports and Case Series

A case report outlines an interesting or new treatment approach and follows up a patient outcome into the future, whereas a case series simply lists a series of patients treated similarly and followed up during treatment in time. Neither of these study designs employs control groups and is thereby considered the weakest form of clinical evidence (Class V and IV, respectively). In general, clinical decisions should not be made using data only from case reports or case series, but these study designs

TABLE 1.1 Summary of Hierarchical Levels of Evidence for Interventional and Observational Studies[2]

Level of evidence	Study design
Level V	Interventional case report
Level IV	Intervention in a series of patients with no comparison group
Level III	Nonrandomized controlled trial (strong level III evidence is a prospective cohort study, moderate level III evidence is a retrospective cohort study or case–control study, and weak level III evidence is a cross-sectional study)
Level II	Randomized controlled trial with high type I error, or low power (high type II error), or both
Level I	Randomized controlled trial with low type I error and high power, or meta-analysis

do play an important role in evidence-based medicine by enabling the medical community to stay current with respect to new treatment options and by fueling ideas for more definitive future studies.

Analytic Cross-Sectional Studies

An analytic cross-sectional study is used to investigate a risk factor for disease as opposed to a treatment or intervention. In this design, a cross-section of people is investigated, simultaneously in time, as to their exposure status and their outcome or disease status. In the analysis, the prevalence of a given risk factor or exposure to it is compared between those who happen to have the outcome of interest and those who do not. Prevalence is defined as the fraction of people who have the condition at a certain point of time. It is important to distinguish prevalence from incidence; incidence is the fraction of people who *develop* the condition over a certain period of time.

An example of a cross-sectional study investigated whether an association exists between the use of angiotensin-converting enzyme inhibitors (ACEIs) and the prevalence of age-related macular degeneration (AMD).[4] Researchers reported that among a cross-section of 3,654 Australians, 1.3% of ACEI users had late AMD while 2.0% of people not using ACEI had late AMD ($p < 0.05$). A group of patients were observed at one point in time and each patient was defined on the basis of his or her exposure status (i.e., current use of ACEI) and on the basis of their outcome status (i.e., photographic evidence of AMD). Results of a cross-sectional study are generally given as the prevalence rate ratio (PRR), calculated as follows:

PRR = Prevalence rate (among the exposed)/ Prevalence rate (among the unexposed)

In the example of AMD among ACEI users, the PRR can be calculated as follows:

PRR = Prevalence of AMD (among ACEI users)/Prevalence of AMD (among ACEI nonusers) = (73/3,654)/(47/3,654) = 1.53

Compared with more intensive observational study designs, a cross-sectional design has the advantage of being less time intensive and cheaper. In addition, it is usually relatively easy to obtain a representative population using this study design. There are, however, some drawbacks to cross-sectional studies.[5] First, cross-sectional studies are designed to look at one point in time and cannot determine the temporal sequence (or cause and effect) between risk factor and disease. Second, since the outcome measure of a cross-sectional study is prevalence, there is a potential for incidence–prevalence bias whereby transitory or fatal disease may be preferentially missed. Third, associations made using current exposure status may not be indicative of past

exposure status and therefore may not fit with the established pathophysiology of the disease. Consequently, cross-sectional studies are considered weak Class III evidence for clinical decision making and should only be employed to study preliminary hypotheses.[2]

Case–Control Studies

Unlike cross-sectional studies, case–control studies employ a true control group and can thereby make valid comparisons between groups of patients. In a case–control design, two sample patient populations are identified: those with the outcome in question (the cases) and those without the outcome (the controls). The study then looks backward in time to measure the frequency of past exposure.

Although case–control studies are considered retrospective, patients are theoretically followed forward from the time of exposure in the past to the time of known disease outcome in the present.[5] In the analysis, cases are compared to controls with respect to the frequency of the exposure of interest to determine if a cause and effect relationship occurs between exposure and outcome.

An example of a recently published case–control study looked for an association between the use of cholesterol-lowering agents and AMD among a group of 15,792 people enrolled in the Atherosclerosis Risk in Communities study between 1987 and 1989.[6] Cases were initially identified as those people found to have AMD after applying a standard definition to their fundus photographs. Controls were participants with no evidence of AMD on fundus photographs. Researchers then established previous exposure to cholesterol-lowering agents through a questionnaire. Exposed patients were those who had used cholesterol-lowering agents during the study period while unexposed patients had never used such agents. The results of case–control studies can be summarized in a simple 2 × 2 contingency table; an odds ratio (OR) is reported as the measure of association between the exposure and the outcome variable. An analytic example of the OR calculation, its interpretation, and the corresponding statistical tests are discussed in Chapter 2.

In a case–control study, selecting appropriate controls is perhaps the most difficult, yet important, methodological consideration since the control group defines what is normal and provides a basis for comparison. A control group ideally should be picked from a population that is similar to the group of cases in all ways except that they do not have the disease in question. Another methodological consideration in case–control studies is the accurate determination of exposure status. Objective exposures should be used whenever possible to minimize the chance of recall bias* and interviewers should be blinded to minimize the chance of observer bias.†

Since case–control studies are not randomized, there is potential for confounding variables to affect the results of the study. Confounding variables go with the risk factor being investigated and are significantly associated with the disease in question. Therefore, it may look as though the exposure in question causes the disease, when in fact the exposure is simply associated with a confounding factor that causes the disease. The most common example of a confounder in most clinical studies is age. In the example above,[6] age is associated with AMD, and older people are also more likely to be on cholesterol-lowering agents. When designing the study and interpreting the results, one must take care to tease out whether cholesterol-lowering agents are temporally associated with AMD after accounting for the effect of age.

Confounding variables can be controlled for in a case–control study during the design phase by matching cases and controls on the basis of known prognostic (or confounding) factors. For instance, if age was thought to be an important confounder, as was the case in the study above,[6] then each case would be matched with a control of the same or similar age. Gender is another common factor that cases and controls can be matched on. When matching cannot be accomplished,

* Recall bias can occur because cases preferentially remember past exposures better than controls.

† Observer bias can occur if observers in the study consciously or unconsciously record observations differently depending on the outcome status of the participant.

stratification is a process of separating a sample into two or more subgroups on the basis of the specified level of a third variable (i.e., the potentially confounding variable) and can be used during the analysis phase of a study to assess the role of confounding. If stratified data are presented in a report, a Mantel-Haenszel OR, which is a combined measure of the stratum-specific ORs, should be reported. Most introductory epidemiology textbooks will provide additional information on this test. A comparable way of accounting for potentially confounding variables that can be a more powerful tool (especially when multiple confounders are considered) is to use a multivariable logistic regression analysis. The principal idea behind both the Mantel-Haenszel OR and multiple logistic regression (which also outputs an OR) is to tease out the effects of the exposure—independent of confounding factors—on the outcome of interest (i.e., provide an adjusted OR). Some basic statistical concepts of logistic regression are discussed further in Chapter 2.

Case–control studies are most helpful in assessing cause and effect relationships. Logistically, these studies tend to be relatively inexpensive and quick to perform. They are especially well suited for studying rare diseases where incidence rates are low because cases can be selected at the outset. Furthermore, multiple potential risk factors may be studied simultaneously among the same group of cases and controls.

A number of important weaknesses are inherent in case–control studies. First, true incidence rates in exposed and unexposed participants cannot generally be determined.[5] Second, case–control studies are not useful in studying rare exposures. Third, information on past exposures or potential confounders may be unknown or incomplete or available information may be different among cases and controls. Finally, it may be difficult to obtain a comparable group of control subjects.

Given these inherent weaknesses, well-designed case–control studies are considered moderate level III evidence.[2] However, they can be very useful in clinical decision making regarding cause and effect when used with caution. The case–control study design is appropriate for hypothesis testing, leading to future definitive research, and making inferences about risk factors for rare diseases when controlled clinical trials are unethical or impractical.

Cohort Studies

A cohort is a group of people who are followed up to look for an outcome of interest. In a cohort study, groups of people are identified at the start of the study and are classified as to their exposure status. The exposure of interest could be an environmental factor, a dietary factor, a pharmaceutical treatment, or any intervention.

After the exposure status of each person in the study has been established, two cohorts are naturally formed: a cohort of exposed persons and a cohort of unexposed persons. The two cohorts are then followed up in time to assess the outcome. The outcome measure in a cohort study is the rate or incidence of disease, or the fraction of the cohort that develops disease over a certain period of time. This design differs from a cross-sectional study where the exposure and disease are identified simultaneously and from a case–control study where the outcome is identified first and the presence of past exposure status is compared between the groups.

Cohort studies may be either prospective cohort studies (PCSs) or retrospective cohort studies (RCSs). In a PCS, exposure status is obtained at the beginning of the study and the cohort is observed forward in time for outcomes of interest to occur. At the beginning of the study, participants must be free from the disease outcome and be at risk for developing the outcome sometime in the future. An RCS is similar to a PCS except for the fact that in the exposed cohort the exposure occurred in the past and participants are then traced from the past to the present for disease development. Constructing an RCS requires records of exposure status from the past and appropriate follow-up to obtain outcome status through medical records or disease registries.

In a PCS, the control group is usually the portion of the cohort that is not exposed; this represents an internal comparison. If an

internal comparison group is not possible (for example, among a group of people exposed to an infectious pathogen), then an external comparison group can be used. In an RCS, the comparison group is usually external because a group of exposed persons from the past is followed up to act as the basis for the study. When an external comparison group is used in any study, it is essential that this unexposed group be similar to the exposed group in all ways except for the exposure of interest.[5]

An example of a recently published PCS investigated the association between C-reactive protein (CRP) levels (exposure) and the development of AMD (outcome).[7] A cohort of 261 patients who had some signs of nonexudative AMD was identified. Inflammatory biomarkers were then collected on each patient, and the cohort was grouped into quartiles on the basis of the CRP level. Patients within the highest quartile of CRP level were defined as exposed, whereas those within the lowest quartile of CRP level were defined as unexposed. The outcome was the incidence of progression of AMD, confirmed on the basis of standardized fundus photographs followed up over a period of 4.6 years.

When critiquing a cohort study, as with any nonrandomized study design, the potential for bias and confounding should be sought out. Bias is minimized by using objective exposure and outcome measures, blinding to exposure and/or outcome status during data collection, and using uniform methods to collect information. Confounding factors must be clearly identified in the study design phase, and data for these factors must be obtained either prospectively or through available records. Confounding variables should then be controlled for either during the design phase of the study or through stratification in the analysis phase with multivariable regression analysis.

The results of a cohort study are generally reported using relative risks (RRs), which is simply the rate of disease outcome among the exposed group divided by the rate of disease outcome among the unexposed group. As with ORs, multivariable methods are available that produce adjusted RRs. Several effect measures involving risk variability are reviewed in Chapter 2.

A properly conducted PCS or RCS can determine the temporal sequence between cause and effect. The cohort study design is particularly useful for studying rare exposures or clinical interventions in a nonrandomized fashion. Indeed, multiple outcomes may be assessed. Cohort studies also allow for the calculation of a disease incidence rate without underestimating transitory or fatal disease processes. A true RR of disease between the unexposed and exposed groups can be calculated.

The disadvantages of cohort studies are as follows.[5] First, PCSs generally require large sample sizes and a long follow-up period and can therefore have significant rates of follow-up loss and expense. Second, in a PCS, there is the possibility of exposure misclassification because of changes in exposure status or in disease detection techniques during the follow-up period. In an RCS, inadequate information regarding exposure status throughout the course of the follow-up can be a problem.

Overall, although prospective and retrospective cohort designs have similar theoretical disadvantages, a PCS is considered much stronger evidence. This is because a PCS can be designed to avoid potential biases and to collect all necessary information, whereas an RCS relies on previously collected data. Cohort studies are considered moderate to strong observational level III evidence.[2] In particular, they are helpful in supporting clinical decision making in situations such as identifying rare risk factors for disease or studying the effect of a treatment or intervention where randomization cannot ethically or practically be employed.

Randomized Controlled Trials

Experimental Design

An RCT is similar to a PCS in that a group of people are assembled and followed up in time to look for an outcome event of interest. However, a clinical trial is superior in that it is experimental. Rather than merely observing exposure and outcome, clinical trials manipulate an exposure of interest in two randomly assigned groups of patients. The experimental arm receives a treatment hypothesized to lead to better outcomes than standard therapy.

The control arm receives only standard therapy. Direct comparison with the control arm ensures that any observed treatment effect in the experimental arm cannot be explained by a placebo effect or regression toward the mean.

A clinical trial may be a preventive trial, an interventional trial, or a therapeutic trial. However, randomization is the crucial element in any RCT that distinguishes experimental evidence from observational evidence. Each patient enrolled in the trial has an equal chance of being placed in the experimental or control arm. In other words, the process of randomization makes certain that all variables (other than the experimental manipulation or treatment) are distributed randomly between the two groups to effectively eliminate selection bias.

The major drawback in an observational study design is the risk of confounding—the chance that study groups will differ with respect to known or unknown prognostic variables and that the treatment effect is actually due to a systematic difference between the study groups as opposed to a true treatment effect. Since an RCT is an experiment, such systematic errors are avoided. Theoretically, any treatment difference between the arms should be due to chance alone or the treatment effect being studied. As a result, RCTs provide the best evidence available from the primary medical literature for guiding clinical decisions and are considered level I or II evidence, depending on study methodology and sample size.[2]

Although an RCT is considered the best available study design, it can still have large methodological flaws, an inadequate sample size, or a nonrepresentative sample population. Therefore, evaluating experimental evidence from RCTs requires a stepwise approach: appraisal of study validity, interpretation of results, and application of results to individual patient care. To illustrate these steps practically, we work through a critical appraisal and interpret the results of a clinical trial evaluating dietary supplementation of antioxidants and zinc to slow the advancement of AMD.[8]

Appraising the Validity of a Clinical Trial

Validity reflects whether we believe the treatment effect reported by a study to be true or whether we believe the treatment effect to be falsely influenced by systematic errors in study design.[9] The internal validity of any trial should be appraised before the results are interpreted or applied to patient care.

Sample. The first important aspect to address is the sample of patients being studied. A population of interest should be targeted by outlining clear inclusion and exclusion criteria. Pharmaceutical RCTs are usually designed with very rigorous inclusion and exclusion criteria to ensure that the sample of people participating in the study are compliant and therefore the most likely to benefit from treatment. Indeed, many pharmaceutical trials employ an initial open label phase whereby patients who are noncompliant with medications can be identified and dropped from further study. Both inclusion and exclusion criteria and the method of sampling play into how well the targeted population is represented in an RCT and help us to assess the generalizability of the study. We discuss the idea of generalizability in greater detail in the sections to follow.

A sample size calculation ensures that an appropriate number of subjects are recruited to answer the specified study question. The sample size should be calculated a priori. Obtaining adequate power in a study depends on the following: (a) alpha or type I error (concluding that a treatment is effective when it is not), (b) beta or type II error (concluding a truly effective treatment to be not effective), (c) treatment effect that is considered clinically significant, and (d) the nature of the data in the study.

Type I error is customarily set at 0.05 and type II error is set at 0.20 (representing 80% power). A clinically relevant treatment effect should be determined such that the study is designed to detect a statistically significant result if the reported treatment effect is equal to or greater than the predetermined effect. It would require a very small sample size to detect a dramatic treatment effect (e.g., cataract extraction by phacoemulsification and intraocular lens placement for dense posterior subcapsular cataracts), but this is rare in clinical trials today. Most new RCTs are designed to

detect relatively small treatment effects and therefore require large sample size. Equivalency trials, which attempt to show that two treatments are equally effective within a certain range of error, tend to require larger sample sizes.

The sample size also depends on the nature of the data in the study. If the outcome measure is a continuous variable such as intraocular pressure, then the sample size will depend on the variation in intraocular pressure among patients in the study. If the natural variation is large, then a large sample size will be required, whereas if the variation is small then a smaller sample size will be adequate. If the outcome measure is an event such as the progression of the disease, then the sample size required will depend on the number of events rather than the number of patients entered. Consequently, studying a rare event outcome in an RCT will require a much larger sample size than studying a common event.[10]

A study with too few patients recruited runs the risk of not having the power to detect a treatment effect, even if a treatment effect truly exists. For example, the results of a study may show a 50% risk reduction that is not statistically significant because of an inadequate sample size. This is a problem because this 50% risk reduction may be a clinically important treatment effect that is reported as an insignificant result simply because too few people were studied. The same study with a larger sample size and equivalent treatment effect would potentially show a significant result. In addition to not answering the question intended, the results of low-powered studies are often misinterpreted as "the treatment was found to be ineffective," when the correct interpretation is that "no significant association was found."

In conclusion, an RCT should report an a priori sample size calculation and the assumptions used in that calculation. When interpreting the results of a trial, if the treatment effect was clinically but not statistically significant, then an error was made in the assumptions of the sample size calculation and too few people were recruited to adequately power the study.

Randomization. The method of randomization should be reported. Before randomization, patients may be stratified according to one or more prognostic variables identified during the design phase of the study. Stratification of patients in a randomized trial produces a truly *equal* distribution (as opposed to a random distribution) of these variables between the treatment arms and is especially useful when the sample size is small and there are known variables that are highly prognostic.

Intervention. The methodology of the treatment being examined in an RCT should be described to a reproducible extent. An ideal treatment is one that can be realistically and straightforwardly implemented into clinical practice if benefit is demonstrated.[10] Often large pharmacological RCTs use complex drug protocols with intensive patient monitoring to ensure that patients are receiving optimal therapy. This is appropriate in an *efficacy* trial when the treatment is being tested under tightly regulated situations. However, the clinical *effectiveness* is the effect of the treatment in the real-world setting. Results of an effectiveness trial are more useful for making clinical decisions, particularly when treatment protocols become complex.

Control Group and Blinding. The therapy administered to the control group should coincide with the current standard of care. If there are no standard treatments being offered for a particular condition, then a placebo is employed. The Hawthorne effect states that patients who are observed or treated intensely do clinically better than patients who are not. Also, patients given a placebo therapy with conviction do better than patients given no treatment.[10] Therefore, aspects of the experimental and control treatments, other than the obvious biologic differences, should be minimized as much as possible.

Blinding attempts to retain a similar prognosis between the two treatment arms after the treatment protocol begins.[9] Trials may be single-, double-, or triple-blinded depending on the nature of the treatment and the flexibility of the study design. In single-blinded trials, only the patients are

kept unaware of their treatment arm. Double-blinded trials blind the patients and the treating physician or observer to eliminate the opportunity for observer bias. Triple-blinded trials also mask statisticians during the analysis phase.

Although in some cases blinding can be difficult or sometimes impossible, every reasonable attempt should be made to minimize bias. For example, in a trial demonstrating that intravitreal pegaptanib sodium injection (Macugen) was effective in treating neovascular AMD,[11] a subconjunctival anesthetic was used in both control and experimental groups to blind the patient to the treatment arm. Also, a second nontreating ophthalmologist performed all postinjection assessments.

Differences between Treatment Arms. Generally, randomization in a clinical trial results in two treatment arms that are similar in every way except for the treatment or intervention being studied. The success of randomization is confirmed by comparing basic demographic variables and known prognostic variables between treatment arms. These variables should be reported in the published study. Any differences that do exist are explainable by either a systematic error in randomization or bad luck. If known prognostic variables are different between the treatment arms, statistical adjustments can be made, but such manipulation should raise serious concerns as to the validity of the randomization process.

As the clinical trial progresses, all patients should receive equivalent follow-up and be treated identically except for the therapeutic intervention under study. Cointervention can occur when a clinician not involved in the RCT prescribes an intervention known to affect the outcome or when the trial physician prescribes additional therapy for the condition in question because of a changing medical picture. Potential cointerventions should be predicted before the study starts and rules should be established as to how to deal with various situations.

For example, in the trial studying Macugen for the treatment of wet AMD, photodynamic therapy (PDT) could be administered to patients freely at the treating physician's discretion. As long as the treating ophthalmologist is blinded to the patient's treatment arm, this is an appropriate means of dealing with this issue. If patients in the treatment arm receive more effective cointerventions more frequently than patients in the control arm, the study results will have questionable validity despite adjustments made during data analysis. In the Macugen trial,[11] there was no significant difference in the administration of PDT—a cointervention known to be effective in treating wet AMD—between treatment arms and, in fact, patients in the control arm received more PDT than patients in the Macugen arm.

Follow-Up. A published RCT should display a flowchart outlining the number of patients recruited, included and excluded, randomized, treated, and lost to follow-up. Researchers must make a reasonable effort to track down people who are lost to follow-up irrespective of the treatment arm. Although there is no set level of acceptable loss to follow-up, any loss can introduce bias if there is a reason as to why one arm is affected preferentially.

In many trials, noncompliance can be a problem and many patients may be randomized to one treatment but end up essentially receiving intervention from the other study arm. In these cases, patients should be analyzed in the groups to which they were originally randomized, the so-called intention-to-treat method. This allows the RCT to answer the question of primary interest to clinicians: *What treatment option is best at the time the decision must be made?* If an intention-to-treat method is not employed, then the validity of the trial must be questioned since the randomization process becomes compromised and there is room for systematic differences between treatment groups.[10]

Throughout the patient follow-up period, adverse events and side-effect data must be collected and periodically reported. These data are an important component in the overall interpretation of the study results.

Interpretation of Results

Treatment Effects. In most trials, the primary outcome is a dichotomous event (e.g.,

a 15-letter loss in visual acuity or mortality). The incidence rate of the primary outcome is measured in both treatment arms for the duration of the follow-up period. The size of the treatment effect is generally reported as an RR, defined as the incidence rate (risk) of the outcome in the treatment group divided by the incidence rate (risk) of the outcome in the control group. A related measure that is also common, the relative risk reduction (RRR), expresses the results as a reduction in risk (i.e., 1-RR). Two alternative measures that can be used to report on the risk differential between two treatment arms in an RCT are the absolute risk reduction (ARR) and the number needed to treat (NNT). Instead of comparing the two groups in relative terms (as with RR), the ARR provides an absolute measure of effect—it is calculated as the difference in incidence rates (incidence [control]—incidence [treatment]) between two groups. The NNT, which is the inverse of the ARR, gives the number of patients who would need to be treated in order to prevent one (usually harmful) event from occurring.

In some cases, researchers may be interested in a continuous outcome, such as the exact number of visual acuity letters (Early Treatment Diabetic Retinopathy Study [ETDRS]) lost from baseline to follow-up. In this case, the difference in mean visual acuity between the treatment (exposed) group and the control (nonexposed) group is compared.

In many clinical trials, it is not only whether or not a disease outcome eventually occurred that is of interest, but more the time that elapsed before an event—or survival time. In these instances, RCTs will often report results from survival analyses such as Kaplan-Meier curves, log-rank statistics, or Cox proportional hazards models.

Along with the size of a treatment effect, statistical tests are used to measure the precision (statistical significance) of estimates and must be reported in the results for clinical studies in the form of a *p*-value or a 95% confidence interval. Statistical significance by convention is set at the 5% level, which expresses the probability that an observed treatment effect is due to sampling error alone. Often times however, too much emphasis is placed on a *p*-value or 95% CI (i.e., statistical significance). There are numerous factors that can influence a test for statistical significance—not all of which are always of clinical importance. It is important to also look at the *clinical* significance of that effect. The *clinical* significance of a result refers to the level of effectiveness of a treatment at which a clinician feels adoption of the treatment would be justified in clinical practice.

A more in-depth review of some of the more fundamental biostatical concepts that are relevant in the ophthalmology literature is provided in Chapter 2. There we take a closer look at hypothesis testing, statistical and clinical significance, as well as different measures of effect size in various clinical settings.

Generalizability to Patient Care. There are two main factors to be considered when deciding if study results are generalizable to the individual clinic patient. First, most RCTs outline detailed inclusion and exclusion criteria that reflect a very specific target population. In real life, physicians are often faced with the decision of whether to apply evidence from these studies to their own patients who may not precisely match the study criteria. A practical way to determine if the results of a particular clinical trial are applicable to the patient is to ask if the patient is different from the study population in any way that would logically affect the treatment result. Second, large RCTs are designed to provide optimal study conditions to maximize any treatment effect that does exist because it is easier to prove efficacy than it is to prove effectiveness. High compliance rates and intensive follow-up may make a large difference to study results, yet may be impractical in regular clinical practice. The physician must evaluate how realistic the treatment—as administered in the RCT—will be for a given patient.

Outcome Measures. Primary and secondary outcome measures should be clearly defined a priori and be clinically meaningful. This includes clearly defining a time frame for the primary analysis. If outcome measures are not defined a priori, the possibility of data dredging

cannot be excluded. If enough analyses are conducted (i.e., over different time frames and using different outcome measures), then there is a high likelihood of finding a statistically significant clinical outcome through chance alone. In general, multiple comparisons should be avoided, or if they are unavoidable the *p*-value considered to be statistically significant in the study should be adjusted downward, using appropriate statistical methodology.

Surrogate measures of disease are less powerful evidence of clinical effectiveness. For example, in a study investigating an antihypertensive agent for the treatment of heart disease, all-cause mortality or cardiac-specific mortality is a much more meaningful outcome measure than blood pressure reduction (a surrogate marker). An analogous situation in ophthalmology is the use of intraocular pressure as a surrogate marker in glaucoma trials. We do know that decreasing the intraocular pressure in patients with glaucoma will result in better visual outcomes. However, using a primary outcome of functional vision loss (e.g., reproducible visual field progression) is a much more powerful measure in a glaucoma trial than using intraocular pressure measurements.

Value of Intervention. Finally, the clinician must consider whether the treatment benefits are worth the potential costs and side effects of treatment. The RCT provides substantial information on the hard medical outcomes of treatment but little information on the true economic and biopsychosocial cost of treatment. The RCT will provide information about the frequency of treatment side effects and the rate of more serious adverse events. However, when initiating treatment, there are other costs to the patient that could negatively affect the quality of life, including the monetary cost of treatment, the label of disease, and the hassle of taking medication or undergoing a procedure. Clearly, the decision as to whether to recommend treatment will depend highly on the individual circumstances of each patient encounter.

Noninferiority Trials. Conventional RCTs, as discussed in the preceding text, are designed to show superiority, meaning that the purpose of a trial is to establish that clinical endpoints in an experimental group are statistically superior to those in a control group. The control group could be an existing treatment (referred to in the literature as the active treatment) or a placebo (if no current treatment exists). With rapid advancements in treatment and pharmacotherapy, instances where there is no active treatment available, and hence a new treatment can ethically be compared to a placebo, are becoming increasingly rare. Moreover, new treatment options often purport advantages other than improvements in efficacy on primary clinical endpoints. For example, a new treatment may have a lower risk of adverse side effects, it could be easier or less intrusive to administer, or it could be a cheaper alternative. In these cases, researchers are solely interested in showing that a new treatment is comparable in efficacy to an active treatment. Equivalency and noninferiority trials are special types of RCTs designed to test for comparability in efficacy. Equivalency trials test whether two treatments are statistically equal in efficacy, whereas noninferiority trials are designed to test whether the clinical outcomes of a new treatment are not worse than those of an active control. Though similar concepts, equivalency trials are uncommon in practice[12]; therefore, noninferiority trials remain the focus of discussion in this section. Much of the methodology discussed earlier (e.g., randomization, control group, blinding, follow-up, treatment effects, and generalizability) applies to both noninferiority trials and conventional RCTs. This section (with more statistical details provided in Chapter 2) is meant to give an outline of some of the key distinctions, primarily with regard to hypothesis testing, of noninferiority trials.

A key step involved in implementing a noninferiority trial is to establish a clinically relevant margin for an acceptable difference between the effects of the experimental treatment and active treatment whereby the experimental treatment would be considered noninferior (or equivalent in the case of an equivalency trial) to the active treatment. The margin should be such that if two treatments have a difference in effect (e.g., difference

in mean Visual Acuity (VA)) that falls within that range, then the experimental treatment can be thought of as not worse than the existing treatment. This margin is denoted by △ and is referred to in the literature as the margin of noninferiority.[12] Determining a meaningful margin (△) is an important step in designing the trial as it has implications on sample size, power of the analysis, validity of conclusions, and interpreting the trial with respect to practical or clinical significance.[12] The noninferiority margin is subjective and often defined by the smallest treatment effect that would be considered clinically relevant—also bearing in mind the placebo effect from previous RCTs.

Two pertinent examples of recent noninferiority trials are the "alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularization" (IVAN)[13] and the "Comparison of Age-related Macular Degeneration Treatment Trials" (CATT),[14] both of which investigated the comparability of bevacizumab (Avastin, Genentech) and ranibizumab (Lucentis, Genentech) for the treatment of exudative AMD. The clinical efficacy of ranibizumab for the treatment of exudative AMD was established with two landmark clinical trials in 2005.[15,16] However, bevacizumab has similar target specificity and is much less costly. The CATT and IVAN trials were designed to test whether visual acuity outcomes of bevacizumab were noninferior to those of ranibizumab. If bevacizumab was found to be noninferior in terms of clinical efficacy, then it would be considered for use much more frequently based on its lower cost. These clinical trials were designed such that bevacizumab was considered noninferior to ranibizumab if the final visual acuity for patients in the bevacizumab groups was not worse than the ranibizumab groups by more than 5 letters (ETDRS) in the CATT trial and 3.5 letters (ETDRS) in the IVAN trial. Specifically, the margin (△) was ±5 and ±3 ETDRS letters of distance visual acuity in the CATT and IVAN trials, respectively. Further methodological and statistical considerations of noninferiority trials are discussed in Chapter 2.

Example—Critical Appraisal

In 2001, the age-related eye disease study (AREDS) Research Group demonstrated that supplementation with antioxidants plus zinc was effective in reducing the risk of progression of neovascular AMD.[8] The following text goes through a brief appraisal outlining the key points in appraising the validity of an RCT and interpreting the results appropriately.

CRITICAL APPRAISAL OF THE VALIDITY OF THE AGE-RELATED EYE DISEASE STUDY

Sample of Patients

Patients with evidence of dry AMD were recruited from the offices of 11 retinal surgeons over a 6-year period. Broad inclusion criteria were used and patients were categorized according to the severity of dry AMD (categories 1–4). Exclusion criteria were minimal. Patients had to be between 55 and 80 years of age and have at least one eye with the best-corrected visual acuity of 20/32 or better. Consequently, the study sample was broad and generalizable to a typical ophthalmic practice. A sample size calculation was reported to ensure adequate power to detect a 25% to 50% treatment effect in progression to advanced AMD. This calculation appropriately accounted for some patients discontinuing treatment medication and some patients in the placebo arms beginning to take new supplementation.[8]

Intervention and Randomization

Four treatment arms were used: antioxidants (vitamins C and E), zinc, both antioxidants and zinc, and placebo. Patients within the less severe AMD category at baseline were randomized with a 50%

probability of placebo or antioxidants. Those patients with more severe AMD at baseline (categories 2–4) had a 25% probability to be in the four treatment arms. Randomization and masking were described completely and stratified by study center and AMD severity. Eligible patients were given a 1-month trial with placebo to demonstrate compliance with the treatment regimen before beginning the trial.

Control Group and Blinding

An internal placebo control group was used in this study (placebo controlled). Patients were blinded to the treatment arm through the use of identical medication containers, similar pill appearance, and similar-tasting supplements. This technique also ensured that physicians and other observers were blinded. It did not explicitly state whether the statistician was blinded.

Differences between Treatment Arms

Randomization seemed to be successful as the two treatment arms were similar with respect to baseline variables. Specifically, they were similar with respect to variables that could have potentially influenced the study outcome (confounding variables) such as age, gender, and dietary intake and supplementation. Cointervention was an important methodological issue in this trial. Patients who were taking supplements before the study (57%) had to agree to supplement their diet with the multivitamin Centrum only. Ninety-five percent of this group continued to take Centrum. Although not encouraged, 13% of people who had not taken supplements before the study began also started to take Centrum during the study. Supplementation other than with the study treatments was recorded in detail; no significant difference in additional supplementation was noticed among the treatment arms. The original randomization assignments were kept for analyses (i.e., an intention-to-treat analysis was employed).

Follow-up

There were identical follow-up procedures between both groups as the trial progressed. A full ophthalmic exam was done at baseline and every 6 months during the trial. Fundus photographs were taken initially and then annually beginning 2 years after randomization and were centrally graded. Visual acuity was measured using standard Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Adverse events were assessed through serum-level measurements, medical histories, and mortality rates and monitored by a data and safety monitoring committee on an annual basis. Follow-up was clearly described and only 2.4% of study participants were lost to follow-up.

INTERPRETATION OF AGE-RELATED EYE DISEASE STUDY RESULTS

Outcome Measures

The primary outcomes were (a) chance of progression to or treatment for advanced AMD and (b) at least moderate visual acuity loss from baseline (≥15 letters). These primary outcomes included a primary time frame (5 years) and are described clearly and were clinically relevant (i.e., not surrogate markers). The statisticians considered the issue of multiple comparisons (because of repeated measure analyses and in-term analyses) during the study design phase and calculated that results should only be considered statistically significant at a level of $p = 0.01$. This p-value should be considered equivalent to $p = 0.05$ if multiple comparisons had not been made.

Statistical Analysis

Comparisons were made using an intention-to-treat analysis. The primary analysis was done using repeated measures logistic regression to account for the fact that the outcome of progression of AMD could come and go in time. This statistical analysis was clearly described and associations were reported as adjusted odds ratios. The results section of the report contained enough primary information to allow the reader to calculate simple RRRs, ARRs, and NNT.

Treatment Effect

Less than 0.5% of patients in AMD category I (essentially free from AMD abnormalities) developed advanced AMD during the study and were therefore excluded from the analysis. The primary outcome showed a significant odds reduction for the development of advanced AMD with antioxidants plus zinc (adjusted OR of 0.72; 99% CI, 0.52–0.98) over placebo among patients in AMD categories II–IV. When patients with more severe AMD at baseline (AMD categories III and IV) were analyzed, the odds reduction increased (adjusted OR of 0.66; 99% CI, 0.47–0.91).

Although not calculated in the report, the paper presented enough primary data for the reader to calculate RRRs, ARRs, and an NNT for patients who had more advanced AMD at baseline (AMD categories III and IV). Although not as statistically comprehensive as the repeated measures logistic regression, these statistics are very useful for grasping the practical effectiveness of this treatment. These simple statistics are calculated as follows:

Risk of AMD advancement in placebo group at 5 years = 0.278

Risk of AMD advancement in the antioxidants/zinc group at 5 years = 0.202

RR ratio = 0.202/0.278 = 0.726

RRR = 100% × (0.278 − 0.202)/0.278 = 27%

ARR = 0.278 − 0.202 = 0.076 = 7.6%

NNT = 1/0.076 = 13 people

Practical Significance

Assessing the practical significance of a treatment effect will depend on many factors specific to the practicing ophthalmologist. Certainly, in many circumstances an RRR of 27% (see preceding text) for developing advanced AMD would be considered a practically significant clinical effect. However, this risk reduction is over a 5-year period and is only applicable to patients at the highest risk of developing advanced AMD. In addition, although there is a substantial RRR over 5 years, the ARR attributable to the treatment is only 7.6%. The practical or clinical significance of this treatment should be assessed on a patient-to-patient basis.

Generalizability

This study included a large sample with fairly broad criteria for inclusion and as such the results should be fairly generalizable to a typical ophthalmic practice. One weakness with respect to generalizability was that the study participants were assessed for their ability to comply with the study protocol before randomization. Therefore, the study was more of an efficacy trial as opposed to an effectiveness trial. An ophthalmologist in clinical practice could not be as sure that his or her patients would comply as well with vitamin supplementation when compared to the patients accrued for this trial. A second weakness for generalizability was that the main results of the study were among a subset of patients at higher risk for development of advanced AMD. Therefore, when applying these results to patient care, an ophthalmologist must assess the risk of advancement when determining if a patient should begin supplementation.

Cost of Intervention

The efficacy of supplementation has been clearly shown through this RCT. However, when beginning a patient on

high-dose antioxidant supplementation to prevent progression of AMD, the costs of intervention must also be considered. In addition to the monetary expense of long-term supplementation, taking four large pills per day may lead to noncompliance and therefore loss of treatment effect among some patients in the real-world setting.

Overall Assessment

This RCT employed very sound methodology and provided clear results to a common clinical problem. Methodological strengths of the study included a large and broad sample size allowing easy generalization to ophthalmic practice. Cointervention with supplementation had the potential to cause problems in this study, but the authors did a good job to account for this problem through a well-thought-out study design. The authors showed a modest treatment effect for preventing advancement of AMD (adjusted OR = 0.72) among patients at higher risk for disease advancement. Thirteen patients among those at higher risk would have to be treated over 5 years to prevent one case of advancement of AMD. One weakness of the study—from the standpoint of its applicability to being applied in a general ophthalmic practice—was that it was more of an efficacy trial than an effectiveness trial. Specifically, compliance may be more of an issue in the real-world setting. As with any study, these results should be applied on an individual basis to an ophthalmologist's individual patient population.

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2 Biostatistics

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Introduction

In Chapter 1 various study designs were discussed in order to provide an overview of some of the more common methodologic approaches used in evidence-based medicine for determining the efficacy and effectiveness of drugs, treatments, and procedures in ophthalmology. In order to objectively examine the literature it is important to gain an understanding of the statistics that will be reported so that informed interpretations that are both unbiased and clinically relevant can be made.

In this chapter we explain the principles of hypothesis testing and statistical significance and discuss some of the more common statistical approaches used to report findings in the ophthalmology literature.

Hypothesis Testing, Statistical Significance, and Clinical Significance

Traditional statistical inference is based on hypothesis testing. To understand the framework that underlies this process, it is constructive to consider the sample of study patients in the context of the larger, true population of interest. Since it is not feasible to obtain data on an entire population, the next best alternative is to make inference about the population of interest based on statistics from a (*random*) sample of individuals that are representative of the target population.

Initially a null hypothesis is made (denoted by H_0); statistical tests are then carried out on the study sample to provide evidence in favor of rejecting or accepting H_0. The null hypothesis states that there is no difference between groups with respect to the outcome of interest, or that a given factor does not affect the outcome. For example smoking is harmless, or monthly ranibizumab has no effect on visual acuity for patients with neovascular age-related macular degeneration (AMD). In the case of a randomized controlled trial (RCT), H_0 assumes that the intervention has no effect, or that the outcome is the same in all treatment arms. The Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA)[1] was a landmark RCT that investigated the effect of monthly intravitreal injections of ranibizumab (0.3 mg and 0.5 mg) versus control (sham injections) for the treatment of exudative AMD. In the MARINA trial, the null hypothesis was that on average sham injections produced the same change in visual acuity over 24 months as did monthly injections of ranibizumab.

Statistical tests provide a measure of how likely it is for the observed study results to have occurred under the assumption that the null hypothesis was true (i.e., no true effect existed). In other words, hypothesis testing measures the probability that the results occurred simply by chance. If the probability is low enough, then H_0 is said to be rejected in favor of the alternative hypothesis: H_a that the factor being examined does in fact have an influence on the outcome of interest.

Statistical Significance

In evidence-based medicine results are generally considered statistically significant at the 5% level. As a probability, the significance level is referred to in the literature as α, which

is the probability of committing a type I error. A type I error occurs if the null hypothesis is rejected when it is actually true (i.e., no true treatment effect exists, yet the statistical test concluded the result was statistically significant). It can also be thought of as a false positive. At $\alpha = 0.05$, by chance alone, if a trial were repeated 100 times then findings with an effect as great, or greater would be found 5 times (under the assumption of H_0). In the literature, the level of statistical significance is generally reported either by a p-value, or a 95% confidence interval (CI). The 95% CI corresponds to $(1-\alpha)$, which is the probability of correctly rejecting a null hypothesis.

A p-value is useful in that it provides the actual probability that the events occurred by chance (i.e., probability of rejecting a true H_0). For example, in the MARINA trial[1] a p-value of < 0.001 was reported comparing visual acuity outcomes between the ranibizumab and the sham-injection groups after 12 months. Specifically, one of the main findings was that 94.6% of the patients receiving 0.5 mg ranibizumab lost fewer than 15 letters from baseline as compared with 62.2% in the sham-injection group; this corresponds to an absolute risk reduction (ARR) of 32.4% (treatment proportion [94.6%] – control proportion [62.2%]). The p-value of < 0.001 is calculated from a statistical test on the difference in these proportions (or ARR). Thus, the probability that a difference of 32.4% (treatment proportion – control proportion) or greater would be found by chance alone—if H_0 was true—is less than 1 in 1,000 (i.e., $p < 0.001$) implying strong evidence for a treatment effect. A null hypothesis can never be proven true or false since an entire population is never analyzed; a p-value measures the strength of evidence against the null hypothesis.

A 95% CI is often more clinically relevant than a p-value, as it defines an actual interval for which the true value is likely to lie. The smaller the CI the more precise the estimate. A CI and a p-value convey similar information. For instance a 95% CI for a difference in proportions (means) that does not contain 0 would be statistically significant at the 5% level (i.e., $p \leq 0.05$). A 90% CI would parallel a p-value ≤ 0.1. If the sample size is known then a CI can be derived from a p-value and vice versa (given that the statistical test used is also known).

It is also important to understand the relationship between sample size and statistical significance. This relationship is related to the probability of committing a type II error. A type II error occurs when the statistical test fails to reject a null hypothesis that is actually false. It can be thought of as a false negative whereby a true difference between treatment groups exists but the difference is not found to be statistically significant. To conceptualize type I and type II errors it is useful to consider the following table:

	H_0 True *(No true treatment effect exists)*	***H_0 False*** *(True treatment effect exists)*
Reject H_0 *(Statistically significant)*	**Type I error (α)**	**Correct**
Fail to reject H_0 *(Not statistically significant)*	**Correct**	**Type II error (β)**

The probability of a type II error occurring is denoted by β and is highly related to the power of a statistical test $(1-\beta)$. The power (generally 80%) refers to the likelihood of *not* committing a type II error. The sample size plays a key role in determining this probability. As the sample size is increased, it becomes less likely that a true difference between groups will not be shown to be statistically significant.

It is important to realize that the conventional cut-point of $\alpha = 0.05$ that denotes statistical significance is actually an arbitrary value. If this cut-off is used absolutely then a p-value of 0.051 would be classified as not statistically significant whereas $p = 0.049$ would be statistically significant. Low p-values and narrow CIs are a direct function of larger sample sizes. Therefore in a small study, an effect that may in fact be clinically relevant may not be statistically significant. The converse can also occur; with a large enough sample size any true treatment effect, no matter how small, can be shown to be statistically significant. Therefore, in addition to the

statistical significance of a treatment effect it is important to look at the *clinical* (or practical) significance of that effect.

Clinical Significance

The *clinical* (or practical) significance of a result refers to the level of effectiveness of a treatment at which a clinician feels adoption of the treatment would be justified in clinical practice. For instance, an ophthalmologist may feel that to justify the cost and risk of adverse events for a particular treatment it should confer a relative risk (RR) of 0.5 or less for a loss of 15 or more letters of distance visual acuity. In this case, if an RR of 0.5 or less was shown in an RCT to be statistically significant (i.e., $p <= 0.05$) then the intervention should be considered for use. However, a larger sample size (and thereby more outcome events) in an RCT leads to more confidence in the results and hence more precision. Practically, this means a smaller *p* value or a narrower 95% CI. In fact, any treatment effect, in theory, can be found to be statistically significant through an RCT if enough people are studied. Therefore, when interpreting a result, the clinician should decide on an RR (or treatment effect) that is practically significant for the clinical application of the study. Then, if the results show a statistically significant treatment effect equal to or greater than the practically significant cutoff point, the clinical intervention may be considered for use. As discussed in the section on sample size calculations, if a given treatment effect is practically but not statistically significant, then the study is inadequately powered and no useful conclusion can be made. Conversely, if a treatment effect is statistically significant (for example in a large study) but not clinically significant then the intervention would not be implemented even though it had true effectiveness since the magnitude of the effectiveness was inadequate.

The next two sections explore some of the more common measures for reporting efficacy, highlighting the different approaches for when dichotomous and continuous outcomes are considered.

Dichotomous Outcomes

By definition, a variable that has two categories (e.g., male/female) is dichotomous. In ophthalmology some outcomes are inherently dichotomous such as adverse events following certain treatments (e.g., occurrence of endophthalmitis after ranibizumab). For measuring efficacy, however, it is more common for variables to be categorized based on meaningful cutoff points of continuous variables. For instance many clinical trials will define an event such as a 15-letter loss of visual acuity as a harmful occurrence of interest. The study is then designed to test the (null) hypothesis that the proportion of individuals with a 15-letter loss in visual acuity is the same between intervention groups.

For dichotomous outcomes, the frequency of clinical outcomes between groups is of primary interest and the effect can be measured based on the risk or the odds of an event occurring. Generally, the measure of effect is reported in either relative terms (i.e., RR or odds ratios [OR]), or absolute terms (through risk differences). The terms "risk" and "odds" are often used interchangeably in the literature; however, the term "risk" implies an actual probability of the outcome occurring, and can only be calculated in certain instances. Specifically if a study captures the temporal sequence (or cause and effect) of the exposure and outcome, as is the case in most RCTs and cohort studies, then results can be reported in terms of risk.

Measures of Risk

The size of the treatment effect versus a control group can be reported as an RR. A risk ratio is another common term for this measure with the same abbreviation (RR). RR is straightforward to calculate, as it is simply the incidence rate (risk) in the treatment (experimental) group divided by the incidence rate (risk) in the control group. It can be thought of as the ratio of the probability of the event occurring in the treatment group compared to the control group. It takes on any value greater than zero.

An RR = 1 (unity) means that there is no difference in the probability of an event occurring between the exposed (treatments) and unexposed (control) study groups. A 95% CI is generally reported alongside the RR to provide a measure of precision (or statistical

significance). If the 95% CI does not cross 1, then the H_0: RR=1 is said to be rejected, and the RR is statistically significant at the 5% level (i.e., $p < 0.05$).

Given a defined outcome and a defined exposure (or treatment), an RR > 1 means that the probability (risk) of the outcome occurring is greater in the exposed (treatment) group versus the unexposed (control) group. Conversely, an RR < 1 suggests that the risk of the outcome occurring in individuals that are exposed (treated) is lower than those who are unexposed (control). The further from unity (in either direction) the greater the magnitude of the treatment effect. When interpreting an RR for direction of the treatment effect one must distinguish whether the outcome of interest is beneficial (e.g., losing 15 or fewer Early Treatment Diabetic Retinopathy Study [ETDRS] letters of distance visual acuity) or harmful (e.g., endophthalmitis). Another related measure, which in some cases has a more intuitive interpretation, is the relative risk reduction (RRR). When an RR is less than unity, it means that an exposure (treatment) has a protective effect against the outcome; the RRR is used to report the size of the risk reduction. The RRR is calculated as (1-RR), and generally expressed as a percentage. For example, if a treatment confers an RR of 0.9 for a particular outcome, the RRR would be 0.1 or 10% (i.e., 1 – 0.9).

Results are often conveyed with complex figures and statistical analyses; however, it is often easiest to convert the main study results into a simple 2 × 2 contingency table as demonstrated in Table 2.1 to allow for clearer conceptualization. From the contingency table, several measures of effect can be calculated. As an example, we consider the results

TABLE 2.1 Standard 2 × 2 Contingency Table

	Outcome (yes)	Outcome (no)
Exposure (+)	a	b
No exposure	c	d
Total	a + c	b + d

TABLE 2.2 Contingency Table MARINA Trial (12-Month Follow-up)[1]

	Lost ≥ 15 letters	Lost < 15 letters
Ranibizumab (0.5 mg) injections	13	227
Sham injections	90	148
Total	103	375

of the MARINA[1] trial where the intervention is monthly intravitreal injections of 0.5 mg ranibizumab and the control is sham injections. One dichotomous outcome of interest was whether or not patients lost > 15 ETDRS letters over 12 months' follow-up. The RR and RRR comparing the risk of losing > 15 ETDRS letters between treatment arms were not explicitly reported in the study. However, a contingency table can be derived from the data given in the manuscript (Table 2.2)* and the effect measures of interest can be calculated by the reader using the formulas provided at the end of the chapter (Table 2.3). The RR and RRR are calculated as follows:

$$\mathbf{RR} = \left(\frac{\mathbf{13}}{\mathbf{(13+227)}} \div \frac{\mathbf{90}}{\mathbf{(90+148)}}\right) = \mathbf{0.143}$$

$$\mathbf{RRR = 1.0 - 0.14 = 0.86}$$

The RR of 0.143 indicates that patients receiving ranibizumab had a lower probability of losing more than 15 ETRDS letters (a "harmful outcome") than patients who were given the sham injections. The ranibizumab injections lowered the risk of the harmful outcome occurring by 86% (RRR = 1.0 – 0.14 = 0.86).

RR and RRR are easy to calculate, and are some of the most fundamental measures of risk. However, other ways to report risk differentials between groups exist, namely absolute risk reduction (ARR) and number needed to treat (NNT). In many instances these

*2 × 2 table was derived from Figure 2.1 by working backwards from the information given: Total sample receiving the sham (n = 238) and 0.5 mg ranibizumab (n = 240) injections, and the percentage of patients who lost <15 letters in each group.

TABLE 2.3 Formulas

Outcome Measure	Formula
Relative risk (RR)	$= \dfrac{\text{Incidence outcome (tx grp)}}{\text{Incidence outcome (control grp)}}$ $= \dfrac{a}{(a+b)} \div \dfrac{c}{(c+d)}$
Relative risk reduction (RRR)	$= (1 - \text{RR}) \times 100\%$ $= 100\% \times \left[1 - \left[\dfrac{a}{(a+b)} \div \dfrac{c}{(c+d)} \right] \right]$
Absolute risk reduction (ARR) (Risk difference)	$=$ Incidence outcome (control grp) $-$ Incidence outcome (tx grp) $= \dfrac{c}{(c+d)} - \dfrac{a}{(a+b)}$
Number needed to treat (NNT)	$= \dfrac{1}{\text{ARR}}$ $= \dfrac{1}{\dfrac{c}{(c+d)} - \dfrac{a}{(a+b)}}$
Odds ratio (OR)	$= \dfrac{\left(\dfrac{a}{c}\right)}{\left(\dfrac{b}{d}\right)} = \dfrac{(ad)}{(bc)}$

measures can offer more clinically relevant interpretations than RR and RRR.

ARR, also referred to in the literature as the risk difference, is the rate of outcome in the control group minus the rate of outcome in the treatment group and can be a useful and intuitive statistic since it accounts for the absolute incidence of disease. For example, a treatment that reduces disease incidence from 20% to 10% over 5 years has the same treatment effect (RR = 2) as a treatment that reduces disease incidence from 4% to 2% over 5 years. However, more patients will benefit from the first treatment (ARR = 10% for the first treatment versus 2% for the second treatment).

ARR can also be mathematically described in an intuitive statistic called the *number needed to treat* (NNT). The NNT is simply the mathematical inverse of ARR and is the number of patients that need to be treated with the intervention to prevent one harmful outcome event. Again, this measure can be useful when deciding whether or not to implement the use of a particular therapy among a group of patients in clinical practice.

In summary, the RR looks at the risk of disease in the treatment group relative to the control group as a ratio, but does not consider the incidence of the outcome. In contrast, the ARR will increase (and hence NNT decrease) when the overall incidence of the outcome in the study population is increased. Therefore, to fully understand the size of a treatment effect as well as its clinical importance both RR and ARR (and thus NNT) should be considered. For a further discussion of RR, RRR, ARR, and NNT in the context of evidence-based medicine see Barratt et al.[2] for a general review.

Unlike well-designed cohort studies and RCTs, many studies, namely those with case control designs, do not capture the temporal

sequence (cause and effect) of events between exposure and outcome. As such, a true risk in the treatment and control groups and thus a true RR cannot be calculated. To report differences in disease and exposure frequency between groups, these studies use odds ratios (ORs) as a measure of association.

Odds Ratios

While the RR is the ratio of the incidence (risk) of disease occurring, the OR is the ratio of odds of disease occurring in the exposure group over the control group, respectively. If the disease (or outcome) in consideration is rare, then the OR will approximate the RR. In other cases (if prevalence of the outcome is more common) then the two measures are distinct.

Like RR, an unadjusted OR is derived from a simple 2 × 2 contingency table. An unadjusted OR reports a *raw* association in that it does not account for confounding effects. To illustrate, we have used the example of the contingency table for the case-control study by McGwin et al.[3] of cholesterol-lowering agent use and odds of developing AMD (Table 2.4). The formula based on a conventional contingency table along with the OR calculation for this example is shown here:

$$OR = \frac{(a/c)}{(b/d)} = \frac{(96/775)}{(1{,}441/10{,}276)} = 0.89$$

The interpretation is as follows: the odds of having a history of using cholesterol-lowering agents among patients with AMD were 0.89 times greater than those among patients without AMD. The OR is a measure of the strength of association between two variables; an OR of 1.0 or close to 1.0 indicates no or little relationship between the variables being studied, whereas a large OR, or an OR close to zero, indicates a strong magnitude of association between the variables. Analogous to the interpretation of RR, whether or not a small OR (close to 0) represents a favorable association depends on how the outcomes were defined. In our example, it can be concluded from the study (i.e., an OR < 1) that those who used cholesterol-lowering agents had lower odds of having AMD (a "harmful" outcome).

TABLE 2.4 Case-Control Study of Lipid-Lowering Agents and Risk of Age-Related Macular Degeneration (AMD)

	AMD Cases	Control Group
History of lipid-lowering agent use	96	1,441
No history of lipid-lowering agent use	775	10,276
Total	871	11,717

In this example, however, the unadjusted OR was not found to be statistically significant. Hypothesis testing for an OR involves testing: H_0: OR=1 (i.e., the null hypothesis that there is no association between exposure variables). To report statistical significance it is standard practice to use a 95% CI around the OR, which is derived from the well-known chi-squared distribution (X^2). Here the authors reported a 95% CI of (0.71–1.11) around the unadjusted OR; since the interval crosses 1, the null hypothesis was not rejected at $\alpha = 5\%$ (i.e., $p > 0.05$).

Confounding factors can be controlled for in the design or statistical phase of a study. For example a matched (or paired) case-control study can be used and an unadjusted OR can be interpreted as a less biased measure of association. To control for confounding factors in the statistical phase a logistic regression is used and an adjusted OR is interpreted.

Logistic Regression

Logistic regression is utilized in studies where the association between an exposure (or treatment) and an outcome requires that other potentially confounding variables are controlled for in the analysis. In many observational studies (e.g., unmatched case-control, cohort, or cross-sectional studies) confounding is not controlled for in the design stage; therefore, it is necessary to control for confounding factors in the statistical analysis. Even in the case of an RCT, if known confounding factors are unevenly distributed (after randomization or in quasi-randomized trials) among the treatment arms then adjustment using statistical methods can be helpful.

An OR derived from a multivariable logistic regression holds the same basic interpretation as an unadjusted OR. It is the odds of the event occurring in the exposed versus unexposed groups; however, the adjusted OR measures the association holding all confounding factors included in the model constant. The aim is to isolate the association of interest, net of other factors that may distort the relationship in question. Additionally, unlike in a basic contingency table, logistic regression can provide ORs for the case when a continuous variable is the exposure of interest (e.g., the effect of age on the odds of getting AMD). For a continuous exposure, the OR would represent the odds of the event occurring for a one unit increase (or decrease) in the exposure (e.g., 1 year), adjusted for the other confounders in the model. Overall, an adjusted OR can provide a less biased estimate of association than an unadjusted OR.

To help illustrate how logistic regression results can differ from unadjusted estimates, we refer back to the case-control study example conducted by McGwin et al.[3] In their study they identified age, gender, and ethnicity as potential confounding factors for which they controlled in a second analysis using logistic regression. After accounting for these variables, a statistically significant association between AMD and the use of cholesterol-lowering agents was revealed (adjusted OR, 0.79; 95% CI, 0.63–0.99). Since the 95% CI does not overlap unity, we can conclude the result was statistically significant at the 5% level (i.e., $p < 0.05$).

While we have largely been referring to the use of logistic regression in a case-control study setting, it is also used in cohort studies and RCTs to control for confounding factors during the statistical phase of the study. The important distinction is that in cohort and RCT studies it is preferred to report RRs—not OR—as the primary measure of effect. In many instances (when the outcome is rare) the OR will well approximate the RR. Therefore, in some cases a study can simply interpret the adjusted OR from a logistic regression as an adjusted RR analogously to what was described above. When the outcome is more common the RR, RRR, NNT can actually be derived from a logistic regression[4] or modeled as a risk ratio with the use of a Poisson regression. These methods are beyond the scope of this chapter, but for further details regarding logistic regression the reader is referred to a text by Hosmer and Lemeshow.[5] When interpreting the literature it is important to note which measures are used to report the results (i.e., risk or odds), and whether or not they are adjusted or unadjusted estimates.

Continuous Outcomes

While examining the difference in proportion of a clinically important outcome between two groups is a classic means of testing for efficacy, continuous outcome measures are more commonly used in the ophthalmology literature. We are fortunate to have a few discrete and reproducible outcome measures that are clinically important (e.g., ETDRS visual acuity, intraocular pressure, mean deviation on Humphrey Visual Field Testing). There are several approaches that are used to report on the statistical significance and magnitude of association between a given factor and a continuous outcome of interest.

When there are two treatment groups (or sample populations) being examined, the primary objective is to determine the magnitude and statistical significance of the difference in means between the two groups. The difference in means is straightforward to calculate. The mean of the outcome of interest is calculated in the treatment group (μ_1) and is subtracted from the mean in the control group (μ_2). To determine if the difference is statistically significant, a two-sample t-test is used. A paired t-test is reported for matched case-control studies, or when two observations on the same person are being compared (e.g., difference before and after treatments). The interpretation between a paired and two-sample t-test is analogous. For two treatment arms the t-test examines the null hypothesis that the mean is equal in both groups (*notation*: $H_0: \mu_1 = \mu_2$ *vs* $H_a: \mu_1 \neq \mu_2$). Under the null hypothesis, the difference in means follows the Student's t-distribution from which p-values and 95% CIs can be reported. If the 95% CI does not contain 0, then the difference

in means is statistically significant at the 5% level.

In some research settings more complex statistical techniques are required. Analysis of variance (ANOVA) is used in studies where more than two groups are being compared, whereas linear regression is utilized when looking for a treatment effect between two groups with a continuous outcome when there are multiple confounders that need to be controlled for.

ANOVA and Linear Regression

One-way ANOVA is a statistical approach frequently used to analyze continuous outcomes. If the means between two groups are being compared, then a one-way ANOVA will provide the same results as a t-test. However, ANOVA is most useful when there are more than two treatment groups being tested. For example, if a study was conducted to test which dosage of a certain drug produced the highest gain in visual acuity then a one-way ANOVA could be used to compare the different dosing regimens. A one-way ANOVA tests whether the mean is the same in all of the groups. If three dosage groups were being compared the following null hypothesis would be tested: $H_0: \mu_{dose\,1} = \mu_{dose\,2} = \mu_{dose\,3}$ *vs* $H_a: \mu_{dose\,1} \neq \mu_{dose\,2} \neq \mu_{dose\,3}$. In one-way ANOVA, an *F*-statistic is used to test the null hypothesis. Statistical significance is usually reported with a p-value for ANOVA and linear regression as opposed to t-tests, ORs, and RRs where CIs are generally used. For ANOVA and linear regression a p-value provides a comprehensive statistic that captures the comparison between multiple groups.

Linear regression is a multivariable extension of the t-test. A simple linear regression with one dummy variable (e.g., treatment vs. no treatment) would produce the same results as a two-sample t-test. Ordinary least squares (OLS) is the conventional method of estimating the coefficients in linear regression. Multivariable OLS linear regression is most useful in a research setting where numerous variables (both continuous and dichotomous) need to be controlled for as confounding factors. The results also provide more detailed inference on the magnitude of effect for *specific* variables and the outcome of interest. The basic notation for an OLS model is as follows:

$$Y = \alpha + \beta_1 X_1 \cdots + \cdots \beta_n X_n \varepsilon$$

In the equation, Y is the outcome (or dependent) variable, and the *X* represents the independent (also referred to as predictor or factor) variables. The β coefficients are of primary interest and tell us what the expected change in the outcome is for a one unit change in the independent variable. When the independent variable is dichotomous (e.g., gender) then β corresponds to the estimated mean difference between categories. Similar to the multivariable logistic regression, there is generally one independent variable of interest (e.g., treatment arm), and a number of other variables that are being controlled for as confounders. For a one unit change in a predictor of interest (e.g., a one-year increase or decrease in age) the β coefficient can be interpreted as the estimated change in the outcome holding all other confounders included in the regression as "fixed." In the multivariable setting, β represents the effect size, net of confounding factors. Similar to the one-way ANOVA, it is common practice for p-values to be reported alongside the regression coefficients. The p-value has the conventional interpretation, where it tests the null hypothesis that $\beta = 0$ (i.e., the independent variable being tested has no effect on the outcome variable). If the p-value is less than 5% then we conclude that the observed association between the dependent and independent variables was not due to chance alone (i.e., the results are statistically significant).

The above methods (i.e., t-test, ANOVA, multiple linear regression) follow a parametric approach to hypothesis testing where it is assumed that observations are independent of each other and that the data follow a normal distribution. Due to the central limit theorem, the assumption of normality is generally valid for studies that are conducted on large samples. However, other statistical methods are sometimes needed for studies with smaller sample size. Nonparametric tests serve to relax some of the more stringent assumptions of parametric tests (i.e., homogenous variance,

independence, normality). For example, the Mann-Whitney U test (*Wilcoxon* for paired data) is the nonparametric functional equivalent of the two-sample t-test and the Kruskal-Wallis test is analogous to one-way ANOVA. P-values obtained from nonparametric statistical testing can be interpreted analogously to their parametric counterparts.

Survival Analysis

In many clinical trials the primary outcome is the time until an event, or survival. The statistics discussed above such as OR and RR only capture whether or not an event occurred. Survival (time to event) analysis provides a more powerful outcome as it incorporates not only the event occurring, but also the time elapsed (from baseline) until the outcome was ascertained or the patient was lost to follow-up.

In survival analysis, a Kaplan-Meier curve is commonly used for descriptive purposes. For one or more groups, it plots the proportion of patients for which the event of interest has not occurred (survival function) on the y axis, across each of the follow-up time points on the x axis. At a given time point, the further the curve is from the x axis, the smaller is the proportion of individuals who have had the event. Hence, if comparing two groups, the one above is indicative of a more effective treatment (assuming that the outcome being studied is "harmful"). The cumulative incidence can also be plotted with a Kaplan-Meier curve, which is just the inverse of the survival function (i.e., the curve starts at 0 and has a positive slope, whereas the survival curve starts at 1 and has a negative slope).

As an example, we use the results of a study performed by the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group[6]; these results will be discussed further in Chapter 3 of this book. Figure 2.1 shows a Kaplan-Meier curve modeling the cumulative incidence of visual

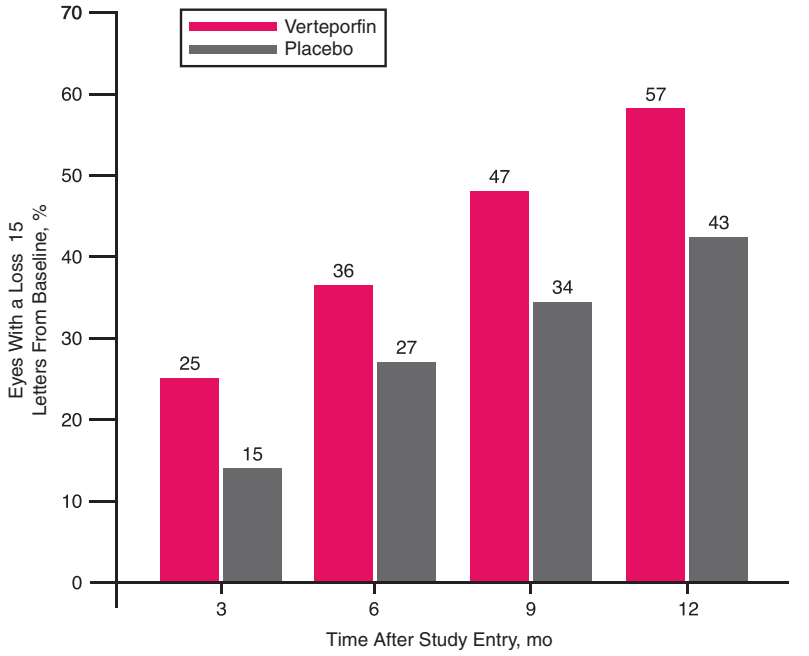

FIGURE 2.1 TAP 12-month results percentage eyes with ≥ 15 letter loss of vision. Modified from Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: One-year results of two randomized clinical trials—TAP report. Treatment of age-related macular degeneration with photodynamic therapy (TAP) study group. *Arch Ophthalmol.* 1999;117(10):1329–1345.

acuity loss ≥ 15 letters (or approximately ≥ 3 lines) for eyes treated with verteporfin (using photodynamic therapy) and those given placebo over a 12-month interval.[6] At each follow-up point there is a higher cumulative incidence of visual acuity loss ≥ 15 letters in the placebo group versus the verteporfin group. To test for statistically different survival functions (or cumulative incidence) between groups a Log Rank Test for homogeneity over strata is often reported. The null hypothesis is that time to event is the same between treatment groups, and a corresponding p-value is given. A p-value < 5% corresponds to a statistically significant difference in the survival function (or cumulative incidence) between groups and consequently a statistically significant treatment effect.

Similar to OR and RR for dichotomous outcomes, and the t-test for continuous outcomes, confounding can be an important issue with time to event analysis that must be controlled for in the statistical phase of a study. Cox Proportional Hazards models can be used to model survival time while taking into account confounding factors. Although statistically they are more powerful, survival analyses may not be as intuitive to the clinician. Even if a variable is time dependent in nature, an RCT should report the raw data needed for a reader to calculate more intuitive basic statistics such as the incidence rates, RR, and ARR.

Noninferiority Trials

Unlike a conventional RCT where the goal is to show that one treatment is therapeutically superior to another (or a control), in a noninferiority trial the purpose is to demonstrate that an experimental treatment is comparable in efficacy to an existing treatment. As such, the null and alternative hypothesis in a noninferiority trial can be thought of as the reverse of those in a conventional RCT. In a superiority trial the null hypothesis states that on average, the outcome of interest in the experimental group is equivalent to the control group; an experiment can then provide evidence against the null hypothesis in favor of a better outcome in the experimental group. Conversely the null hypothesis in a noninferiority trial is that the (active) control group is superior to the experimental group; the experiment can then provide evidence toward the alternative hypothesis that on average the two treatments are in fact no different with respect to the therapeutic benefit of the outcome.

Noninferiority trials can test both continuous (e.g., difference in means) or dichotomous (e.g., difference in proportions) outcome measures. The effect measures and the statistical distributions (e.g., chi square, Student's t, normal) used to derive statistical significance remain the same in noninferiority trials as in superiority trials. Unlike a superiority trial however, where a p-value can be used to determine statistical significance, in the case of a noninferiority trial a CI approach is used. For testing the differences in means (continuous outcome) between two treatment groups, the notation for a conventional (superiority), and noninferiority hypothesis test would be as follows:

Hypothesis test for superiority:

$$H_0 : \mu_1 - \mu_2 = 0 \ vs \ H_a : \mu_1 - \mu_2 \neq 0$$

Hypothesis test for noninferiority:

$$H_0 : \mu_1 - \mu_2 \geq \Delta \ vs \ H_a : \mu_1 - \mu_2 < \Delta$$

where μ_1 represents the mean outcomes in the active control group and μ_2 represents the mean outcome in the experimental group, and Δ represents the predefined margin of noninferiority.

Results are most often presented in a figure that shows the 95% CI of the statistic of interest (e.g., difference in means or OR) along with the margin of noninferiority Δ (Fig. 2.2). Four possible areas for which the CI could span with respect to the null region (0 for testing difference in means) and $+ -\Delta$ are shown below in Figure 2.2.

This figure depicts a scenario in which a smaller value represents a better outcome (e.g., loss in Visual Acuity VA) meaning that a negative mean difference between the experimental and active treatments favors the experimental treatment. In scenario I, the 95% CI spans the null region (0), and does not cross the lower limit of the margin of noninferiority. It is therefore said that the experimental treatment

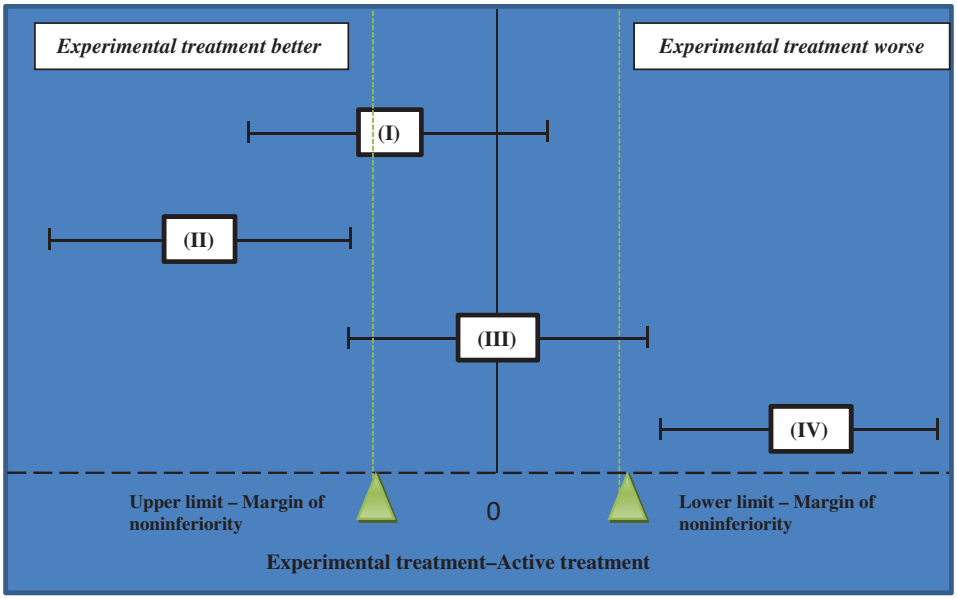

FIGURE 2.2 Interpretation of primary outcome results in noninferiority trial. Note: Error bars represent 95% confidence intervals. *Dashed lines* and Δ signify margin of noninferiority.

is not worse than (or noninferior to) the active treatment by a margin of Δ. It is also common in the literature for researchers to use the term *equivalent* to describe this result.[7] In scenario II, the experimental treatment can actually be interpreted as statistically superior to the active control as the CI lies wholly above 0 and the upper limit of Δ. In situation III, the CI crosses the null region, which means that there is no statistically significant difference between the two treatments; however, because the CI also crosses the margin of noninferiority, the result is deemed inconclusive. Specifically, the result is inconclusive in regard to the treatment being noninferior by the prespecified margin of Δ. The final situation in IV represents an instance where the experimental treatment is clearly inferior to the active control given that the result is both statistically significant (and the CI does not cross 0) and it lies to the left of the margin of noninferiority. The same reasoning applies to dichotomous outcomes where an OR is tested where the main difference is that an OR of unity (1) would lie on the midpoint representing a null effect.

For a concrete example, the 1-year results of the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT)[7] are

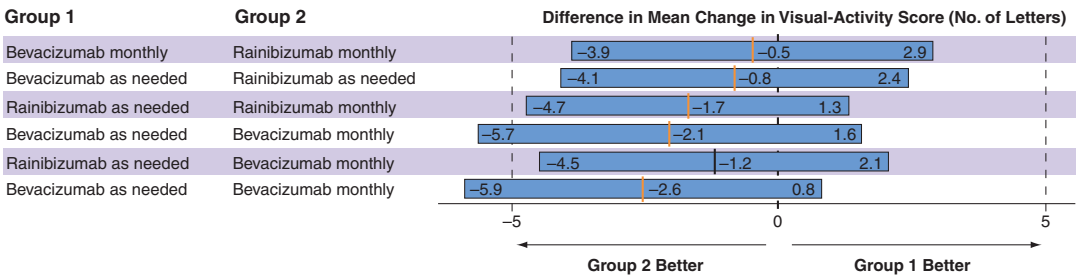

FIGURE 2.3 Differences between pairs of study groups in the mean change from baseline to one year in the visual acuity score. Reprinted from CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2011;364(20):1897–1908.

shown in Figure 2.3. The primary outcome of interest was mean change in visual acuity at 1 year where the noninferiority margin Δ was defined as ± 5 ETDRS letters. The principal research question was whether treatment with bevacizumab (either monthly or as needed) for wet AMD was comparable in efficacy to treatment with ranibizumab (either monthly or as needed). Comparing monthly versus as-needed treatment regimens (regardless of drug) was also a study question of interest. The two dosing regimens were compared both within and between the two drugs as shown in Figure 2.3.

The primary findings were that mean change in vision for patients treated with bevacizumab was equivalent to patients who received ranibizumab. This was true for both monthly and as-needed dosing regimens as the CI for the mean difference in VA spanned the null region and lay wholly within the margin of noninferiority (Δ = +− 5 ETDRS letters). Specifically, the trial failed to reject the null hypothesis that ranibizumab had superior clinical efficacy. This conclusion, however, did not hold up when bevacizumab dose as needed was compared to ranibizumab treated monthly. Since there was no statistically significant difference (i.e., the CI spanned 0) comparing bevacizumab as needed versus ranibizumab monthly—but the lower end of the CI crossed the noninferiority margin—the results were considered inconclusive. The comparison of bevacizumab as needed versus bevacizumab monthly was also inconclusive using the same reasoning.

Conclusion

The statistical concepts described in this chapter can provide a useful foundation for interpreting results presented in the ophthalmology literature. They will be most useful for interpreting larger well-designed studies such as clinical trials, prospective cohort studies, and case-control studies. Often, however, researchers must deal with challenges including small sample sizes, extremely rare outcome events, missing data, and data that does not follow the normality and independence assumptions required for strict adherence to statistical techniques. In these situations an array of more complex statistical techniques exist and more advanced statistical consultation is usually required. For more detailed information regarding basic techniques, the reader can refer to a number of useful introductory biostatistics textbooks including one by Rosner.[8]

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3 Health Economics

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Introduction

Economic evaluation in medicine has the potential to greatly influence policy decisions in both the public and the private sectors of society, thereby impacting many facets of health care. Recently, both government agencies and academic researchers have realized the need for collaboration between policy makers and academics. Specifically, policy makers and governing bodies are becoming increasingly interested in basing their policy decisions on rigorous scientific evidence, while academics are trying to make their research more relevant to the people who will eventually be applying it.

An economic evaluation of a health-care program is meant to aid in a decision regarding whether, from a particular perspective, a program should be undertaken, when compared with another available use of resources. A basic assumption is that the cost-effective analysis (CEA) is being performed to optimize the total health of a target population with access to a finite amount of resources. Consequently, this technique is not appropriate for individual physicians making decisions about their patients since it is a physician's duty to maximize the health of his or her individual patients.[1] However, an economic evaluation and analysis in health care, if performed using rigorous scientific methods, is arguably one of the most relevant research studies available to a policy maker as an aid to decision making. There have been a number of good books on CEA in health care[2–4]; it is the purpose of this chapter to give only an overview of the important aspects of an economic evaluation.

When referring to a health-care program we refer to any intervention that will cost money and is being considered for implementation for the purpose of improving health. This definition is purposefully broad and could include, for example, a public health safety program, a governmental health policy, or a decision by a third-party insurer or government agency to fund a certain drug or medical treatment. Before a particular health program is taken up for an economic evaluation, it should have been previously proved both safe and efficacious, usually through a well-designed randomized controlled trial (RCT).[2]

A full economic evaluation has two key elements that distinguish it from a partial evaluation.[2] First, it measures the cost-effectiveness of a health-care program against another option—preferably against the next best available alternative or another option that could potentially be implemented. Second, it evaluates both the health outcomes of the program (effectiveness) and the cost simultaneously.

A CEA, as first described by Weinstein, forces decision makers to be explicit with respect to the benefits and values that underlie a resource allocation decision.[3] It is important that a CEA is broad and comprehensive and oriented toward outcomes. The ratio of incremental cost per unit of health outcome gained through a health program is referred to as the cost-effectiveness ratio and can be used to compare the cost-effectiveness of different

health programs. League tables are lists of cost-effectiveness ratios whereby the cost-effectiveness of different health programs or interventions can be compared.

Full evaluations can be classified into four subgroups: cost-effectiveness analyses, cost-minimization analyses (CMAs), cost–benefit analyses (CBAs), and cost–utility analyses (CUAs). A full economic evaluation will compare both the effectiveness and the cost of two or more health-care programs. In each subgroup, the cost of the program is measured, but it is the measurement of effectiveness that distinguishes the different types of analyses. We will briefly examine each of the subtypes of CEAs.

Cost-Effective Analysis

A CEA is the most general, full, economic evaluation and can be distinguished from the other subgroups because the effectiveness of the health program being evaluated is measured in natural units of effect. The most common unit of effect is length of life, such that an analysis would compare the cost per life-year saved between two potential health programs. In medicine, many clinical trials measure survival as the primary outcome and are therefore well suited to be used in a CEA. However, life-years saved may not be the most appropriate outcome measure if the program is designed to improve quality of life (QOL), such as is the case in ophthalmology. It is possible to base a CEA on a natural outcome measure that is assumed to be associated with better health. For instance, the cost per vision-year saved could be calculated in a CEA. Irrespective of the natural outcome unit chosen for the analysis, the purpose of a CEA is to compare the cost per natural health outcome between the health programs under consideration.

Cost-Minimization Analysis

In a CMA, one assumes that the effectiveness of the health programs under consideration is equivalent. In a CMA, the cost of two or more health programs is compared and the program with the lower cost is considered the "preferred" option from the health policy maker's perspective. For example, consider a situation in which an equivalence trial had shown that there was no statistically significant difference between two drugs for the treatment of glaucoma. An equivalence trial is a type of RCT specifically designed to test the hypothesis that a treatment option is as good as another alternative that has previously been proved to be efficacious. Here, the treatment option with the lower cost would be preferred.

Cost–Benefit Analysis

In the real world, there are many situations where a number of important health outcomes such as length of life, QOL, and potential complications or consequences with treatment must be considered simultaneously to fully assess the effectiveness of a program. In addition, it may be necessary to directly compare programs that provide drastically different health benefits. CBA and CUA have been designed to account for different health outcomes and may be important in evaluating the true cost-effectiveness of a program and to allow for the comparison of programs or treatment interventions designed to effect health in different ways.

A CBA is also a special form of CEA, except that in this case the effectiveness of a program is measured monetarily. Costs can clearly be measured monetarily, but to measure the effectiveness in this way it is necessary to convert health outcomes into dollars. Consequently, a monetary value must be placed on all health outcomes pertinent to the analysis including length of life, QOL, and other health consequences. If the outcome of interest is simply years of life, then annual earnings per life-year saved can be defined as a monetary measure of effectiveness. However, when other factors such as QOL and potential complications must be considered, effectiveness is generally measured using a willingness-to-pay method. In this technique, a separate study would be conducted and subjects would be asked how much money they would be willing to pay to completely avoid a certain negative health outcome. A CBA should report results in the form of a net benefit in dollars, or the difference between the monetary values of the health benefits derived minus the cost of the health program.[4]

The major advantage with using a CBA is that health programs with widely varying health outcomes can be compared with each other. In addition, by definition a CBA compares the net benefit with the net cost of a health program so that one can determine whether the benefits outweigh the costs of initiating the program. However, assigning a price of a health outcome is a very difficult and controversial task that may only be possible in a limited number of situations. The main disadvantage with this method is that people from different sociodemographic backgrounds may be willing to pay vastly different dollar amounts for the same health outcome. In addition, whether a person lives in a country with a universal health-care system or whether the person has full health insurance will dramatically affect a person's willingness to pay. These differences can drastically bias a study toward or against a certain demography of the population. Also, these differences make it very difficult to compare CBAs with each other.

Cost–Utility Analysis

A CUA is another type of CEA that allows different health outcomes of a program to be combined into one overall measure of effectiveness, thereby allowing for health programs designed to achieve different health outcomes to be compared. In addition, the difficult task of assigning monetary values to health outcomes is avoided. The effectiveness measure for a CUA is usually a quality-adjusted life year (QALY), where years of life are adjusted using utilities as a weighting factor. Measuring a health outcome in terms of QALYs allows for incorporation of both morbidity and mortality into one measure. Therefore, a CUA can investigate the cost per QOL adjusted year gained from the implementation of a particular health program compared with an alternative.

A utility is a measure of the strength of preference for a particular health outcome and has a theoretical foundation in economics and decision theory. Essentially, a utility is a measure of the value that a person places on a certain outcome or health state. Using utilities, the QOL associated with a particular health state that may have many important aspects can be measured using one method and can be reported with one value. Common methods of utility valuation are the time trade-off (TTO) technique, standard reference gamble (SRG), and rating scale. We will examine the details of utility theory later in the chapter.

Important Aspects of an Economic Evaluation

Cost-Effectiveness Ratio

A true CEA must measure both the cost and the effectiveness of a health program against the next best alternative. As mentioned earlier, the cost-effectiveness of a health program will usually be expressed in terms of an incremental cost-effectiveness ratio (ICER). Ideally, this will be defined as the difference in cost between the health program under question and the next best alternative (the numerator, or cost) divided by the difference in effectiveness between the health program under question and the next best alternative (the denominator, or effectiveness). It is important to differentiate between a marginal ICER and an average ICER. In the former, the cost and effectiveness both represent differences in costs and effectiveness between the treatment in question and the next best alternative, whereas in the latter the costs and effectiveness are measured independently of any alternative strategy.[1] Through the use of an ICER, it is possible to discern the true opportunity cost of a program, or the health outcomes that could be achieved by implementing the program of interest as opposed to the next best available option. By examining health policy in this way, it is possible to compare the cost-effectiveness of various health interventions in a consistent manner.

Perspective

The first fundamental question that must be answered in an economic evaluation is the perspective that the decision maker is taking when conducting the analysis. For instance, the decision of whether photodynamic

therapy for patients with age-related macular degeneration is cost-effective could be drastically different depending on whether the decision is being made from the perspective of a for-profit third-party insurer or society at large. The insurer's viewpoint may simply take into account the incremental cost of treatment and a health outcome in terms of vision-years saved or QALYs gained. However, society's viewpoint may have to consider the cost of blindness that could include the utilization of many social and disability services provided by a government. The conclusion of a CEA could easily be different depending on the perspective taken. Unless a CEA is inherently being undertaken from a specific viewpoint (e.g., from the perspective of a third-party insurer or hospital), it has been recommended that the most general societal perspective be used.[4] However, if the evaluation is undertaken from a societal viewpoint, it may be relatively easy and informative to provide other viewpoints in a CEA.

Designing the Study

In designing a CEA, a clear problem that can be realistically answered through the analysis must be identified. The objective, method, and target population of the program alternatives must also be clear. A description of the effectiveness of the health intervention should be included as it is not logical to investigate the cost-effectiveness of something that has not been proved to be effective. To visualize health outcomes being modeled in the analysis, it may be useful to draw a flow diagram using a hypothetical cohort of people who begin the program and follow that cohort through every possible event outcome. Consultation with medical and economic experts is usually required.

Measuring Effectiveness

Survival is a basic and very useful outcome measure in a CEA and can be the sole outcome or can be incorporated with other data. If survival does not fully explain the health outcome that is conferred by a program, then another method to measure effectiveness must be used. It is often easy and useful to base a CEA on an intermediate outcome measure that is assumed to be associated with better health. For instance, the cost per vision-year saved could be calculated for an ophthalmic intervention. If an intermediate health outcome is being used, a strong link with QOL or survival must be established.

Real-world situations commonly arise where a number of important health outcomes such as survival, QOL, and potential complications or consequences of treatment must be considered simultaneously to fully determine the effectiveness of a program. It is also desirable to be able to compare programs that provide drastically different health benefits. When the effectiveness of a health outcome is measured in dollars, the economic evaluation is known as a CBA. The most critical aspect in a CBA is valuing health using money; often the value of a health outcome, health state, or health scenario is measured by the willingness to pay or by annual earnings on the basis of expected length of life. As mentioned earlier in the chapter, there are many inherent biases involved in doing this.

The most comprehensive measure of health outcome combines both length and QOL into a QALY. A QALY can be conceptualized further by examining Figure 3.1, where the *y*-axis represents health-related quality of life (HRQL), the *x*-axis represents duration of life, and the curve represents various health states that a hypothetical person could potentially go through within a certain period. The area under the curve represents the QALYs associated with that particular set of health states over the specified time frame.

Measuring Health-Related Quality of Life. It has been generally accepted that QOL should be measured with a broad-based definition of health, accounting for physical/mobility function, emotional/psychological function, sensory function, cognitive function, pain, dexterity, and self-care.[5] However, there remain many alternatives in measuring HRQL. HRQL measurement tools can be classified as generic, which attempt to measure overall HRQL, or specific, which focus on certain aspects of health such as disease, population, and function.[6]

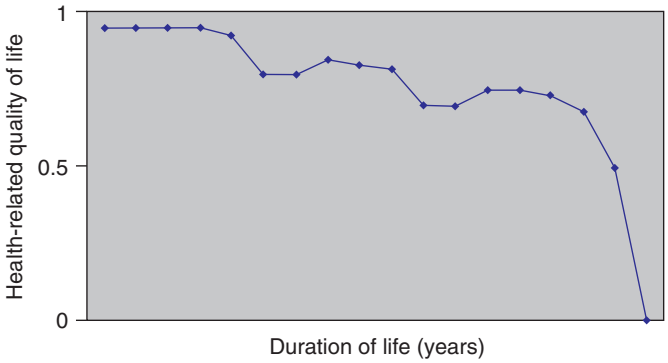

FIGURE 3.1 Graphic depiction of a quality-of-life adjusted year. The area under the curve represents QALYs associated with this particular set of health states. QALY, quality-adjusted life year.

Specific HRQL instruments such as the 51-item National Eye Institute Visual Function Questionnaire[7] and the Visual Function 14 (VF-14)[8] in ophthalmology give more information about certain aspects of health (i.e., visual function) and are considered more responsive to changing health states. Generic HRQL instruments use one measure to encompass all aspects of HRQL and are comparable across different health conditions. One example of a generic HRQL instrument is a health status profile. Health status profiles are single instruments that can detect differential effects on various aspects of health status. Examples of health status profiles include the Medical Outcomes Short Form-36 (SF-36)[9] and the Sickness Impact Profile.[10]

HRQL measurement tools can also be classified as preference based or nonpreference based. Health status profiles are nonpreference based and do not account for a patient's judgment on how disease affects them. In contrast, preference-based methods allow for a person's values toward the consequences of various health outcomes to be determined according to what is personally important. The measure of HRQL using patient preferences is called a *utility* and is considered the most appropriate HRQL weighting factor for use in a CEA.[4]

Sources for Utility Valuation. Utilities can be obtained from people who have the disease state in question (such as current patients and former patients) or from those who do not (including the general public, people with other disease, or health-care professionals). It has been shown empirically that people in the health state in question respond with higher utilities than people not in the health state and are making hypothetical utility assessments.[11] Additionally, these differing responses can dramatically affect the outcome of commonly accepted decision analyses.[12] The main argument for using current patients to derive utilities is that they have first-hand knowledge of the disease. However, using current patients can limit the number of disease states investigated simultaneously and can bias the results against the ill, disabled, or elderly.[4] In addition, using community-derived utility values allows for more consistent comparisons across studies performed in different fields.

The final decision as to whose utilities to use in a CEA will eventually depend on the specific situation, the availability of data, and the preference of the investigators. Community-based utilities are recommended as the default and should be used unless there are specific reasons to choose another sample. Using utilities derived from health professionals is not recommended and should only be used as a last resort.[4]

Techniques for Eliciting Utilities. Utilities were first introduced and applied in economics and game theory by Von Neumann, a Hungarian mathematician, and Morgenstern, an economist, in their classic text *The Theory of Games and Economic Behavior*.[13] They described a method of decision making under conditions

of *uncertainty* that enables a reasonable decision maker to make the best decision in accordance with his or her fundamental preferences. From a health-care perspective, the first fundamental axiom states that a person can quantify a probability (p) of indifference between the following two outcomes: (a) a sure outcome of the health state that is to be evaluated and (b) a gamble with probability p of the best possible outcome (perfect health) and $(1 - p)$ for the worst possible outcome (death). This probability (p) is defined as the SRG utility for a particular outcome. The SRG is said to measure utilities under *risky*, or *uncertain*, conditions because an individual is forced to quantify a probability, but is not assured of any particular outcome (i.e., the individual is playing a game of chance).

Popular riskless utility instruments (measured under conditions of *certainty*) include the TTO and a rating scale. The TTO method was initially developed by Torrance et al.[14] and requires a patient to hypothetically trade off years of remaining life in exchange for perfect health to quantify the QOL of the particular disease state. Two pieces of information are needed to quantify the utility of an individual in a particular disease state: (a) an expected life span (x) available for trading and (b) the number of years (y) that an individual is willing to trade off out of the x available years, in return for restoring perfect health. TTO utility is calculated as [(number of years expected to live (x) – number of years willing to trade off (y))/number of years expected to live (x)]. For example, if a patient expects to live for 12 years and is willing to trade off 4 years for perfect health, then the utility of the current health state is $[(12 - 4)/12] = 0.67$. The rating scale requires a participant to rate a certain health state (either a hypothetical state or the state that they are currently in) between two set extremes, usually death (utility = 0) and perfect health (utility = 1).

Different utility elicitation techniques are known to produce different utility values[5,15,16] and consequently the decision about what utility instrument to use in an analysis is important. TTO and rating scale utilities are easier to understand and obtain than SRG utilities. However, only the SRG method of utility elicitation is equivalent to the axiom put forth by Von Neumann and Morgenstern, and therefore, TTO and rating scale utilities are approximations. Regardless of the method used, in a given situation, utilities should be valid, reliable, and responsive to changing health states. In 1996, the Panel on Cost-Effectiveness in Health and Medicine was unable to come to a conclusion on the best utility assessment technique.[17] The decision of which utility assessment tool is appropriate will therefore differ, depending on the population of participants, the nature of the study, the preferences of the researchers, and the nature of the current QOL literature in the particular field of interest.

Outcome Probabilities

Ideally, a full prospective study that measures the health outcome of interest and relevant costs associated with the program in a randomized fashion would be employed. In this way, the study would be designed to answer the study question and the results would be easily transferable to a cost-effective model. In the absence of a randomized prospective CEA, level I evidence in the form of a well-designed RCT or meta-analysis should be used to estimate outcome probabilities (or treatment effect) and adverse reactions in a CEA. If a suitable RCT is not available, outcome probabilities may be based on observational studies such as prospective cohort designs. However, this introduces the potential for bias and is less than ideal. In many situations, a trade-off between the level of evidence (or internal validity) and generalizability to the situation and population of interest will exist and will need to be considered. Again, it is important to emphasize that before studying the cost-effectiveness of a health intervention, the intervention must have been shown to be clinically effective.

Estimating Costs

To assess the true opportunity cost of an intervention, cost should be valued as the difference in resource use between an intervention and an alternative intervention. Consequently, costs should refer to the incremental resources consumed or saved rather than the total resources

used.[17] Although it is difficult to measure true opportunity costs, costs in a competitive economy are thought to reflect the opportunity cost of resources. Costs should be measured in dollars during a specific year, and a broad long-term societal outlook should be taken when relevant costs are being identified. When measuring costs in an economic evaluation, four main classifications have been identified as important[4]: (a) health-care resources, (b) nonhealth-care resources, (c) informal caregiver's time, and (d) patient time.

It is useful to classify costs as direct costs or productivity costs (also known as indirect costs). Direct costs are defined as the value of all goods, services, and other resources that are consumed in the provision of an intervention or in dealing with the side effects or other current and future consequences linked to it.[4] Direct health-care costs can include costs of tests, pharmaceuticals, and other medical treatments relating to the procedure, as well as any potential costs in the future that may result from the health program or intervention. Direct nonhealth-care costs can include such items as the cost of child care needed to complete an intervention or transportation. Changes in the use of informal caregiver's time should also be considered a direct cost and can be measured using average wages in the community. Finally, direct costs due to patients' time associated with the intervention should be considered a cost and can also be measured using average wages from the community.

When determining which health-care costs to include in a cost analysis, any health-care costs in the future that are associated with the disease should be considered. However, health-care costs unrelated to the intervention should not necessarily be included. Productivity costs are associated with the loss (or gain) in productivity because of a health program or intervention and by convention are not counted in a CEA because they are inherently incorporated into the effectiveness component of the CEA.

Modeling the Problem

Unless a fully prospective economic evaluation is being performed, relevant cost and effectiveness data must be combined through analytic modeling to determine an ICER. Clearly, an economic evaluation can be very complex and incorporate a large number of variables; consequently, the purpose of modeling the problem is to simplify reality to a level where it is of practical use. The first task in modeling a problem is to decide on a time horizon. It is usually advisable to perform a short-term analysis where data are available and a long-term analysis where data are modeled into the future. All health outcomes and costs will be discounted to their net present value; therefore, health outcomes and costs that are incurred in the distant future will have a smaller effect on the outcome than those incurred at the beginning of the analysis.

The most common method for modeling is to employ expected value decision analysis to the problem. There is a large body of literature on medical decision analysis, and the reader is recommended to read Sox et al.[18] for a detailed description of modeling methods and points of consideration. Decision analysis has its roots in economics and game theory and is useful in aiding decision making when the consequences of actions are uncertain. In essence, decision tree models are a sequence of chance events and decisions over time where every chance event is assigned a probability.[19] Each path through the tree consists of a combination of chance and decision nodes and is associated with a final outcome, or utility. Each decision alternative is evaluated with an expected utility value, and the preferred decision choice is defined as the alternative with the largest expected utility. If a problem is simple and does not have to be modeled into the future, then a simple decision tree will often be adequate.

Modeling becomes more difficult when recurrent events over time are considered in the analysis. In this case, a transition state model is required and is commonly performed using a Markov cycle decision tree. In a Markov model, a hypothetical participant will have the option of changing health states at the end of each time period, or cycle, according to predefined transition probabilities. The hypothetical patient is then given appropriate credit in the form of a utility for each cycle the patient spends in a given Markov state. An

expected utility for each decision alternative can then be calculated mathematically.

A CEA should employ the simplest modeling technique possible that incorporates all relevant data and can adequately represent the problem.[4] There are a number of decision analysis software programs available that can be useful in formulating the decision tree and performing the CEA.

Discounting

The rationale for discounting costs in an economic analysis is derived from the idea that a dollar today is worth more than a dollar tomorrow. This time preference of money is due to a number of factors, including inflation, rate of return on investment, and degree of risk associated with the investment being considered. Discounting is a simple calculation and can be described easily through an example. If $1,000 is spent n years from now, and we assume a fixed rate of interest of 10%, then that $1,000 is worth $\$1{,}000/(1.10)^n$ today. This follows from the idea that this value ($\$1{,}000/(1.10)^n$), invested at a 10% annual return for n years, will yield $1,000 at the end of the n years. Therefore, if something of value is gained in the future, it is worth less than if it was obtained today.

It is widely understood that costs should be discounted to reflect the time value of money; however, it is the discount rate that is controversial. Many discount rates have been proposed, but the Panel on Cost-Effectiveness in Health and Medicine recommended 3% as a riskless real discount rate to be used in economic evaluations. In sensitivity analyses, this rate should be varied between 0% and 7%.

In an economic evaluation, QALYs should be discounted at the same rate as costs. The reason for discounting future life years is not that years of life lived in the future are less valuable than years of life lived earlier, or that a year of life in the present can be invested today (analogously to a dollar) to produce an increase in life at a later date. The reason is that QALYs are being valued relative to the dollar and since the dollar is being discounted, so must the QALYs. Weinstein[3] walks readers through a simple scenario demonstrating the fundamental break in logic that will occur if years of life are not discounted at the same rate as cost in an economic evaluation.

Sensitivity Analysis

When modeling a health intervention versus an alternative, there are many potential uncertainties that must be considered. The most important uncertainties are associated with point estimates used in the model. These can include health outcomes (such as length of life, QOL, and other intermediate health outcomes), costs, probabilities, or discount rates. To access the robustness of a model, one-, two-, three-, or n-way sensitivity analyses can be performed by varying one or more parameters in the model simultaneously. If the model is large and complex, there will be many sensitivity analyses possible. Sensitivity analyses should be reported on variables that will have a large impact on the study outcome when varied.

Another method for assessing the robustness of a cost-effectiveness model is to perform a Monte Carlo simulation. Most decision analysis software programs have a Monte Carlo simulation procedure whereby a hypothetical trial of the model is performed. In a primary Monte Carlo simulation, the model is performed using the reference-case point estimates, and a hypothetical cohort is put through the model using random number generators at each chance node. The outcome is an "observed" ICER that will be similar to the expected ICER. The average "observed" ICER will be very close to the expected ICER if the simulation is performed a large number of times. Through the use of this method, a measure of uncertainty in the model can be determined, and statistical tests can be employed. A primary Monte Carlo simulation does not, however, consider the inherent variability of the point estimates (such as outcome probabilities, costs, or survival) in the model. In a secondary Monte Carlo simulation, during each simulation, some of the variables will be sampled from their respective distributions and then random number generators will be used to determine an expected ICER. In a complicated analysis with good effectiveness and outcome data, it is possible for a large

number of variables to be defined statistically as distributions and sampled in this manner. Secondary Monte Carlo simulation generates a more accurate estimate of the inherent variability in the model.

Roles and Limitations

Limitations

There are a number of limitations with current economic evaluations that account for why CEA is not more readily applied in the field of health policy. An economic evaluation is not an exact science, and the methods used are not always systematic among analysts. An economic evaluation is by definition a multidisciplinary study design requiring input from the fields of economics, epidemiology, public policy, and mathematics. Methodological controversies such as the decision perspective, the method for measuring QOL, and the rate used to account for the time preference of money have led to inconsistent study designs being employed.

Varying methodologies in evaluating cost-effectiveness in health care have made it necessary to define guidelines. The broadest sets of guidelines were developed by the Panel on Cost-Effectiveness in Health and Medicine in 1996, and discuss a reference case, which is a standard set of methodological practices. However, economic evaluations are performed for a number of reasons, and consequently, different procedural guidelines have been defined for these different purposes. The multidisciplinary nature of an economic evaluation along with potentially differing methodological guidelines depending on the perspective of the study and the intended audience provides another challenge for researchers in the field.

Another limitation of CEA is the varying quality of resources available. Most economic evaluations rely heavily on previously published data because performing a fully prospective evaluation with sufficient power to detect a meaningful effect would be prohibitively expensive. Consequently, it may be difficult to follow commonly used guidelines when there is a limited amount of previously published research available on a subject.

In addition to methodological limitations, there are distributional consequences inherent in allocation decisions that are based on CEA. A basic assumption of CEA in health care is that the decision maker has the sole objective of maximizing the net health benefit of a target population with limited resources, and that all persons in the target population are valued equally by the decision maker. When decisions are based on this method, then although the net health benefit of the population will be maximized, some groups of individuals will benefit and some will lose. For example, if a Health Maintenance Organization (HMO) uses CEA results to relinquish funding of photodynamic therapy for patients with macular degeneration in favor of funding a novel treatment for diabetic retinopathy on the basis of a more favorable ICER, then those beneficiaries with diabetic retinopathy will gain at the expense of those with macular degeneration.

A CEA, by definition, values incremental QALYs equally for all persons. However, a particular decision maker may value QALYs gained by a particular group of people over QALYs gained by another group. For instance, QALYs gained by unidentified people who benefit from a prevention program or those with mental illness may be valued less than QALYs gained by a group of people suffering from a widely publicized disease such as cancer, AIDS, and heart disease. In addition, QALYs gained by children are considered more valuable by decision makers and the public than QALYs gained by adults.[1] In these situations, the net health of the population may not be maximized as determined by the CEA.

Uses

CEA has been used increasingly to evaluate health interventions over the past decade. This increase can be attributed to a number of sources including interest from pharmaceutical companies in demonstrating the value of their products and the advancement of the scientific methods used in evaluating cost-effectiveness.

Most formulary committees for hospitals, HMOs, and Medicaid programs in the United States require data on the cost-effectiveness of a pharmaceutical company before funding it

through their insurance plan. In the province of Ontario, Canada, the Ministry of Health and Long-Term Care requires any pharmaceutical company submitting a request to have their drug funded through the provincial formulary (which covers drug costs for seniors and those on social assistance) to submit a cost-effectiveness analysis that meets a certain set of criteria. However, formulary committees generally use these submissions subjectively in making final decisions. In addition, other funding agencies such as the federal and state or provincial government, nonprofit research organizations, universities, and insurers are increasingly interested in the cost-effectiveness of current medical treatments and are subsequently funding this research more heavily.

In recent years, the scientific interest in CEA has also increased, thereby allowing more scientifically rigorous studies to be performed and published. The financial support of agencies with an inherent interest in the potential results of economic evaluations—including insurers, pharmaceuticals, and government—has facilitated this academic interest. In addition, the relative abundance of effectiveness trials being published has allowed for full economic evaluations to be performed more easily. The increase in computing power in recent years has also played an important role by allowing more sophisticated computer programs to be designed and more iterations and complex analyses to be performed more quickly.

Although there has been an increasing interest in the economic evaluation of health interventions, the actual applications of scientifically rigorous studies have not been well documented. The most common application of rigorous full economic evaluations is likely to be in the decision by a formulary committee on whether to fund a new drug or medical treatment. Even in this case, the CEA is used subjectively in the decision-making process. CEA can also be used by private or government insurers, but it is difficult to know how often this is being done or how important the CEA is in the decisions being made; it is presently not good public relations to announce that a medically effective treatment is not being funded because it is not cost-effective.

As the scientific methods of CEA develop and become more systematic, and the public begins to understand the importance of basing funding decisions on the *value* of a medical treatment, there will be many more potential applications of CEA in health policy. For instance, the cost-effectiveness of a treatment or medical practice is not currently considered when agencies determine best practice guidelines for medical or public health. In future, these guidelines could consider not only the effectiveness of medical treatments but also their value when compared with comparable alternatives. In addition, as cost-effective literature becomes more systematic and easily comparable, it will be possible to create valid league tables, or lists of health interventions, along with their respective ICER. If the cost-effectiveness of the various programs in a league table has been measured rigorously using similar methods, then the cost-effectiveness of a wide variety of health interventions could potentially be compared and difficult resource allocation decisions could be aided.

In conclusion, as the costs and complexities of health care in North America continue to rise faster than available budgets, assessing the value of health-care interventions will become increasingly important. At present, CEA in health care offers a method that combines available data in a logical way and forces decision makers to consider both the costs and the benefits of different resource allocation alternatives. Resource allocation decisions in the real world will never be based solely on CEA, but as the methodologies used in economic evaluations improve, they will begin to play a more important role as an aid in making difficult funding decisions in health care.

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4 Anterior Segment: Cornea and External Diseases

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Herpes Simplex Virus Eye Disease of the Anterior Segment

Introduction and Epidemiology

Herpes simplex virus type 1 (HSV-1) constitutes the vast majority of herpetic ocular infections of the anterior segment. Diagnosis is typically made clinically, although serologic and molecular testing is available.[1,2] Humans are the only natural reservoir, and an estimated 50% to 80% of the adult population has antibodies to HSV-1.[3] After primary infection by HSV, which typically manifests with nonspecific upper respiratory symptoms, the virus may achieve latency in the trigeminal ganglion. Any structure in the anterior segment can be involved and the infection presents, sometimes simultaneously, in several major forms: blepharoconjunctivitis, infectious epithelial keratitis, neurotrophic keratopathy, stromal keratitis, endotheliitis, iridocyclitis, and trabeculitis.

There is considerable variation in the literature regarding the incidence, presentation, and recurrences of herpetic keratitis, which may be the result of differing study populations, disease definitions, length of follow-up, and/or other factors. In the United States, estimates from a relatively homogenous white population in the upper Midwest indicated the prevalence to be 149 per 100,000 population, with an incidence of 8.4 per 100,000 person-years.[4] Bilateral involvement is less common, usually associated with atopy or other systemic immunosuppression and, depending on the definition used, can range from 3% to 12%.[3,5] In one study, primary ocular HSV presented as infectious epithelial keratitis in 15% of patients and stromal keratitis in only 2% of patients.[6] Another study found that initial episodes involved the eyelids or conjunctiva in 54% of cases, the superficial cornea in 63%, the deep cornea in 6%, and the uvea in 4%.[4] In susceptible individuals, recurrence of the virus can lead to blinding keratitis or uveitis. In patients who suffered from primary ocular HSV followed up from 2 to 15 years, 32% had recurrences, with 51% of those patients having multiple recurrences,[7] but most of the recurrences did not involve the cornea. Recurrence rates for any form of ocular HSV have been estimated at 9.6% at 1 year, 22.9% to 33% at 2 years, 36% to 40% at 5 years, and 63.2% at 20 years.[4,8–10]

The Herpetic Eye Disease Studies (HEDS) I and II were a set of six trials, supported primarily by the National Eye Institute of the United States National Institutes of Health (NEI/NIH), whose goals were to answer clinical questions about the treatment and recurrence of HSV keratitis and uveitis (see Tables 4.1–4.6). The studies were well designed and monitored, with intervention by the Data and Safety Monitoring Committee in three of the trials. One systematic review (see Table 4.7) details the available therapeutic interventions for infectious epithelial keratitis.[11] Taken together, the HEDS and systematic review provide valuable insight into the clinical management of HSV keratitis (see Table 4.8).

Infectious Epithelial Keratitis. The initial phase of HSV-1 epithelial disease presents as minute corneal vesicles that stain negatively with fluorescein dye.[1] This may progress to a dendritic keratitis (see Fig. 4.1), a geographic

TABLE 4.1 The Herpetic Eye Disease Studies (HEDS) I—The Herpetic Eye Disease Studies-Stromal Keratitis, Not on Steroid Trial (HEDS-SKN)

Study question	Efficacy of topical corticosteroids in treating herpes simplex stromal keratitis in conjunction with topical trifluridine
Study design	Prospective, multicenter, randomized, double-masked, placebo-controlled trial. Nine clinical centers and a data coordinating center
Inclusion/exclusion criteria	**1.** Active HSV stromal keratitis, diagnosed clinically, with no topical steroids in the preceding 10 d **2.** Age over 12 y **3.** No active HSV epithelial keratitis **4.** No prior keratoplasty of the involved eye **5.** Not pregnant
Interventions	**1.** All patients received topical trifluridine as prophylaxis **2.** Randomized to treatment with topical prednisolone phosphate 1% drops or topical placebo drops. Schedule started with eight drops/d for 1 wk and tapered over 10 wk so that patients received one drop/d of 0.125% prednisolone for last 3 wk. Placebo drops were given using the same schedule
Primary outcome measure	Time to the development of treatment failure in corticosteroid and placebo groups during the 26-wk period of examination
Major findings	**1.** Faster resolution of stromal keratitis and fewer treatment failures with prednisolone phosphate therapy **2.** Delay in initiation of corticosteroids did not affect eventual visual outcome at 26 wk **3.** The trial was terminated before the completion of the planned enrollment due to a statistically significant difference in the primary outcome between treatment groups, no convincing evidence of increased recurrence in either group, and little chance that additional data would alter the study conclusions
Unanswered questions	It is unclear whether a longer treatment schedule, in conjunction with oral antiviral coverage, would have shown a benefit over placebo

HSV, herpes simplex virus.

TABLE 4.2 The Herpetic Eye Disease Studies (HEDS) I—The Herpetic Eye Disease Studies-Stromal Keratitis, on Steroid Treatment (HEDS-SKS)

Study question	Evaluation of the efficacy of oral ACV in treating herpes simplex stromal keratitis in patients receiving concomitant topical corticosteroids and trifluridine
Study design	Prospective, multicenter, randomized, double-masked, placebo-controlled trial. Eight clinical centers and a data coordinating center
Inclusion/exclusion criteria	**1.** Active HSV stromal keratitis, diagnosed clinically, already being treated with topical steroids **2.** Age over 12 y **3.** No active HSV epithelial keratitis **4.** No prior keratoplasty of the involved eye **5.** Not pregnant
Interventions	**1.** All patients received topical trifluridine as prophylaxis **2.** Randomized to either 400 mg five times/d ACV (200 mg capsules) for 10 wk or identical frequency of placebo capsules

(continued)

TABLE 4.2 Continued

	3. Prednisolone phosphate 1% drops or topical placebo drops. Schedule started with eight drops/d for 1 wk and tapered over 10 wk so that patients received one drop/d of 0.125% prednisolone for the last 3 wk
Primary outcome measure	Time to the development of treatment failure in ACV and placebo groups during the 26-wk period of examination
Secondary outcome measures	**1.** Proportion of patients who were treatment failures at 16 wk **2.** Proportion of patients whose stromal keratitis had resolved at 16 wk **3.** Best-corrected visual acuity at 26 wk and change from randomization
Major findings	Over 16 wk, no difference between treatment groups suggesting no apparent benefit to adding oral ACV to corticosteroid + trifluridine
Unanswered questions	In the absence of topical antiviral therapy, one would expect oral ACV to have benefit

ACV, acyclovir; HSV, herpes simplex virus.

TABLE 4.3 The Herpetic Eye Disease Studies (HEDS) I—The Herpetic Eye Disease Studies-Iridocyclitis, Receiving Topical Steroids (HEDS-IRT)

Study question	Evaluate the efficacy of oral ACV in treating herpes simplex iridocyclitis in conjunction with topical corticosteroids and trifluridine
Study design	Prospective, multicenter, randomized, double-masked, placebo-controlled trial. Eight clinical centers and a data coordinating center
Inclusion/exclusion criteria	**1.** Active iridocyclitis, with HSV diagnosed clinically or with the presence of serum antibodies **2.** Age over 12 y **3.** No active HSV epithelial keratitis **4.** No prior keratoplasty of the involved eye **5.** Not pregnant
Intervention	**1.** All patients received topical trifluridine as prophylaxis **2.** Randomized to either ACV 400 mg five times/d (200 mg capsules) for 10 wk or an identical frequency of placebo **3.** Prednisolone phosphate 1% drops or topical placebo drops. Schedule started with eight drops/d for 1 wk and tapered over 10 wk so that patients received one drop/d of 0.125% prednisolone for the last 3 wk
Primary outcome measure	Time to the development of treatment failure in ACV and placebo groups during the 26-wk period of examination
Major findings	**1.** Treatment failures occurred at a higher rate in the placebo group compared with the ACV group, but trial too small to be statistically significant **2.** Trial stopped due to slow recruitment (only 50 of planned 104 patients enrolled over 4 y)
Unanswered questions	Unclear benefit of adding ACV to corticosteroid + trifluridine

ACV, acyclovir; HSV, herpes simplex virus.

TABLE 4.4 The Herpetic Eye Disease Studies (HEDS) II—The Herpetic Eye Disease Studies-Epithelial Keratitis Trial (HEDS-EKT)

Study question	Determine whether early treatment of HSV epithelial keratitis ulceration with oral ACV prevents blinding complications of stromal keratitis and iridocyclitis
Study design	Prospective, multicenter, randomized, double-masked, placebo-controlled trial. One national coordinating center, 8 regional coordinating centers, 60 clinical sites (university- and community-based practices)
Inclusion/exclusion criteria	**1.** Dendritic or geographic epithelial ulceration clinically consistent with HSV with less than 1 wk onset **2.** Age over 12 y **3.** No active HSV stromal keratitis or iritis **4.** No prior keratoplasty or refractive surgery of the involved eye **5.** Not pregnant or nursing **6.** No history of immune dysfunction or immunosuppression
Intervention	**1.** Patients received topical trifluridine 1% drops eight times/d until epithelial ulcerations resolved, then decreased to four times/d for 3 d and stopped (Three patients were treated with vidarabine 3% ointment due to trifluridine allergy) **2.** Randomized to either ACV 400 mg five times/d (200 mg capsules) for 3 wk or identical frequency of placebo
Primary outcome measure	Time to the development of first occurrence of HSV stromal keratitis or iridocyclitis in the study eye
Major findings	**1.** Recruitment stopped at 287 of planned 502 patients because of lack of any suggestion of efficacy of treatment protocol **2.** No benefit from the addition of oral ACV to treatment with trifluridine in preventing stromal keratitis or iritis **3.** Risk of stromal keratitis or iridocyclitis was low in the year following an episode of epithelial keratitis treated with trifluridine alone (7% if first episode, 26% if multiple episodes) **4.** At 3 wk of treatment, 99% of epithelial keratitis had resolved
Unanswered questions	Can oral ACV be used instead of trifluridine? Would a longer duration of therapy with ACV have shown a benefit? Should these patients receive long-term oral ACV?

ACV, acyclovir; HSV, herpes simplex virus.

TABLE 4.5 The Herpetic Eye Disease Studies (HEDS) II—The Herpetic Eye Disease Studies-Acyclovir Prevention Trial (HEDS-APT)

Study question	Determine efficacy of oral ACV in preventing recurrent HSV eye infection in patients with previous episodes of herpetic eye disease
Study design	Prospective, multicenter, randomized, double-masked, placebo-controlled trial. One national coordinating center, 8 regional coordinating centers, 60 clinical sites (university- and community-based practices)
Inclusion/exclusion criteria	**1.** Any kind of ocular HSV infection (blepharitis, conjunctivitis, keratitis, or iridocyclitis) in preceding year. Inactive infection and untreated for at least 30 d **2.** Age over 12 y **3.** No prior keratoplasty of the involved eye **4.** Not pregnant

(continued)

TABLE 4.5 Continued

Intervention	**1.** Randomized to either ACV 400 mg two times/d (200 mg capsules) for 1 y or identical frequency of placebo
Primary outcome measure	Time to first recurrence of any type of HSV eye disease in either eye
Major findings	**1.** Oral ACV reduced by 41% the probability that any form of herpes of the eye would return in patients who had the infection in the previous year **2.** Oral ACV reduced stromal recurrence by 50% among patients who had stromal keratitis in the past year **3.** Oral ACV reduced the incidence of epithelial keratitis from 11% to 9% and the incidence of stromal keratitis from 13% to 8% **4.** Four percent of patients in the ACV group and 9% in placebo group had more than one recurrence
Unanswered questions	When does one discontinue ACV?

ACV, acyclovir; HSV, herpes simplex virus.

TABLE 4.6 The Herpetic Eye Disease Studies (HEDS) II—The Herpetic Eye Disease Studies-recurrence factor study (HEDS-RFS)

Study question	Determine the role of external factors (ultraviolet light or trauma) and behavioral factors (e.g., stress) on ocular recurrences of HSV eye infections and disease
Study design	Prospective, multicenter trial. Fifty-eight clinical centers and a data coordinating center
Inclusion/exclusion criteria	**1.** History of HSV ocular infection within the preceding year **2.** Age over 18 y and immunocompetent
Intervention	Questionnaire completed every Sunday for 52 wk to track acute and chronic stressors
Primary outcome measure	Development of recurrent HSV ocular disease
Major findings	**1.** Higher levels of psychological stress were not associated with an increased risk of recurrence **2.** No association was found between any of the other exposure variables and recurrence **3.** When an analysis was performed including only the recurrences for which the exposure week log was completed late and after symptom onset, there was a clear indication of retrospective overreporting of high stress and systemic infection
Unanswered questions	What are the risk factors for HSV recurrence?

HSV, herpes simplex virus.

keratitis (see Fig. 4.2), or a marginal keratitis with limbitis (see Fig. 4.3). Although these conditions may resolve spontaneously without therapy, antiviral therapy is generally indicated to accelerate resolution. Rates of healing appear equivalent between acyclovir (ACV), trifluridine, and vidarabine.[11] Debridement alone does not appear effective, but in conjunction with antiviral therapy may speed epithelial healing rates.[11] The addition of a 3-week course of oral ACV to trifluridine was found by the HEDS epithelial

TABLE 4.7 Herpes Simplex Virus

Therapeutics
Topical antivirals
1. Increase healing rates of epithelial keratitis
2. No significant differences between vidarabine, trifluridine, ganciclovir, or ACV
Topical interferons
1. Increase healing rates of epithelial keratitis
Topical corticosteroids
1. Reduce stromal inflammation and lessen the duration of stromal keratitis
2. May induce epithelial keratitis if not given concomitantly with an antiviral
Oral ACV
1. Effective in treating epithelial and stromal keratitis
2. Long-term oral ACV (400 mg twice daily) is effective in preventing recurrence of HSV keratitis
3. May offer additional benefit to patients with HSV iridocyclitis
4. Does not offer any additional ocular benefit to immunocompetent patients already on trifluridine for the treatment of epithelial or stromal keratitis
Treatment recommendations for disease subsets
Dendritic or geographic epithelial keratitis
1. Treatment with a topical or an oral antiviral is sufficient
2. For initial episodes, long-term ACV usage is unnecessary for most patients
3. For patients with a history of multiple recurrences, long-term oral ACV prophylaxis may be more valuable
Stromal keratitis
1. Resolution of symptoms is more rapid with corticosteroids
2. Recurrence is reduced with long-term oral ACV prophylaxis
3. If topical steroids are used, many patients require greater than 10 wk of therapy
Iridocyclitis
1. It is unclear whether short-term high-dose oral ACV is beneficial, but there are few negative side effects and there is a suggestion of benefit to this regimen
Corneal Transplantation
1. Oral ACV prophylaxis appears to reduce HSV recurrence and improve graft survival

ACV, acyclovir; HSV, herpes simplex virus.

keratitis trial (EKT) (Table 4.4) to provide no additional benefit in epithelial healing rates or prevention of stromal keratitis or iridocyclitis.[12]

Topical ganciclovir ophthalmic ointment has been demonstrated to have noninferiority compared with topical trifluridine,[13–15] with some studies suggesting a trend to better tolerance and faster epithelial healing when compared with topical trifluridine.[14,16]

In spite of the injury invoked by episodes of disease activity, most patients affected will have a final visual outcome that remains acceptable.[4]

Stromal Keratitis and Endotheliitis Manifestations of HSV-1 stromal disease include immune stromal keratitis (see Fig. 4.4) and necrotizing keratitis. While the latter is potentially devastating in the acute period, immune stromal keratitis leads to corneal

TABLE 4.8 Interventions for Herpes Simplex Virus Epithelial Keratitis

Study question	Compare the effects of various treatments for dendritic or geographic herpes simplex virus epithelial keratitis.
Study design	Systematic review
Inclusion/exclusion criteria	**1.** Comparative clinical trials that assessed 1 and/or 2-wk healing rates of topical ophthalmic or oral antiviral agents and/or physical or chemical debridement in people with active epithelial keratitis **2.** Age over 18 y and immunocompetent
Intervention	Sources searched for relevant studies were the Cochrane Central Register of Controlled Trials—CENTRAL, MEDLINE (1966 to August 2002), EMBASE (1980 to August 2002), LILACS (up to 2002), Index Medicus (1960–1965), Excerpta Medica Ophthalmology (1960–1973), reference lists of primary reports and review articles, and conference proceedings pertaining to ocular virology
Primary outcome measure	Interventions were compared by the proportions of participants healed at 7 d and at 14 d after trial enrollment
Major findings	**1.** Compared with idoxuridine, the topical application of vidarabine, trifluridine, or acyclovir generally resulted in a significantly greater proportion of participants healing within 1 wk of treatment **2.** Insufficient placebo-controlled studies were available to assess debridement and other physical or physicochemical methods of treatment **3.** Interferon was very useful combined with debridement or with another antiviral agent such as trifluridine
Unanswered questions	Is debridement useful in treating herpes simplex virus epithelial keratitis?

blindness through a chronic relapsing and remitting course (see Fig. 4.5). Endotheliitis can accompany stromal keratitis and manifests with microcystic corneal edema and keratic precipitates (Fig. 4.4). The value of corticosteroid treatment of stromal keratitis was assessed in the HEDS stromal keratitis, not on the steroid (SKN) trial (Table 4.1).[17] The main conclusion was that a 10-week course of topical corticosteroid treatment contributes

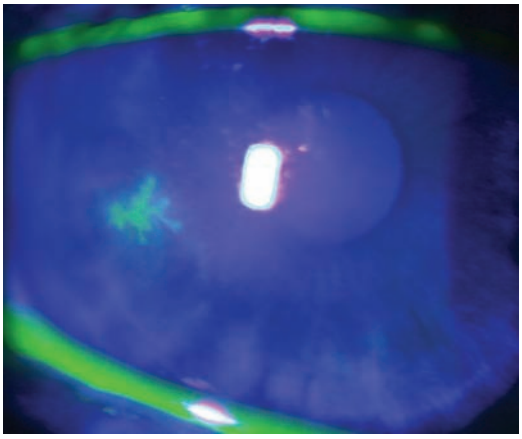


FIGURE 4.1 Dendritic herpes simplex virus keratitis.

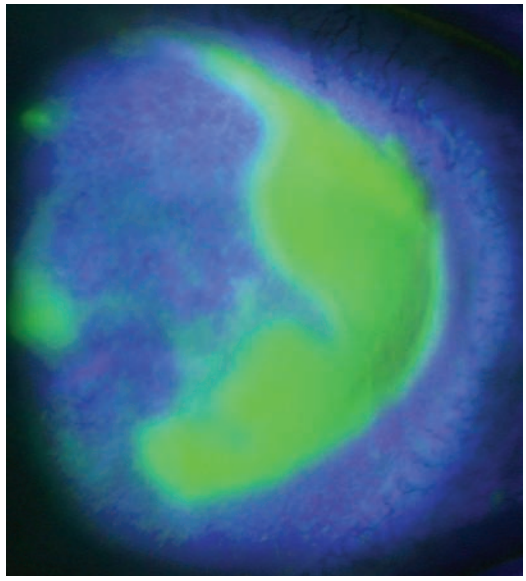


FIGURE 4.2 Geographic herpes simplex virus keratitis.

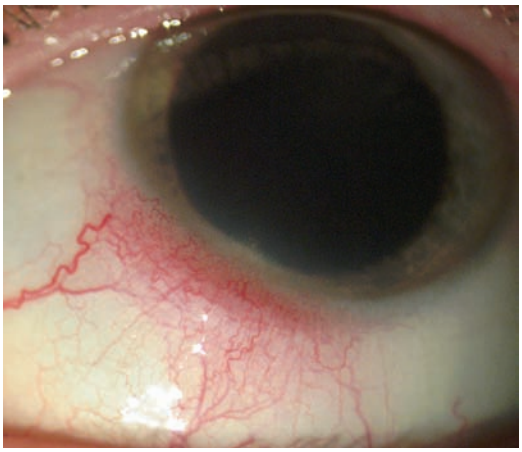


FIGURE 4.3 Herpes simplex virus limbitis and marginal keratitis.

to a faster visual recovery, although a delay in therapy does not affect final visual outcome at 6 months. The major question that remains unanswered by this study was whether a 10-week course was sufficient. Half of the patients in the corticosteroid group of the study who "failed treatment" did so in the 6 weeks after discontinuation of the topical steroid. Currently, in clinical practice, topical steroids may be continued for many months, and perhaps indefinitely at low dosages and frequencies, often in conjunction with chronic oral ACV therapy. Although the final visual outcome was not affected by delay in treatment, it should be noted that 76% of the placebo group failed treatment, and 72% of the placebo group that showed visual improvement was eventually treated with topical corticosteroids. In fact, by 16 weeks after randomization, the total duration of topical corticosteroid usage was similar in both the placebo and corticosteroid groups. It is important to note, however, that 22% of patients had resolution of stromal keratitis with only topical antiviral treatment.

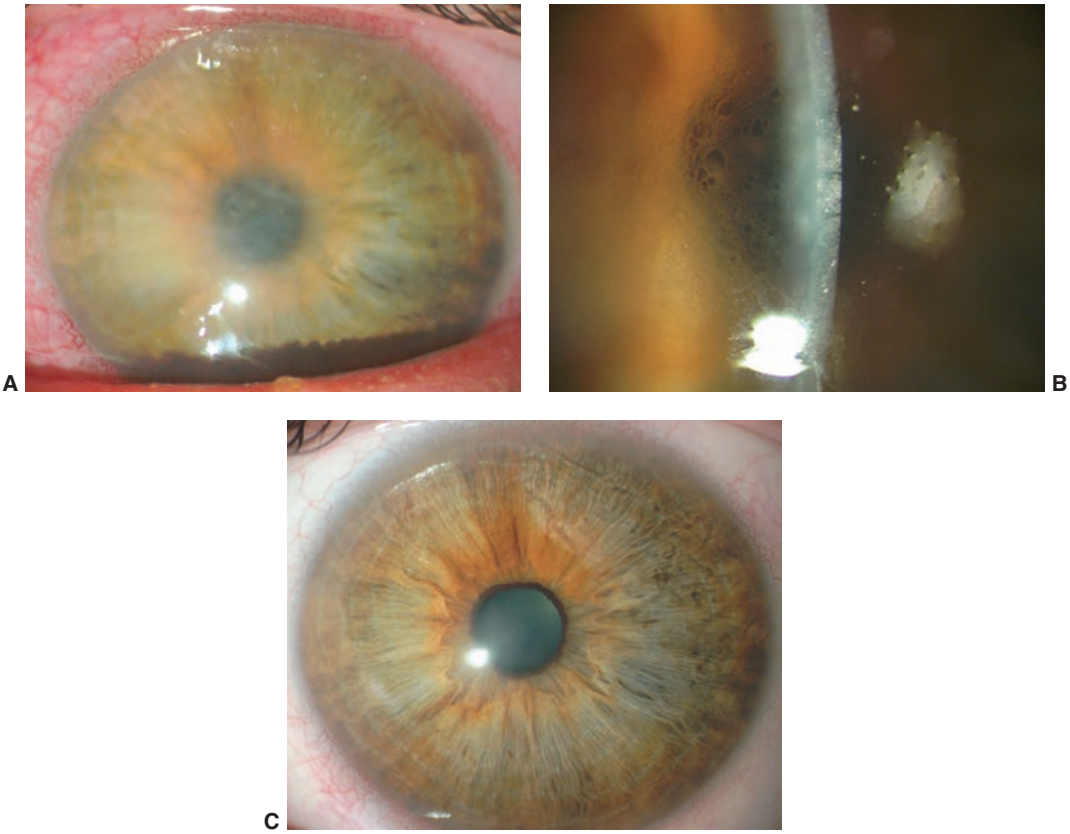


FIGURE 4.4 Pretreatment stromal keratitis and endotheliitis **(A)** with microcystic corneal edema **(B)**. Posttreatment with topical steroids and oral acyclovir **(C)**.

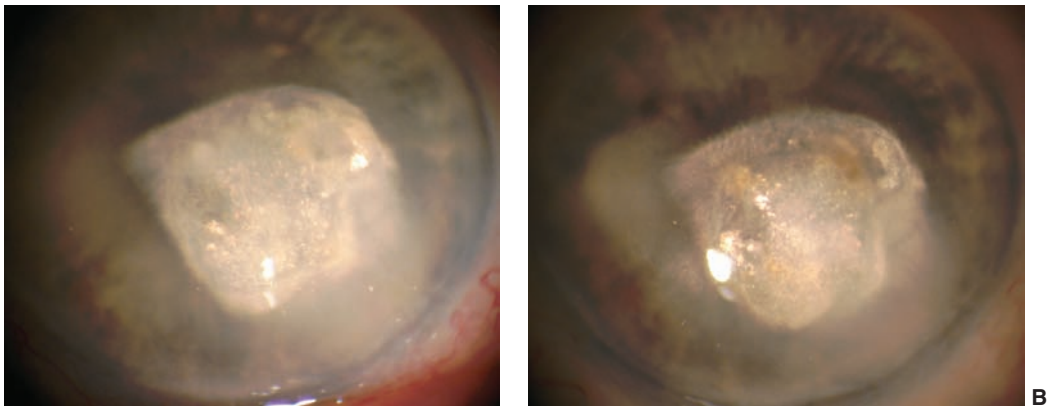


FIGURE 4.5: Chronic stromal keratitis leading to lipid keratopathy **(A)**. The lipid will be slowly reabsorbed with prolonged disease inactivity **(B)**.

Iridocyclitis and Trabeculitis. HSV iridocyclitis and trabeculitis are uncommon conditions. The HEDS iridocyclitis, receiving topical steroid (IRT) trial (Table 4.3) was stopped because of low recruitment, with only 50 of the planned 104 patients recruited over 4 years.[18] These conditions can occur concomitantly with other forms of HSV infections, as noted in the HEDS-SKN trial in which 34% and 16% of the eyes with stromal keratitis had concomitant iridocyclitis and trabeculitis, respectively. The iridocyclitis can be either granulomatous or nongranulomatous. Intraocular pressure (IOP) increase from trabeculitis, when stromal keratitis or iridocyclitis is present, may easily be misinterpreted as being a steroid-induced glaucoma. In fact, HSV should be included in the differential diagnosis of any iridocyclitis associated with increase in IOP. Owing to its small sample size, the HEDS-IRT trial (Table 4.3) suffered from low recruitment, between the ACV and placebo groups in the rates of treatment failure in patients treated with corticosteroids and trifluridine. There was a trend, however, toward a reduction of treatment failures in patients treated with oral ACV.

Prevention of Recurrence

It had been previously demonstrated in a small, prospective randomized series that oral ACV reduced recurrences of HSV keratitis and improved graft survival after penetrating keratoplasty (PKP).[19] The reduction in recurrence rate was confirmed by the HEDS ACV prevention trial (APT) (Table 4.5) and yielded, perhaps, the most important results from the HEDS. It demonstrated that not only was oral ACV 400 mg, taken twice daily, able to reduce the recurrence rate of any form of ocular HSV compared with placebo, it also reduced nonocular recurrences.[20] Given that recurrent stromal keratitis leads to progressive corneal scarring and potential corneal blindness, it was clinically significant that oral ACV reduced stromal recurrence by 50% among patients who had stromal keratitis in the previous year.

Lingering questions remain, such as whether a lower dosage would have been equally efficacious or whether a higher dosage would be more successful in preventing recurrences.[21] Likewise, the end point for treatment with oral ACV remains unclear, as recrudescence occurs upon discontinuation of the medication.[22] As the HEDS-EKT demonstrated a low risk of developing stromal keratitis or iridocyclitis after a primary episode of epithelial keratitis, it does not seem necessary to begin therapy, perhaps lifelong, with oral ACV in these patients. Additionally, ACV prophylaxis may be relatively cost-ineffective and a theoretic model for treatment, targeting patients with stromal keratitis, found no increase in cost-effectiveness compared with targeting any patient with a history of HSV ocular disease.[23] Long-term treatment may therefore be best reserved for patients with recurrent disease or

cases in which visual acuity is already threatened or compromised.

Although long-term oral ACV therapy was found helpful in the HEDS-APT, other HEDS trials could not definitely elicit a benefit of high-dose short-term therapy with oral ACV in patients already taking trifluridine 1% drops concomitantly. In the HEDS stromal keratitis, on steroid treatment (SKS) trial (Table 4.2), no apparent benefit of a 10-week course of oral ACV (400 mg five times daily) was found over placebo.[24] Likewise, the HEDS-IRT and HEDS-EKT (Tables 4.3 and 4.4, respectively) trials did not find significant advantages in using short-term courses of oral ACV in conjunction with trifluridine. It should also be noted that in the HEDS, some patients had recurrences in spite of treatment with oral ACV and/or topical trifluridine.

Risk Factors

On the basis of the study of 260 patients enrolled in the HEDS-SKN, HEDS-SKS, and HEDS-IRT trials, it was suggested that during treatment for stromal keratouveitis, there was a greater risk of recurrent epithelial keratitis in nonwhite patients and patients with a previous history of HSV epithelial keratitis.[25] Identifying potential triggering factors for HSV ocular disease was attempted by the HEDS recurrence factor study (RFS). The goal was to ascertain whether any specific external or behavioral factors such as psychological stress, exposure to sunlight, menstrual cycle, contact lens wear, or eye injury could be determined as definitive risk factors. From self-reported questionnaires, high stress did not appear to be associated with recurrence.[26] Likewise, none of the other factors studied were noted to be associated with recurrence; however, this trial had limited power to detect true differences between these factors. In addition, measures such as "sunlight exposure" proved difficult to quantitate. Interestingly, a recall bias was observed in patients who had onset of symptoms, but did not complete their exposure log in a timely manner, with overreporting of high stress and systematic infection.

Alternative Therapies and Future Directions

Development of better diagnostic and therapeutic options for HSV, and other *herpesviruses*, remains essential, given the morbidity of these viruses and the chronic nature of these infections. It is unknown as to how many cases of ocular HSV are undiagnosed or misdiagnosed. Likewise, although oral ACV is assumed to be an effective treatment for most patients, ACV-resistant HSV strains have been found in 7% of immunocompromised individuals.[27] As such, various medical and alternative therapies are under investigation. There is mixed evidence on the usage of oral or topical forms of lysine in the management of herpes labialis.[28,29] A proposed mechanism of action is that high intracellular concentrations of lysine competitively inhibit arginine, which is necessary for HSV reproduction.[30] Currently, there are no available topical ophthalmic preparations of lysine. If there is a beneficial effect from oral lysine supplementation, it will likely need to be administered as a chronic treatment at high dosages (1,000–3,000 mg/day) to help prevent recurrences. There have been some studies that have demonstrated efficacy of topical light-activated rose bengal in the reduction of extracellular herpes viral quantization, but more limited effects on intracellular viral load.[31,32] Considering the relatively innocuous nature of rose bengal, this may be a useful adjunct to current therapies, especially for HSV keratitis unresponsive to standard treatment. Other drugs that inhibit the ability of HSV to enter noninfected cells may offer hope for prevention of disease acquisition.[33]

Virus-specific Th1 cytokines and active innate immunity can prevent HSV recurrence.[34] This knowledge has been incorporated into vaccine strategies and one vaccine reduced the clinical symptoms of primary HSV-2 infection by over 70%, but only in women who were both HSV-1 and HSV-2 seronegative.[34–36] Although there are still no clinical vaccines available for HSV and significant challenges remain, these results suggest the eventual development of more effective options. Through a better understanding of the biology of HSV, either new medications or

vaccines should be able to interfere with the acquisition of the primary infection or recurrence of the infection or possibly eradicate the virus altogether.

Corneal Transplantation

Indications and Epidemiology of Penetrating Keratoplasty

The annual rate of corneal transplantation in the United States had slowly declined from 1991 until 2005 and has since dramatically rebounded.[37] In 2011, with 79 member U.S. eye banks reporting, there were 46,196 corneal transplants performed in the United States with increasing numbers of tissue being exported and harvested internationally. However, this increase appears to be mostly in endothelial keratoplasty procedures as the number of PKPs has been steadily declining and amounted to 21,620 in 2011. It is expected that the total number of endothelial keratoplasty procedures will surpass PKP in 2012 or 2013.

Studies on the indications for PKP vary depending on the time frame assessed, classifications used, region of origin, and specific practice-style sampled.[38] For example, in the United States, keratoconus (KC) is now the leading indication for PKP as endothelial causes of corneal dysfunction are now treated with endothelial keratoplasty instead.[37] Worldwide, the trends also appear to be shifting,[39] with greater adoption of deep anterior lamellar keratoplasty than in the United States.[40–42]

KC continues to be an important indication for corneal transplantation worldwide (see Fig. 4.6). The prevalence and incidence, as well as disease severity, appear to vary with ethnicity. In the United Kingdom, patients aged 10 to 44 with an Asian origin had a prevalence of 229 per 100,000 as compared with 57 per 100,000 in white patients.[43] In the same age group, Asians had an annual incidence of 19.6 per 100,000 versus 4.5 per 100,000 in white patients. Age at diagnosis and age at corneal transplantation were also lower in Asians. In the United States, the prevalence of KC in a mainly white population was 54.5 per 100,000, with an annual incidence of 2.0 per 100,000.[44] The disease process tends to be bilateral and asymmetric, with roughly 50% of clinically normal fellow eyes progressing to KC over a 16-year time span.[45] Occasionally, breaks occur in the Descemet's membrane, leading to corneal hydrops (see Fig. 4.7), which then resolves with associated corneal scarring. Although mechanical factors may play a role in its development, KC is felt to have a genetic origin based in part on studies examining the videokeratography of family members with KC.[46–49]

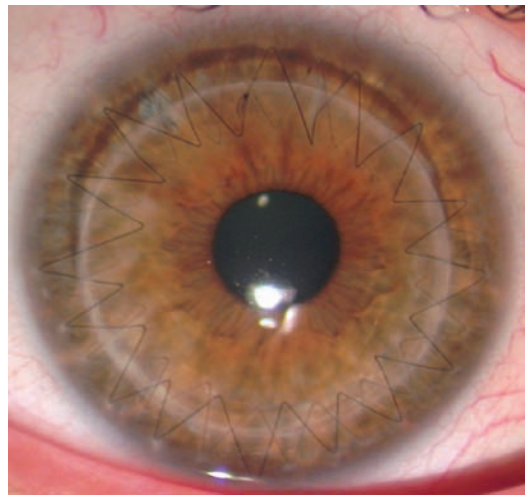


FIGURE 4.6 Penetrating keratoplasty for keratoconus with a double-running suture technique. Larger donor grafts are commonly used and arcus senilis, as in this photograph, may be evident.

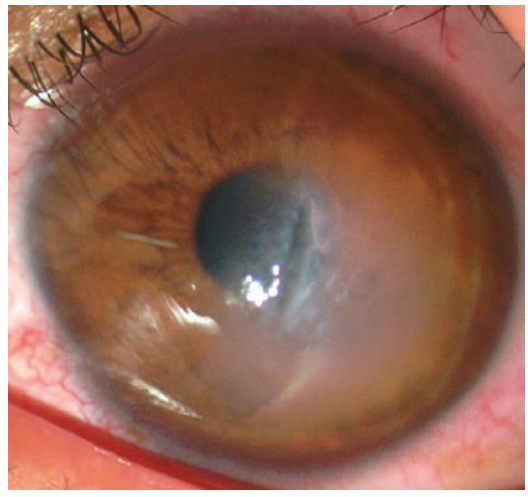


FIGURE 4.7 Keratoconus with hydrops.

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study (see Table 4.9) is a prospective observational study intended to describe the clinical course of KC and identify predisposing or protective factors influencing the severity and progression of the disease. It is primarily funded by the NEI/NIH and conducted mainly through academic optometric sites. In published results, KC has been found to be bilateral and asymmetric with a greater asymmetry and corneal steepening in patients with a history of eye rubbing

TABLE 4.9 Collaborative Longitudinal Evaluation of Keratoconus (CLEK)

Study question	**1.** Describe the clinical course of KC **2.** Describe relationships among its visual and physiological manifestations, including high- and low-contrast visual acuity, corneal curvature, slit lamp findings, cornea scarring, and quality of life **3.** Identify risk factors and protective factors that influence the severity and progression of KC
Study design	Prospective, multicenter (15 clinical optometry centers), observational study of 1,209 KC patients
Inclusion/exclusion criteria	**1.** 12 y or older **2.** Irregular cornea as determined by keratometry, retinoscopy, or direct ophthalmoscopy in at least one eye **3.** Vogt's striae, Fleischer's ring, or corneal scarring characteristic of KC in at least one eye **4.** Available for 3 y of follow-up **5.** Ineligible if they had bilateral corneal transplants or bilateral nonkeratoconic eye disease (cataract, intraocular lens, macular disease, or optic nerve disease other than glaucoma)
Intervention	Annual examinations for 3 y
Outcome measures	Visual acuity, patient-reported quality of life, manifest refraction, keratometry, photodocumentation of central corneal scarring, photodocumentation of the flattest contact lens that just clears the cornea, slit lamp biomicroscopy, corneal topography, photodocumentation of rigid gas-permeable lens fluorescein staining pattern if patient is wearing them
Major findings	**1.** Over an 8-y period of follow-up, 11.8% of study participants, without previous PKP, had a PKP in one or both eyes. Risk factors for progression to PKP were younger age at baseline, corneal scarring, best-corrected Snellen acuity worse than 20/40, and corneas steeper than 52 D **2.** KC patients with more severe disease are also more asymmetric in disease status **3.** Corneal scarring in KC is significantly associated with decrease in high- and low-contrast visual acuity **4.** Corneal scarring is associated with corneal staining, contact lens wear, Fleischer's ring, a steeper cornea, and increasing age **5.** KC is not associated with increased risk of connective tissue disease
Unanswered questions	**1.** These patients were recruited from optometric centers and may not be applicable to patients seen in ophthalmology practices as most patients in the study had mild to moderate KC **2.** KC in the United States may not have a similar course as elsewhere in the world and disease severity may differ by race

HSV, herpes simplex virus; KC, keratoconus; PKP, penetrating keratoplasty.

or ocular trauma.[50] Not unexpectedly, this trial has found that corneal scarring in KC is also significantly associated with decreased high- and low-contrast visual acuity.[51] Perceived visual function in the CLEK study, as measured by the NEI Visual Function Questionnaire, has been found to be disproportionately lower than measured visual acuity.[52] This is similar to a previous article suggesting that the best predictors of patient satisfaction after PKP were subjective outcomes rather than objective measures such as visual acuity.[53] Importantly, the CLEK study has confirmed that younger age, corneal scarring, steeper corneas, decreased best-corrected Snellen acuity, reduced visual function, and decreased contact lens comfort had a greater risk of progression to PKP over 8 years of follow-up.[54] While the CLEK study has contributed to the understanding of KC, it is unclear whether it is possible to generalize the patient population being studied to ophthalmology practices or different ethnic populations. Likewise, the role of PKP continues to evolve with the advent of corneal collagen cross-linking and deep anterior lamellar keratoplasty.

Graft Survival after Penetrating Keratoplasty

Graft failures after PKP may be due to immunologic rejection, recurrence of the original disease process (see Fig. 4.8), nonimmunologic late endothelial failure, surface problems, infection, glaucoma, or other factors. Primary graft failure, defined as a diffusely edematous corneal graft that fails to clear in the early postoperative period, is uncommon, and as many as 33% of cases may be due to HSV.[55] The leading cause of graft failure within the first 1 to 3 years after transplantation is immunologic rejection,[56] whereas late failures are more attributable to nonimmunologic endothelial failure.[57,58] The risk factors for graft failure can be primarily divided into host factors, including ancillary intraoperative procedures, and donor factors. Postoperative immunosuppression and surgical complications are also important factors in maintaining a clear corneal graft.

With current eye banking standards, the greatest predictive role in determining PKP graft survival are host factors, with presenting diagnosis, in particular, as the most significant factor. PKP for KC has the best graft survival results, with >90% survival from 5 to 12 years after transplantation.[56,58–65] Five-year or longer graft survival for an initial diagnosis of Fuchs corneal endothelial dystrophy (see Fig. 4.9) ranges from 81% to 98%,[56,58,64–66] interstitial keratitis ranges from 95% to 100%,[64,65] herpes simplex keratitis ranges from 65.3% to 89.5%,[56,60,65,67] and pseudophakic bullous keratopathy (PBK) ranges from 50% to 76%.[56,60,65,68] As recurrence of corneal stromal dystrophies is known to occur after PKP,[69] phototherapeutic keratectomy is

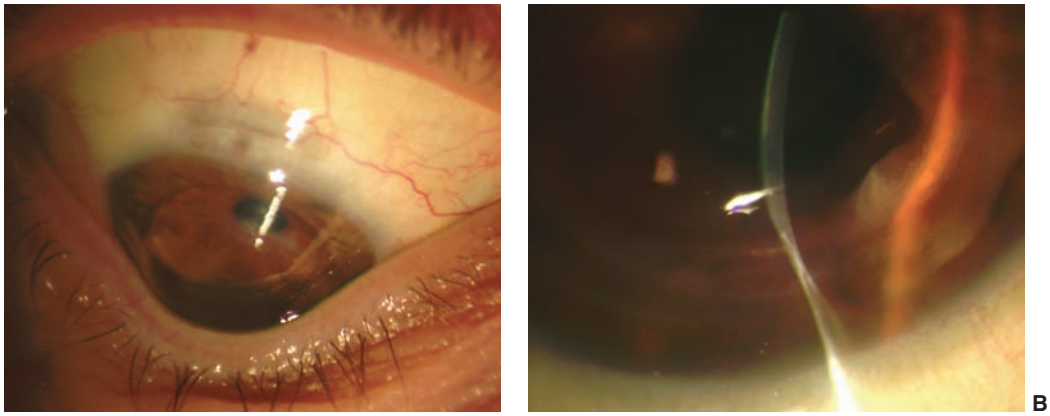


FIGURE 4.8 Recurrence of keratoconus after penetrating keratoplasty, performed 30 years earlier. A Munson's sign is present **(A)** with thinning and ectasia of the donor, graft–host junction, and host cornea **(B)**.

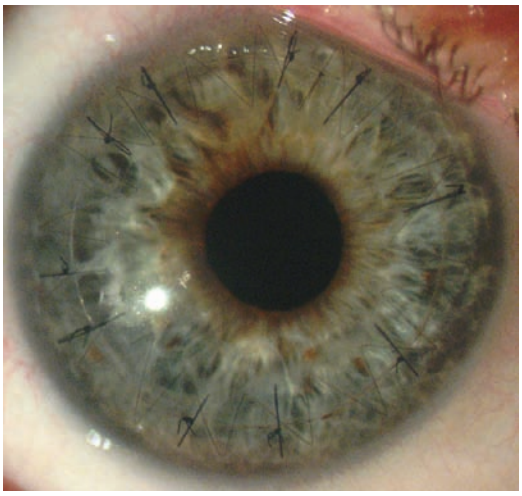


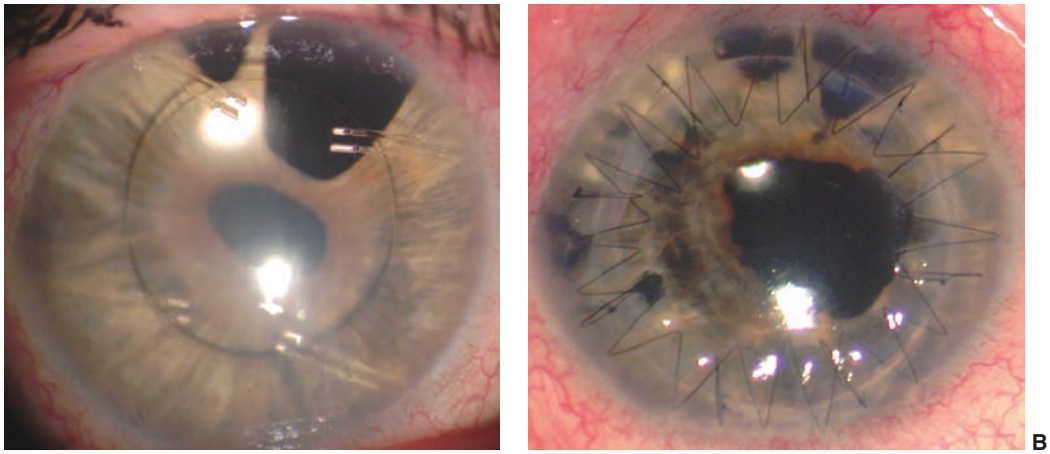
FIGURE 4.9 Penetrating keratoplasty for Fuchs corneal endothelial dystrophy with a combination of interrupted and running sutures. At 1 year, with selective suture removal uncorrected visual acuity measured 20/20 in this eye.

emerging as an alternative treatment option given its efficacy and shorter recovery period, although recurrences occur after that procedure as well.

The recipient age may also play an important role. Young children have lower graft survival rates, roughly 66% to 80% at 1 year,[70,71] varying again with the indication for transplantation.[72–75] In younger patients, a more vigorous healing or immune response, in addition to greater difficulty with compliance to the prescribed postoperative regimen, may contribute to worse outcome. Even with a clear transplant, visual outcome may be limited by amblyopia in young children.[70] Outside of the pediatric population, there is no apparent relationship between graft clarity and recipient age.[76]

Graft survival rates of PKP also vary depending on whether the graft is combined with secondary procedures. Exchange of an anterior chamber intraocular lens (IOL) during PKP for PBK has been reported to increase graft survival (see Fig. 4.10), as well as the placement of an IOL in cases of aphakic bullous keratopathy.[58] Studies of implantation of secondary anterior chamber IOLs during PKP have reported survivals of 87% to 95% at 2 to 3 years[77,78] and 65% at 8 years.[77] Grafts with secondary scleral-sutured IOLs have an 87% survival at 3 years[79] and iris-sutured IOLs have survival rates of 89% to 91.2% at 2 years and 81% at 5 years.[80,81] There does not appear to be a clear superiority of one lens type over another during PKP.[82,83]

Although graft survival decreases when PKP is combined with glaucoma surgery, the combined procedures may offer better long-term graft survival and IOP control than staged procedures.[84,85] Corneal transplants with glaucoma drainage devices have reported survivals of 50% at 3 years with adequate IOP



A B

FIGURE 4.10 Pseudophakic bullous keratopathy with a closed loop anterior chamber intraocular lens (IOL) **(A)**. One-week postoperative appearance after penetrating keratoplasty, IOL exchange with an iris-sutured posterior chamber lens implant, anterior vitrectomy, and pupilloplasty **(B)**.

control in 86%,[86] as compared with trabeculectomy with mitomycin-C with 60% graft survival at 2 years and adequate IOP control in 50% of the cases.[87] Placement of the drainage device into the vitreous cavity, rather than the anterior chamber, may improve graft survival[88] but may also be associated with greater posterior segment complications.[89]

When PKP is combined with a temporary keratoprosthesis and vitreoretinal surgery, graft survival is relatively poor[90,91] but may be more successful if the etiology is ocular trauma (see Fig. 4.11) and surgical intervention is performed relatively proximal to the injury.[92,93] Labeling of these cases as "successes" is more difficult as it requires a clear graft, control of IOP, and a good anatomic retinal result. Even in successful cases, visual acuity may be severely limited and most articles gauge the percentage of eyes with improvement in vision rather than the final visual result. If patients are adequately prepared for the postoperative regimen and limited outcomes, these complex procedures can be worthwhile undertakings as the results exceed the natural history of the untreated conditions.

Multiple factors have been suggested to be "high risk" for graft failure after PKP. From published studies, the most important of these factors is an earlier corneal transplant failure (see Fig. 4.12). Repeat transplantation has a reported 2-year survival of 76%,[94] a reported

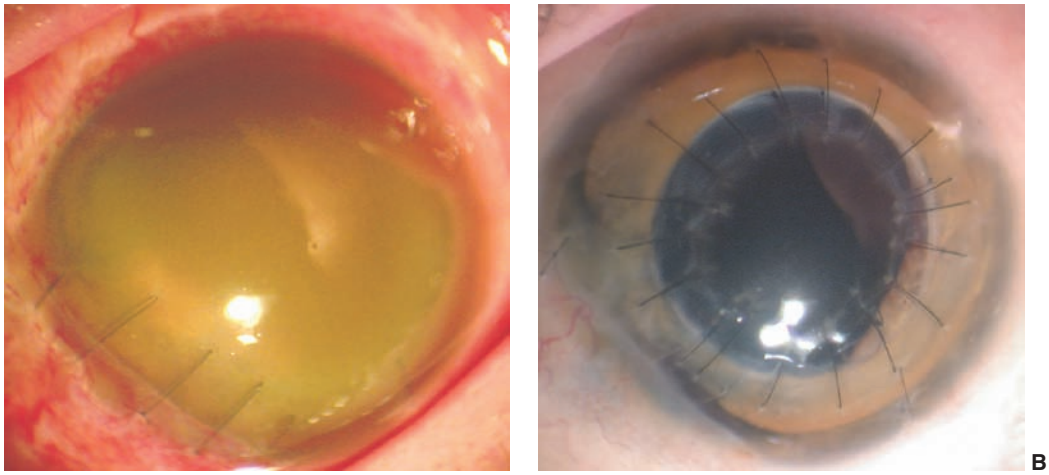


FIGURE 4.11 Corneal blood staining from trauma **(A)**. Three-month postoperative appearance after penetrating keratoplasty combined with a temporary keratoprosthesis and vitreoretinal surgery **(B)**.

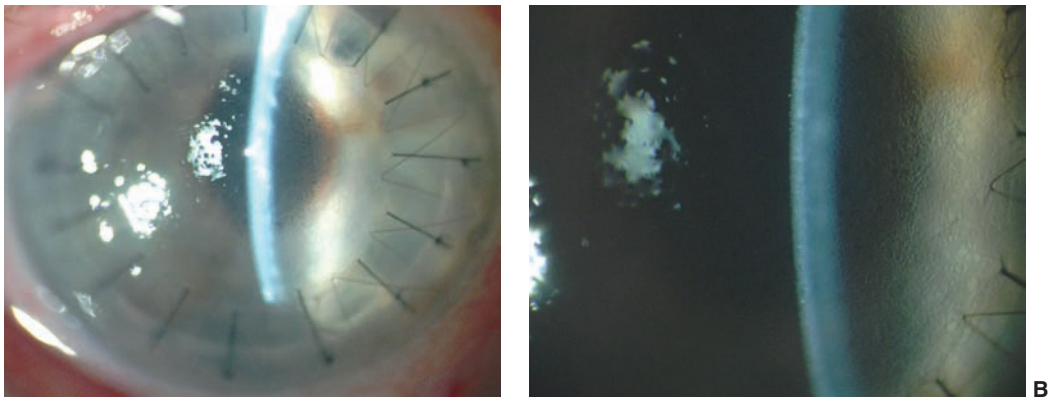


FIGURE 4.12 Failed penetrating keratoplasty with diffuse corneal edema **(A)**. Diffuse microcystic edema is present **(B)**.

5-year survival of 21.2% to 45.6%,[59,95] and, in other series, a reported 10-year survival of 41% to 46%.[56,58] Deep stromal vascularization of greater than one quadrant is also highly associated with graft failure.[58–60]

Collaborative Corneal Transplantation Studies

Collaborative Corneal Transplantation Studies (CCTS) (see Tables 4.10 and 4.11) were designed to assess whether histocompatibility (human leukocyte antigen, HLA) matching improved corneal graft survival in high-risk patients. *High-risk patients* were defined as patients who had two or more quadrants of neovascularization and/or a history of allograft rejection. Specifically excluded were the patients with conditions that may be predisposed to higher levels of nonimmunologic graft failure (e.g., patients with severe ocular surface disorders). Patients in the CCTS were recruited into either the Antigen Matching

TABLE 4.10 Collaborative Corneal Transplantation Studies (CCTS)—Antigen Matching Study (AMS)

Study question	Determine the effectiveness of HLA-A, -B, and -DR donor-recipient matching in high-risk patients who had no lymphocytotoxic antibodies
Study design	Prospective, randomized, double-masked multicenter trial. Six university-based clinical centers
Inclusion/exclusion criteria	**1.** Age 10 y or older **2.** Two to four quadrants of corneal stroma vascularization or a history of allograft rejection in the eye considered for surgery **3.** Willing to participate in 3 y of follow-up **4.** No condition that would greatly increase the risk of nonrejection graft failure (e.g., xerophthalmia or severe exposure) **5.** No patients with systemic disease or with medication usage that might alter their immune response **6.** Not pregnant
Intervention	Patients received corneas of negatively crossmatched donors and were grouped into "high" or "low" antigenic matching for HLA-A, HLA-B, and HLA-DR antigens
Primary outcome measure	Time to irreversible failure of corneal allograft due to any cause
Secondary outcome measures	**1.** Time to first immunological graft reaction **2.** Time to irreversible graft failure due to allograft rejection **3.** Visual acuity
Major findings	**1.** Donor–recipient tissue typing had no significant long-term effect on the success of corneal transplantation **2.** Matching patient and donor blood types (ABO compatibility) might be effective in improving patient outcome **3.** High-dose topical steroids, good patient compliance, and close patient follow-up appear to be important factors to successful transplantation in high-risk patients **4.** Lymphocytotoxic antibodies, especially directed against donor class I HLA antigens following corneal transplantation in high-risk patients, are associated with immune graft rejection and can be an indicator of allograft rejection
Unanswered questions	Determination of the exact immunologic reactions after penetrating keratoplasty needs further clarification as well as the involved donor and recipient factors

HLA, human leukocyte antigen.

TABLE 4.11 Collaborative Corneal Transplantation Studies (CCTS)—Crossmatch Study (CS)

Study question	Determine the effectiveness of crossmatching in preventing graft rejection among high-risk patients with lymphocytotoxic antibodies
Study design	Prospective, randomized, double-masked multicenter trial. Six university-based clinical centers
Inclusion/exclusion criteria	**1.** Age 10 y or older **2.** Two to four quadrants of corneal stroma vascularization or a history of allograft rejection in the eye considered for surgery **3.** Willing to participate in 3 y of follow-up **4.** No condition that would greatly increase the risk of nonrejection graft failure (e.g., xerophthalmia or severe exposure) **5.** No patients with systemic disease or with medication usage that might alter their immune response **6.** Not pregnant **7.** CCTS Central Laboratory confirmation of lymphocytotoxic antibodies on two separate occasions
Intervention	Patients received a cornea from either a positively or negatively crossmatched donor
Primary outcome measure	Time to irreversible failure of corneal allograft due to any cause
Secondary outcome measures	**1.** Time to first immunological graft reaction **2.** Time to irreversible graft failure due to allograft rejection **3.** Visual acuity
Major findings	A positive donor–recipient crossmatch was not found to increase the risk of corneal graft failure
Unanswered questions	Low prevalence of detectable lymphocytotoxic antibodies limited recruitment and study only had an 80% power to detect a 50% difference in groups

Study (AMS) or the Crossmatch Study (CS) based on the absence or presence of preexistent lymphocytotoxic antibodies to a standardized panel. Patients in the CS were further segregated into "positive" or "negative" groups, indicating whether preformed antibodies against the specific donor tissue to be transplanted were present. The strongest risk factors for immunologic graft failure at 3 years postoperatively in these high-risk patients included a younger recipient age (<40 years), the number of previous failed transplants, and previous anterior segment surgery.[96] Race did not appear to be a risk factor for graft failure in these patients, in agreement with a previous study.[97] The AMS found that in these patients donor-recipient tissue typing HLA-A, -B, and -DR had no significant long-term effect on the success of the transplant,[98] but ABO blood type incompatibility appeared to incur a greater risk of graft failure. The CS did not find a higher rate of corneal graft failure in patients with a positive donor–recipient crossmatch, although lymphocytotoxic antibodies were associated with immune graft rejection.[99] Interestingly, the 65% graft survival rate at 3 years was much higher than expected and was felt to be due to intensive topical steroids, good patient compliance, and close patient follow-up.

The CCTS raised important questions regarding the etiology of immunologic graft failures after corneal transplantation. If neither HLA-A, -B, and -DR antigens nor preexistent lymphocytotoxic antibodies explain the immunologic failures, then other factors must exist. Although it has been suggested that the multicenter and multisurgeon protocol in the

CCTS may have led to differing surgical and clinical management, graft failure rates were not substantially different among the centers. The CCTS also did not assess whether these factors improved graft survival in non–high-risk patients. A more recent study of non–high-risk corneal transplantation performed at a single institution found a 92% graft survival at 4 years with 0 to 2 mismatches versus a 66% graft survival in patients with 3 to 6 mismatches in the A/B/DR loci, respectively.[100] Given that PKPs in non–high-risk patients have generally high success rates, it remains questionable whether the time and expense of HLA matching appears to be of benefit to these patients.

Cornea Donor Study

The Cornea Donor Study (CDS; see Table 4.12) was initiated to study the effect of donor age on graft survival. The CDS found that for the study population, consisting

TABLE 4.12 Cornea Donor Study (CDS)

Study question	**1.** Determine whether the graft failure rate over a 5-y follow-up period following corneal transplantation is the same when using corneal tissue from donors older than 65 y compared with tissue from younger donors
	2. Assess the relationship between donor/recipient ABO blood type compatibility and graft failure due to rejection
	3. To assess corneal endothelial cell density as an indicator of the health of the cornea and as a surrogate outcome measure (in the optional Specular Microscopy Ancillary Study)
Study design	Prospective, randomized, double-masked multicenter observational study of 1,101 patients undergoing corneal transplantation
Inclusion/exclusion criteria	**1.** Patients must be in the age range of 40–80 y
	2. Corneal disease associated with endothelial dysfunction, including pseudophakic corneal edema, Fuchs' dystrophy, posterior polymorphous dystrophy, endothelial failure from another cause, interstitial keratitis (nonherpetic), or perforating corneal injury
	3. Donor criteria: Age 10–75 y, endothelial cell count 2,300–3,300, tissue quality very good to excellent, death to preservation time <12 h if body refrigerated or eyes on ice and <8 h if not, and death to surgery time <5 d
Intervention	Routine examinations over 5 y
Primary outcome measure	Time to graft failure defined as a persistent cloudy cornea for 3 mo or regrafting of the study eye
Major findings	**1.** No difference in graft survival was found at 5 y between the groups that received tissue from younger and older donors
	2. ABO incompatibility did not increase the risk of graft failure due to graft rejection in Fuchs dystrophy or pseudophakic corneal edema
	3. Patients undergoing PKP for pseudophakic or aphakic corneal edema and a fourfold increased risk of graft failure compared with those who had a PKP for Fuchs dystrophy
	4. Variation in endothelial cell density between local eye banks and reading center of >10% was found in 38% of cases suggests need for better eye bank standards and technician certification
Unanswered questions	**1.** Are the study results transferable to PKP performed for other indications, such as keratoconus or high-risk corneal transplants?
	2. Will longer follow-up show a difference in graft survival between the groups?

PKP, penetrating keratoplasty.

primarily of older patients with Fuchs corneal dystrophy and pseudophakic/aphakic corneal edema, that donor age did not affect graft survival at 5 years postoperatively.[101] There was a fourfold greater survival when Fuchs dystrophy was the indication compared with pseudophakic or aphakic corneal edema.[102] The CDS also found that for Fuchs dystrophy or pseudophakic corneal edema, ABO incompatibility did not increase the risk of transplant failure due to graft rejection.[103]

The Specular Microscopy Ancillary Study (SMAS), nested within the CDS, has followed endothelial cell counts prospectively. An interesting finding has been greater endothelial cell loss at 5 years in the group of older donors, which may affect long-term graft survival.[104] Preoperative endothelial cell density was not found to be predictive of graft survival, but cell density at 6 months postoperatively strongly correlated with graft failure.[105] Surprisingly, 14% of clear grafts at 5 years had cell densities below 500 cells/mm^2. The CDS-SMAS has also identified variation between local eye banks and the central reading center of >10% in 38% of cases,[106] emphasizing a need for better standards and training among eye banks.

Immunosuppression

Topical corticosteroids are the mainstay of postoperative care after corneal transplantation and may need to be continued indefinitely (see Fig. 4.13). As noted in the CCTS, close patient follow-up and intensive topical corticosteroid therapy appeared to reduce corneal graft failure to rates lower than expected by natural history alone. Additionally, topical cyclosporine 2% appears to improve graft survival after pediatric keratoplasty[107] and reduce allograft rejection[108] and possibly improve graft survival.[109] The effectiveness of topical cyclosporine 2% may vary depending on the vehicle in which it is compounded, but this has not been well studied. In contrast, the evidence of benefit of systemic cyclosporine is mixed. In patients with deep stromal vascularization, systemic cyclosporine may reduce the rate of immunologic rejection and graft failure[110]; however, other studies suggest no additional benefit relative to topical steroids alone.[111–113] This variability may be due to patient selection and/or increased graft failure from nonimmunologic mechanisms such as surface reepithelialization.[114] Newer agents such as tacrolimus (FK506) appear to be effective in reducing immunologic graft reactions both topically[115] and systemically.[116] Mycophenolate mofetil may reduce allograft rejection episodes[117] and have similar or greater efficacy than oral cyclosporine.[118]

All forms of immunosuppression carry risks, and the regimen to be utilized must be individualized for each patient. Topical agents may mask infectious keratitis, and corticosteroids are well known to contribute to increased IOP and cataracts. Topical cyclosporine and tacrolimus ointments have been

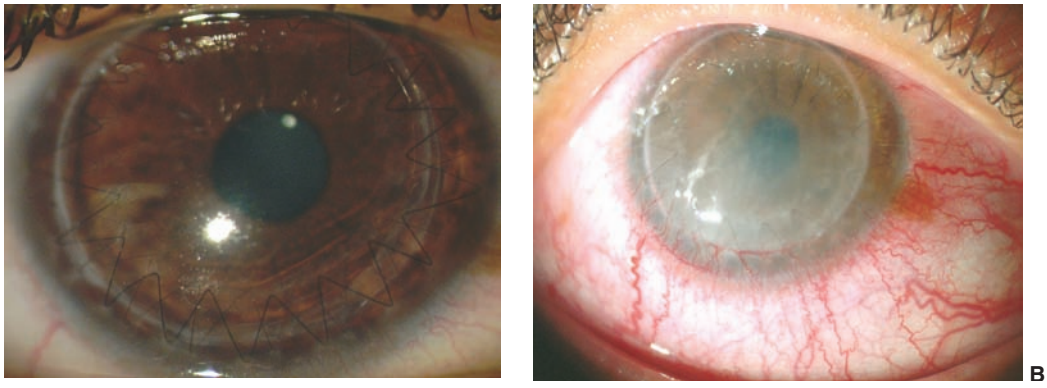


FIGURE 4.13 Four-month postoperative appearance of an initial penetrating keratoplasty for keratoconus **(A)**. Florid graft rejection is present at 11 months postoperatively after discontinuation of topical steroids **(B)**.

associated with HSV epithelial keratitis.[119,120] Systemic administration of cyclosporine, tacrolimus, and other agents can be associated with significant complications including hypertension, systemic infection, irreversible renal failure, and lymphoproliferative disorder (see Table 4.13).[116,121]

Evolving Techniques and Future Directions

Advances in corneal transplantation will hopefully improve patients' functional and visual outcomes while hastening recovery and reducing complications. Rates of endophthalmitis appear to be on the decline.[122] Endothelial replacement techniques, such as Descemet's stripping endothelial keratoplasty (see Fig. 4.14) and Descemet's membrane stripping endothelial keratoplasty, can reduce or eliminate induced surface astigmatic error and improve visual acuity.[123,124] These techniques, while still developing, are already supplanting PKP for endothelial disease, and graft survival in the short term seems comparable to PKP.[125] As is typical with new techniques, the published evidence is still developing.[126] Anterior lamellar keratoplasty techniques are gaining traction worldwide,

TABLE 4.13 Corneal Transplantation

Epidemiology
1. Rates of PKP are slowly declining in the United States.
2. The leading indications for PKP worldwide are PBK, KC, and corneal scarring
3. Rates of PKP for HSV appear to be declining.
Keratoconus
1. Prevalence, incidence, and disease severity vary with ethnicity
2. Mechanical factors, as well as genetic predisposition, play a role in its etiology
3. Visual function is much lower than measured visual acuity
Graft Survival after PKP
1. HSV may account for one-third of primary graft failures.
2. Failure within the first couple of years is usually immunologic, whereas late failures are generally nonimmunologic in etiology
3. Graft survival is highest for KC and lowest for repeat PKPs and eyes with deep stromal vascularization
4. Graft survival is reduced in pediatric populations and patients requiring concomitant ancillary procedures
5. Antigen matching and donor–recipient crossmatch do not appear to be significant determinants of graft survival in high-risk eyes
6. ABO incompatibility may be predictive of graft survival
7. Rates of endothelial cell density loss are greatest within the first few years after PKP and roughly normalize after 10 y
Immunosuppression
1. Topical corticosteroids are the mainstay of postoperative care
2. Topical cyclosporine 2% may be an effective adjunct in certain eyes
3. Oral cyclosporine has questionable effect on graft survival rates
4. Newer agents such as tacrolimus and mycophenolate mofetil may reduce allograft rejections and improve graft survival
5. All immunosuppressive agents carry negative, and sometimes severe, side effects
Topical and oral tacrolimus may reduce allograft rejection episodes.

HSV, herpes simplex virus; KC, keratoconus; PBK, pseudophakic bullous keratopathy; PKP, penetrating keratoplasty.

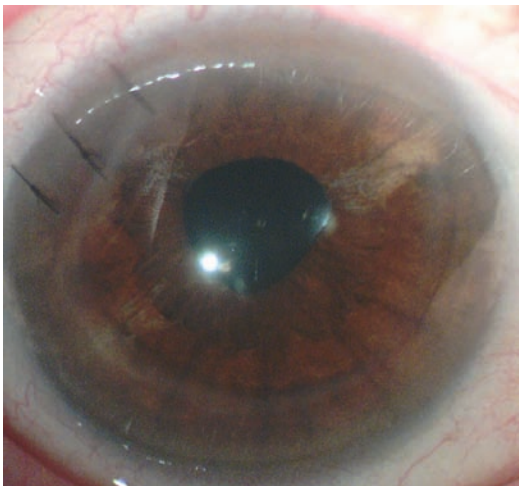


FIGURE 4.14 One-month postoperative appearance after combined Descemet's stripping endothelial keratoplasty with phacoemulsification and intraocular lens implantation.

if not in the United States, and may reduce the risk of donor rejection and improve graft survival.[127] The use of a femtosecond laser to assist in corneal transplantation may further refine these techniques.[128–131] Corneal collagen cross-linking continues to mature as a technique to prevent or delay corneal transplantation for KC by collagen–cross-linking therapies.[132,133] New tissue adhesives may also reduce suture-related complications.[134] Bioengineered corneas may eventually reduce or eliminate the need for donor tissue altogether.[135] Finally, a better understanding of corneal genetics, proteomics, and ultrastructure may lead to medical therapies and/or corneal gene therapy.

Bacterial Keratitis

Introduction and Risk Factors

The diagnosis and management of bacterial keratitis can be challenging, and varying opinions exist within the ophthalmic community as to the best approach for these cases.[136] Although the keratitis can be eradicated in many circumstances, visual acuity is frequently diminished as a consequence of the infection.[137] The damage to the visual function is determined by the virulence of the organism, the inoculum, host defenses, adequacy of therapy, and the proximity of the keratitis to the central visual axis (see Figs. 4.15 and 4.16). For example, highly virulent gram-negative bacterial keratitis may leave little functional impairment if outside the visual axis, whereas a small central corneal scar from a mildly virulent gram-positive organism will have more severe consequences. The ability of the organisms to form biofilms, defined as functional consortiums of microorganisms organized within an extensive extracellular polymer matrix, may inhibit the host immune response as well as limit the bioavailability of antibiotics.[138] This has become more recently recognized in chronic bacterial keratitis, such as infectious crystalline keratopathy (see Fig. 4.17).[138–140]

A variety of inciting or risk factors have been recognized in cases of bacterial keratitis. Surface factors such as contact lens wear, trauma,[141] previous corneal surgery or sutures,[142,143] chronic exposure or irritation, persistent or recurring epithelial defects (see Fig. 4.18), tear deficiency or limbal stem cell deficiency states can predispose to the development of bacterial keratitis. Likewise, systemic factors such as immunosuppression, atopy, diabetes mellitus, or connective tissue diseases increase the risk of infection. Geographic location, medicamentosa, and unusual exposure to animals, contaminated water, or other higher-risk environments (including medical facilities) should always be considered. The

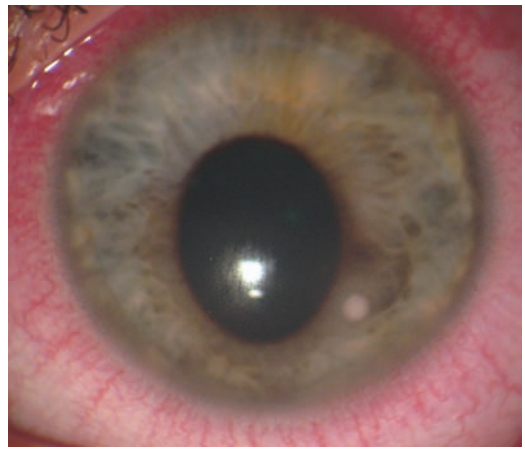


FIGURE 4.15 Contact lens–associated peripheral bacterial keratitis.

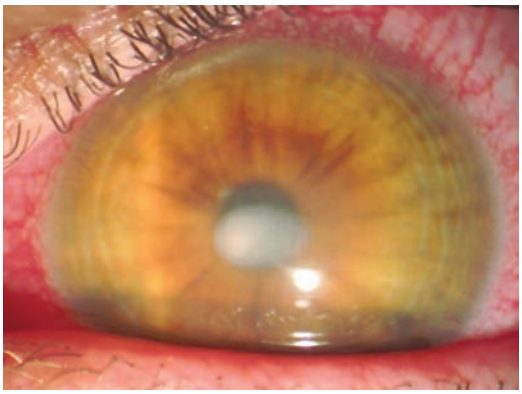


FIGURE 4.16 Central bacterial keratitis from *Propionibacterium acnes*.

presence or absence of these factors is important to elicit as they may suggest the causative organisms.

In North America, as well as in Europe[144] and Asia,[145,146] most cases of microbial keratitis arise from a bacterial etiology. In the western United States, gram-positive bacteria, especially the *Staphylococcus* and *Streptococcus* species,[147] were found to be prominent causes. In the southeastern United States although gram-positive bacteria were also prominent, *Pseudomonas* species were more frequently isolated,[148,149] attesting to geographic variability. Other organisms, such as fungi, mycobacteria (see Fig. 4.19), and acanthamoeba (see Fig. 4.20) may also have geographic variability in frequency.[150] The estimated annual incidence of bacterial keratitis in the United States has been reported to be 5.3 per 100,000 people,[151] with an increasing frequency in the 1980s and associated with contact lens wear in over 50% of cases. Some studies show a reversal of this trend in the United States.[148] For contact lens wearers in the Netherlands, the estimated annualized incidence of microbial keratitis was 1.1 per 10,000 users

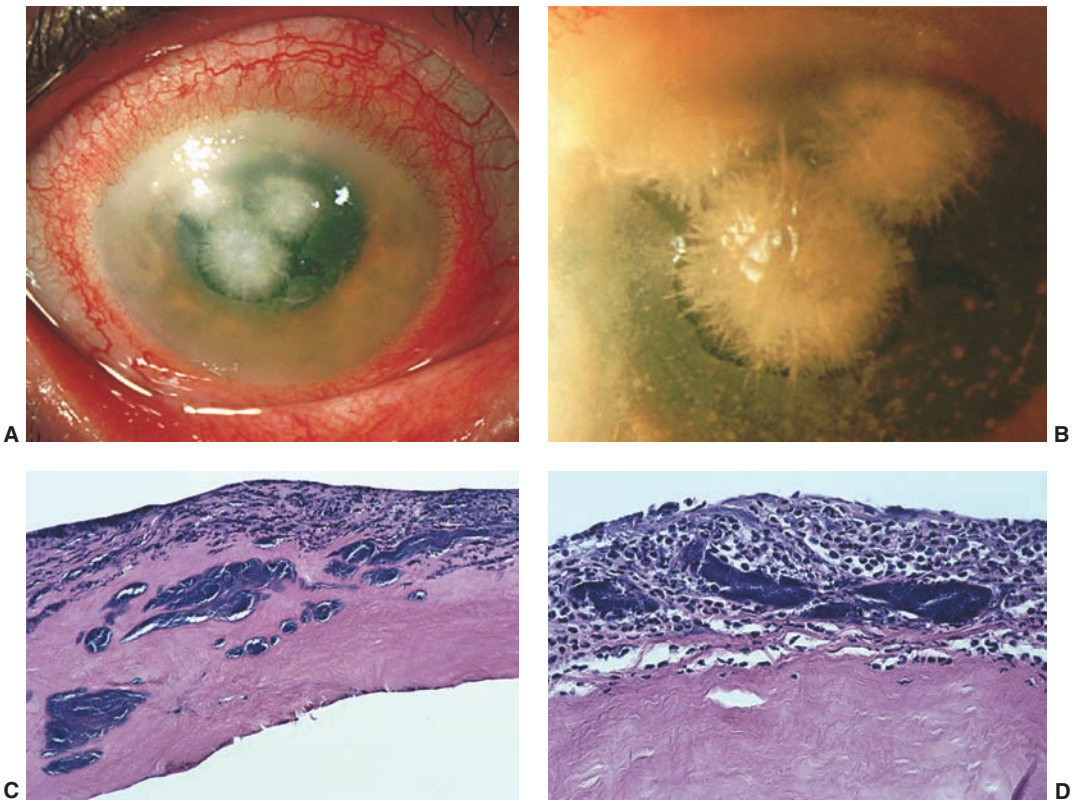


FIGURE 4.17 Slit lamp biomicroscopic appearance of infectious crystalline keratopathy caused by *Streptococcus viridans* **(A and B)**. Histopathologic examination of a lamellar biopsy reveals copious clusters of bacteria with varying levels of inflammatory response **(C and D)**.

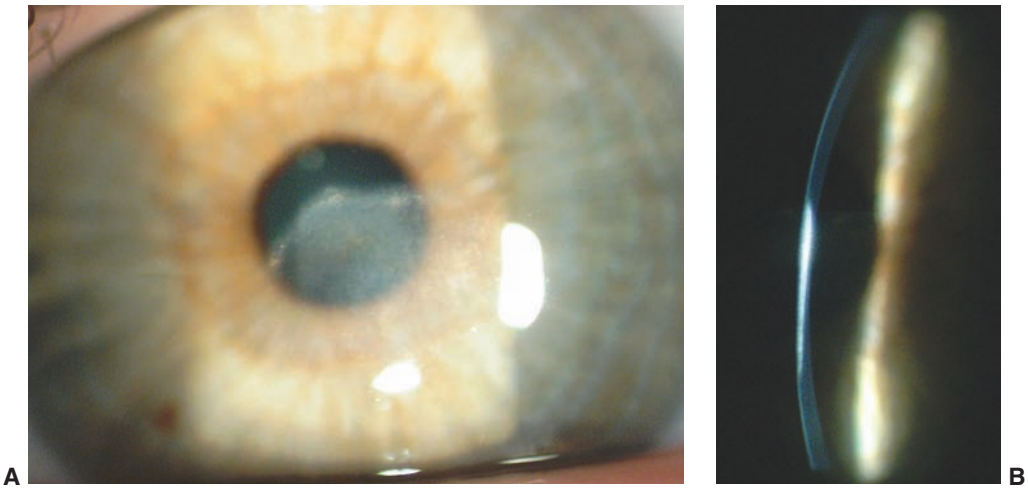


FIGURE 4.18 Corneal thinning and scarring centrally after bacterial keratitis following a recurrent corneal erosion **(A and B)**.

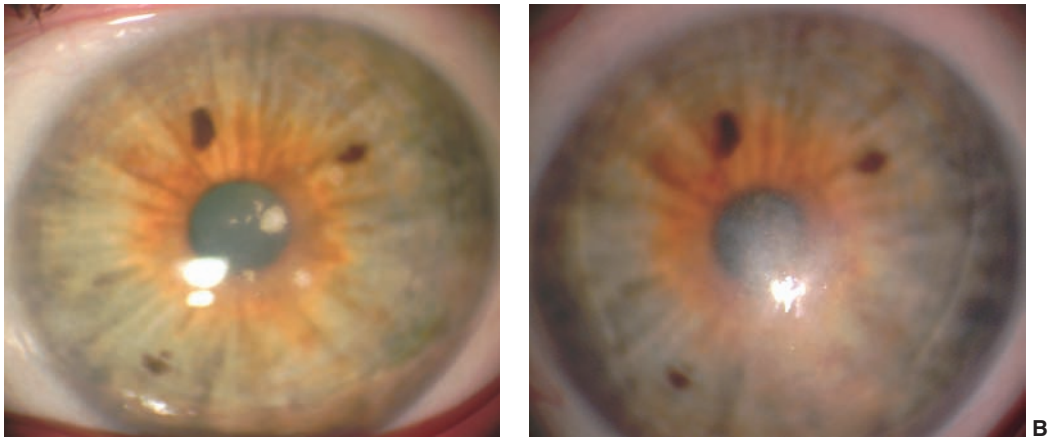


FIGURE 4.19 *Mycobacterium chelonae* keratitis presenting 1 month after laser in situ keratomileusis **(A)**. After flap amputation and 3 months of topical therapy, residual corneal scarring is evident **(B)**.

of daily-wear rigid gas-permeable lenses, 3.5 per 10,000 users of daily-wear soft lenses, and 20.0 per 10,000 (10.3–35.0) of users of extended-wear soft lenses.[152] This variability in rates of contact lens–related microbial keratitis may be due to contact lens material, design, usage, and/or oxygen transmissibility.[153–157] Contact lenses remain by far the most important risk factor for development of corneal infections.

Diagnosis

Ideally, all corneal ulcers would be cultured and antimicrobial therapy tailored specifically to the organism identified. This does not occur in clinical practice as empiric therapy is typically effective,[158] maintenance of culturing supplies can be costly, and there is a lag in obtaining culture results. A meta-analysis of studies in which culture was performed also found that culture results did not affect 1-week cure rates.[159] However, cultures are valuable in establishing trends in microbial keratitis, especially in regard to resistance to antibiotics. Likewise, when cases demonstrate atypical and/or inadequate response to empiric therapy, as may be seen in a cornea subspecialty practice, cultures should be

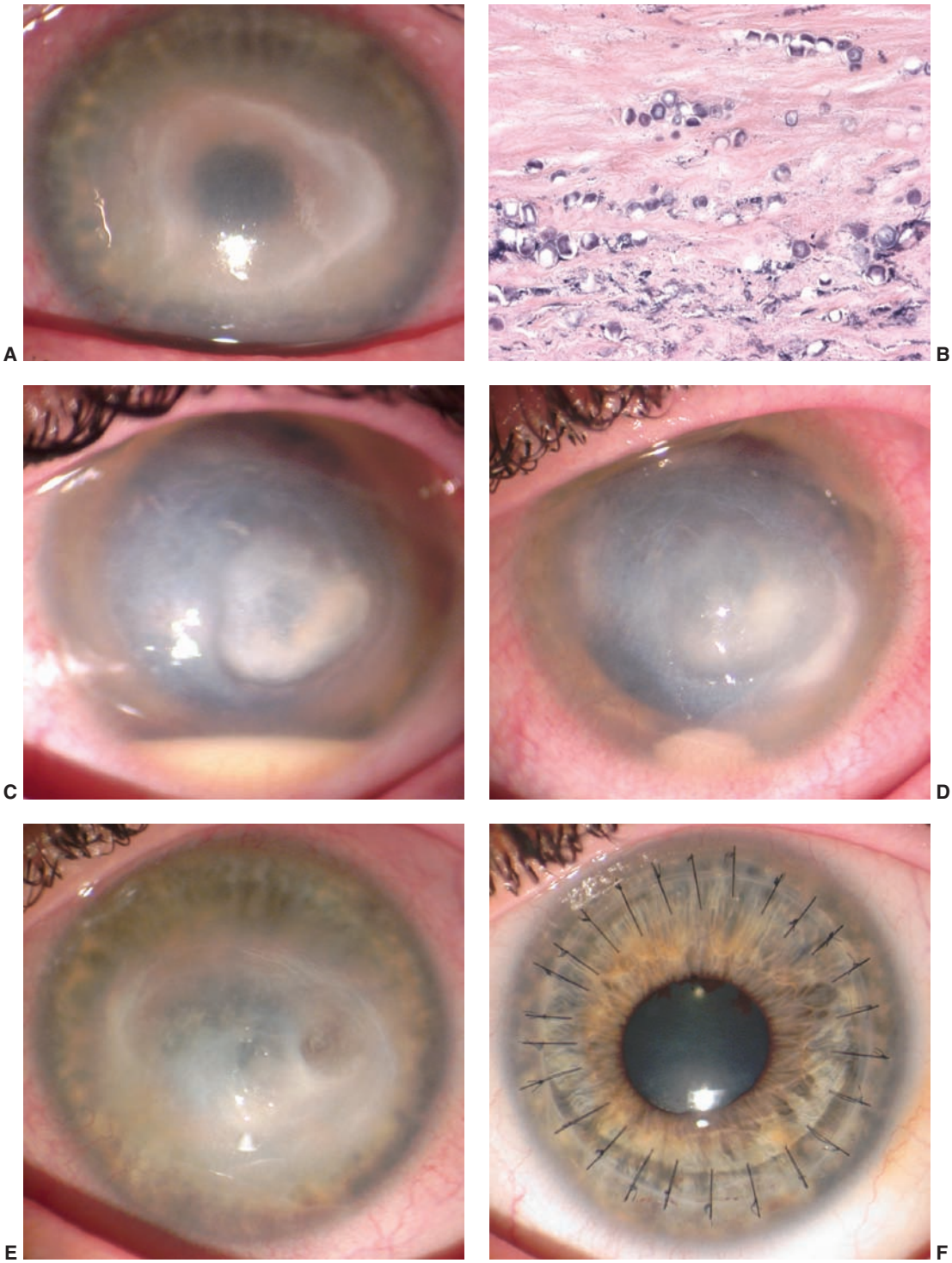


FIGURE 4.20 Acanthamoeba keratitis. Initial presentation **(A)** with lamellar corneal biopsy revealing numerous cysts **(B)**. Appearance after 2 months **(C)**, 4 months **(D)**, and 6 months of therapy **(E)**. Two months after penetrating keratoplasty, uncorrected visual acuity measures 20/40 **(F)**.

performed or repeated.[160] It is also important to consider the possibility of a polymicrobial infection in these cases.

Confocal microscopy, although not widely available, may be helpful in diagnosing acanthamoeba and fungal keratitis.[161,162] However, when culture results are negative, deep stromal infiltrates are present, and/or the clinical scenario does not improve in spite of vigorous therapy, a corneal biopsy may be needed to establish a definitive diagnosis. Some surgeons perform an epithelial biopsy alone, but for severe cases a deeper resection not only provides greater tissue for histopathology but also debulks the infectious process, permits greater penetration of antimicrobials, and provides more substantive material for culture.

Management

Initial therapy plays an important role in the outcome of bacterial keratitis.[163] For cases of presumed bacterial keratitis, one should combine the knowledge of the most likely causative organism and local antibiotic resistance patterns, with delivery of sufficient antimicrobial(s) to overwhelm bacterial defenses. Aggressive broad-spectrum antibiotic therapy should be promptly initiated with discontinuation of any aggravating or inciting factors such as contact lenses. Although inconvenient for the patient, it is best to begin with a very frequent dosing schedule for loading purposes, such as every 5 to 15 minutes for the first 30 to 60 minutes, then subsequently reduce to a maintenance dosage. If multiple antibiotics are used, it is not necessary to alternate them on different schedules, once a loading dose has been achieved. Patients who cannot comply with the dosing schedule may need hospitalization or home health assistance. Traditional in vitro minimum inhibitory concentration data do not necessarily apply to topical ophthalmic medications as the generally higher local ocular concentrations can result in clinical response even for organisms deemed "resistant." Topical fluoroquinolone antibiotics have contributed to improved success in treatment as they can be used as monotherapy and are effective against a broad spectrum of organisms. Unfortunately, resistance to these agents is inevitable and it is not a good practice to prolong therapy or taper antibiotics after the infection has resolved. Likewise, if there is an atypical response, consideration should be given to using fortified antibiotics as guided by cultures and/or the organism(s) most likely to be present.

Topical corticosteroids have an unclear role in the management of bacterial keratitis. The typical objective is to reduce an exaggerated inflammatory response and minimize corneal scarring, while not impairing the healing response. The Steroids for Corneal Ulcers Trial (SCUT; see Table 4.14) found no general differences at 3 months in patients randomized to antibiotic alone or antibiotic/steroid groups for bacterial corneal ulcers.[164] However, those with central corneal ulcers or best-corrected vision of counting fingers or worse did have better vision at 3 months when treated with steroids. One systematic review (see Table 4.15) found that prior usage of corticosteroids increased the risk of antibiotic treatment failure or other infectious complications.[165] From this review, two recommendations reached "most important" levels. First, topical corticosteroids should be avoided if the causative agent is unknown and, second, topical corticosteroids should be utilized when, after using clinical or laboratory criteria, it is deemed important to aid reepithelialization or minimize stromal alteration and scarring. In practice, before administering topical corticosteroids, the American Academy of Ophthalmology Preferred Practice Pattern on this subject suggests waiting 2 to 3 days after topical antibiotic therapy has been initiated and in which progress is being made in treating the infection.[166] If topical corticosteroids are initiated, it is important to follow-up the patient closely in the initial period to insure against recrudescence of the infectious process.

Concomitant pain management is an important consideration for these patients. One simple measure is the administration of a topical cycloplegic agent in the office. In patients responding to therapy, the pain is typically stabilized or improved by the first day after treatment, although the clinical

TABLE 4.14 Steroids for Corneal Ulcers Trial (SCUT)

Study question	Determine whether adding topical corticosteroids improves best spectacle-corrected visual acuity at 3 mo in patients with bacterial corneal ulcers
Study design	Randomized, double-masked, placebo-controlled comparative multicenter clinical trial
Inclusion/exclusion criteria	**1.** Eligible patients had a culture-positive bacterial corneal ulcer with no evidence of fungal, herpetic, or acanthamoeba keratitis
Intervention	Patients were randomized to prednisolone phosphate 1% or placebo drops after culture-positive bacterial corneal ulcer and 48 h of treatment with topical moxifloxacin. **1.** Moxifloxacin was administered hourly for the first 2 d while awake, then every 2 h until reepithelialization and then four times daily until 3 wk postenrollment. **2.** Corticosteroid or placebo was given four times daily for 1 wk, then twice daily for 1 wk then once daily for 1 wk postenrollment
Primary outcome measures	**1.** Best spectacle-corrected visual acuity **2.** Time until reepithelialization **3.** Size of scar and/or infiltrate
Major findings	**1.** No significant differences were found in 3-mo best spectacle-corrected visual acuity, infiltrate/scar size, time to reepithelialization, or corneal perforation **2.** In subgroups with poorer best spectacle-corrected visual acuity or more central ulcer location, eyes treated with corticosteroids had statistically significant better visual acuity at 3 mo compared with placebo **3.** No safety concerns were noted with topical corticosteroid usage
Unanswered questions	**1.** What is the best timing and steroid to use for corneal ulcers? **2.** Would using steroids more vigorously have a different impact, particularly on subgroups who were found to benefit in this study?

TABLE 4.15 Corticosteroids for Bacterial Keratitis

Study question	Determine the effects of topical corticosteroids with bacterial keratitis
Study design	Systematic review
Inclusion/exclusion criteria	**1.** Bacterial keratitis was defined as a stromal infiltrate with an overlying epithelial defect that warranted intensive antibacterial therapy **2.** All topical corticosteroids studied were considered equivalent
Intervention	Sources included electronic searching of MEDLINE and EMBASE through 2000; used the text words *keratitis* or *corneal ulcer* combined with *corticosteroid*, *cortisone*, *dexamethasone*, or *prednisolone*, without language restrictions. Other sources were identified by manually searching Index Medicus from 1960 through 1965, Excerpta Medica Ophthalmology from 1960 to 1973, and Ophthalmic Literature from 1950 to 1999. Reference lists of primary reports, review articles, and corneal textbooks were searched for additional relevant articles dating from 1950

(continued)

TABLE 4.15 Continued

Primary outcome measures	Positive and negative effects of corticosteroids used before and during therapy for bacterial keratitis
Major findings	**1.** Avoid topical corticosteroids if the causative microorganism is unknown **2.** Add a topical corticosteroid if the organism is known, and treatment, by clinical or laboratory criteria, is necessary to aid reepithelialization and/or minimize stromal alteration
Unanswered questions	If topical corticosteroids have value: **1.** Who is a good candidate for therapy? **2.** When should topical corticosteroids be initiated? **3.** At what frequency and dosage should they be initiated? **4.** How long should they be continued?

appearance may appear worsened. Oral narcotics can be used adjunctively, but are frequently unnecessary and can potentially mask clinical worsening or reduce compliance with the treatment regimen. These agents also tend to have an unwanted sedative effect in many patients. It may be best to reserve oral narcotics for patients who are expected to have long therapeutic courses. Topical anesthetics are not advisable for these patients, given the potential for abuse and delayed healing. For severe cases of keratitis, as well as those with current or impending perforation, therapeutic PKP may sometimes be a better option than weeks and months of topical therapy (see Fig. 4.21 and Table 4.16).

Future Directions

Multiple advances are still needed in the management of bacterial keratitis. Of foremost necessity are better preventative measures, particularly in the design, materials, and usage of contact lenses. Silicone hydrogel lenses appear to be a step in this direction and may reduce the risk of infection for extended-wear contacts.[153] In spite of this, infections associated with silicone hydrogel lenses still occur and can be severe with reported greater adhesion of organisms such as acanthamoeba to this material.[167] Use of extended-wear contacts increases the risk of infection, and patient education in this regard remains important. A better understanding of the specific virulence factors of each bacterium, and how these interplay with the host, may lead to medications or devices that reduce the rate of infectious keratitis. From a diagnostic standpoint, the development of rapid, preferably office-based, assays to identify the causative organism and its sensitivities would be worthwhile. Education regarding the appropriate use of topical antibiotics, especially within the nonophthalmic community, remains an important goal to reduce the spread of resistance. Avoiding long-term treatment at low doses and avoiding the tapering of antibiotics are important in the prevention of resistance. More research is still needed to understand the appropriate role and timing of corticosteroids in adjunctive therapy. Finally, as microorganisms develop resistance to current antibiotics, a steady supply of alternatives will become necessary.

Acknowledgments

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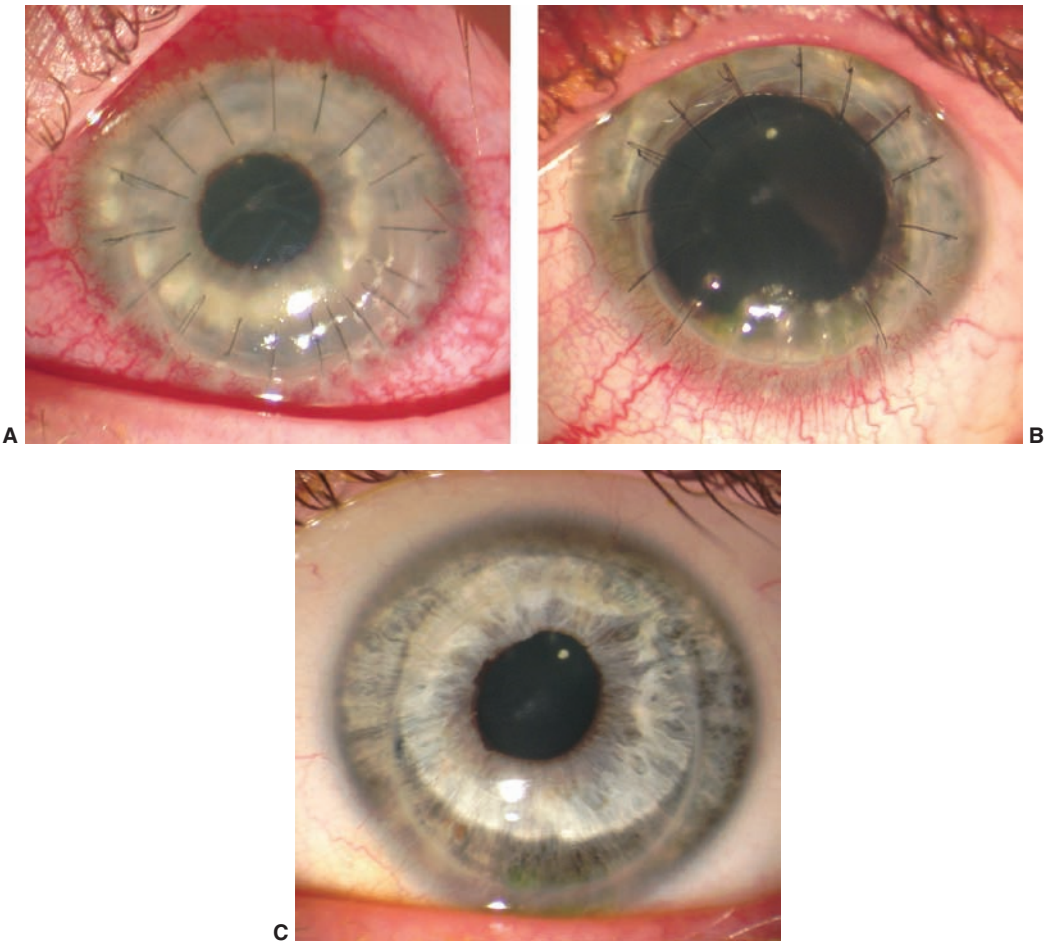

FIGURE 4.21 Appearance of a therapeutic penetrating keratoplasty performed for a perforated fungal (*Aspergillus sp.*) corneal ulcer at 1 day **(A)**, 6 weeks **(B)**, and 1 year **(C)**.

TABLE 4.16 Bacterial Keratitis

Epidemiology
1. Contact lenses are the greatest risk factor for bacterial keratitis
2. Gram-positive bacteria, especially *Staphylococcus*, and *Streptococcus* species, are the most commonly cultured organisms
Diagnosis
1. For primary bacterial keratitis, culture results do not affect 1-wk cure rates
2. Cultures should be performed or repeated when there is an atypical response to therapy
3. Corneal biopsy can establish a definitive diagnosis
Management
1. Aggressive broad-spectrum antibiotic therapy should be initiated promptly
2. Unnecessary prolongation of antibiotic therapy should be avoided as well as tapering of the antibiotics to avoid the possibility of creating resistant organisms
3. Topical corticosteroids have an unclear role in the treatment of bacterial keratitis, but may aid reepithelialization and/or minimization of corneal scarring
4. Severe cases may require therapeutic penetrating keratoplasty

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5 Refractive Surgery

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Refractive surgery has at least two unique characteristics when compared with the other subspecialties of ophthalmology. The preoperative and postoperative refractive evaluations allow calculations of efficacy, predictability, and stability that provide for detailed analysis and comparison. Refractive surgery is a purely elective procedure that the patients continuously evaluate visually for the rest of their lives. This means that the success of refractive surgery is entirely based on the results; patients pleased with the outcomes will refer others, whereas those displeased will not. Understandably, refractive surgeons and laser providers focus equally on the outcomes to achieve the expectations of the patients.

With the achievement of perfect uncorrected vision, success in refractive surgery has become an obsession for surgeons, equipment manufacturers, and patients. There are many studies and comparisons available to evaluate the various refractive procedures.

Options for Refractive Surgery

Before discussing the results of the various studies on refractive surgery, it is first necessary to provide a brief outline of each of the procedures available in the armamentarium of the refractive surgeon and the indications for each procedure (see Fig. 5.1). The reader should note that the indications for each refractive procedure are rapidly changing as new technologies become available and replace other procedures.

LASIK and *photorefractive keratectomy (PRK)* remain the mainstay of the armamentarium of refractive surgery. For PRK, the ideal treatment for maximum spherical myopia is –6.0 D (extended range up to –10.0 D). For LASIK, the ideal treatment for maximum myopia treatment is now –10.0 D (extended range –12.0 D). Other factors that influence the amount of correction include corneal thickness, flap thickness, pupil size, and the amount of ocular aberrations. Mitomycin-C (MMC) is used intraoperatively with higher myopic PRK,[1] and after more than a decade, MMC has been found to be effective when used for the prevention and treatment of corneal haze.[1,2] The limits of the hyperopic corrections have been reduced because of regression and disturbances in night vision associated with the smaller postoperative hyperopic optical zones noted with corrections over +3.0 D spherical equivalent.

Cochrane reviews of PRK versus LASIK for myopia and hyperopia have been conducted. For myopia, the effectiveness of these two procedures is comparable, but LASIK gives faster visual recovery than PRK.[3] For hyperopia, no robust, reliable conclusions could be reached, but the nonrandomized trials reviewed resulted in comparable efficacy for either procedure.[4] High-quality, well-planned open randomized control trials are needed in order to obtain a more robust base of clinical evidence.

Custom wavefront PRK and LASIK are now being performed for the same refractive range as conventional LASIK. Currently, wavefront treatments are available for up to –11.0 D of myopia and –4.0 D of astigmatism. Custom wavefront procedures have not consistently demonstrated superiority in terms of visual acuity and low aberration outcomes when

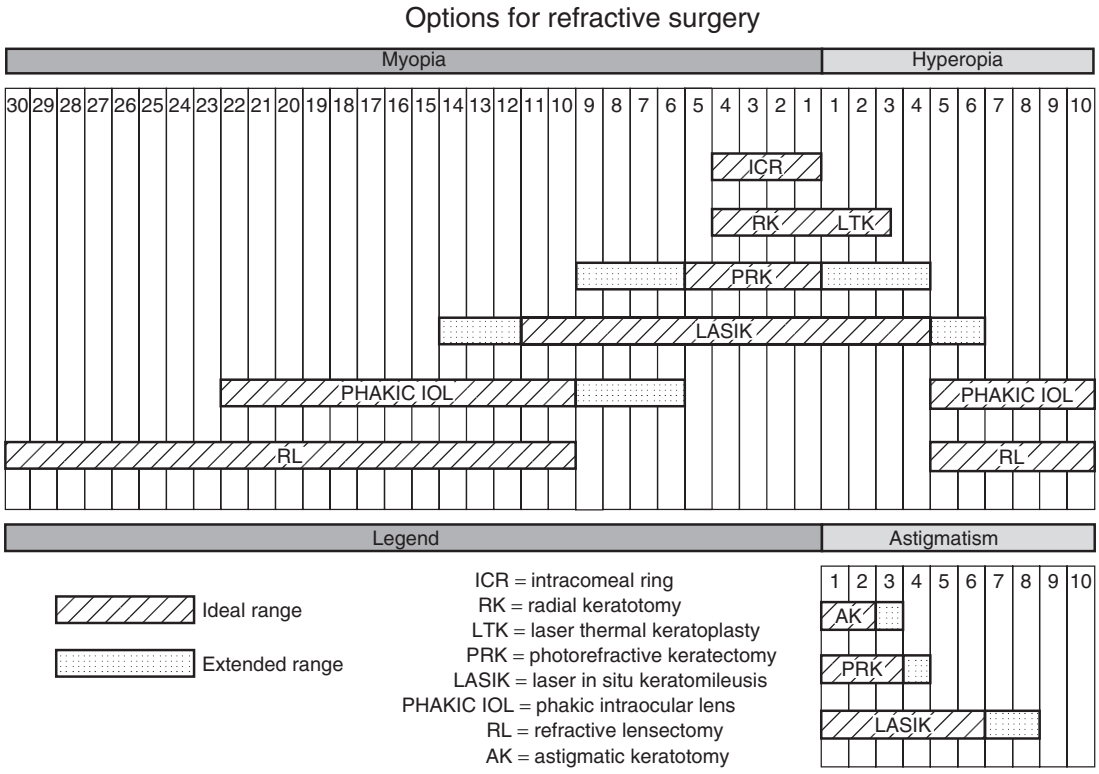


FIGURE 5.1 The options for refractive surgery demonstrate the ideal and extended ranges for treatment of the various refractive options for myopia, hyperopia, and astigmatism. The indication for each of these procedures is constantly changing as more experience is gained and other options become available.

compared with conventional LASIK and PRK; however, the induction of higher order aberrations is reduced.[5]

Laser epithelial keratomileusis (LASEK) is a hybrid of PRK and LASIK. LASEK utilizes an epithelial flap created by exposing the cornea to ethanol. Proponents of LASEK believe that it reduces the risk of intraoperative flap complications and preserves posterior corneal stroma. Critics are concerned about the slow visual recovery and the risks of corneal haze. However, numerous reported studies have shown quicker visual recovery and reduced postoperative pain levels after LASEK than after PRK.[6] A recent meta-analysis of studies involving LASEK versus PRK concluded that LASEK-treated eyes had no significant benefits over PRK-treated ones with regard to clinical outcomes, but there was less corneal haze observed with LASEK-treated eyes at 1 to 3 months after surgery.[7]

Epi-LASIK is a variation of LASEK. For epi-LASIK, the epithelial flap is created with a modified microkeratome or femtosecond laser. Proponents state that the flaps created with *Epi-LASIK* heal faster and the results are comparable to LASIK, although no randomized clinical trials have been conducted to confirm these claims.

In 2005, it was estimated that nearly 70% of all LASIK patients in the United States chose to have the procedure performed with the femtosecond laser, if given the option.[8] Early comparisons between the femtosecond laser and the microkeratome in LASIK flap creation showed that the femtosecond laser group had significantly more diffuse lamellar keratitis postoperatively and the microkeratome

group had significantly more epithelial defects intraoperatively.[9] Earlier femtosecond lasers required higher total energy to cut a flap.[10] Morphologic alterations in the corneal stroma produced by the currently available models of the IntraLase (Abbott Medical Optics Inc., Santa Ana, CA) laser are comparable to those produced by mechanical microkeratomes.[10] Advances have resulted in a reduction in the total amount of energy delivered by the laser when it cuts the flap, and there is a decrease in the inflammatory response associated with femtosecond flap formation to the point that it is indistinguishable from the microkeratome at the cellular level.[10] Current models of the femtosecond laser, the 150 kHz IntraLase machine, can create a flap in about 10 seconds. This is half the time that was required by the previous 60 kHz system.

The improved results of faster visual recovery and uncorrected visual acuity (UCVA) and enhanced safety profile, including less post-LASIK dry eye, have led to most surgeons choosing the femtosecond laser for flap creation.[11–13] A systematic review concluded that while LASIK with the IntraLase femtosecond laser may offer limited benefit over LASIK with microkeratomes in regard to safety and efficacy, it has advantages in predictability of target refraction and flap thickness.[14]

Conductive keratoplasty (CK) has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of hyperopia.[15] The thermal corneal burns are applied with a radiofrequency probe down to about 90% of the corneal depth (500 µm). It is hoped that the deeper corneal penetration will help avoid the problems with regression associated with laser thermal keratoplasty (LTK).[16,17] CK is no longer performed by most refractive surgeons; however, it is occasionally used to create "blended vision" in one eye for the correction of presbyopia.

Intracorneal rings (ICRs) or *Intacs (Contact Addition Technology, Des Plaines, IL)* are now rarely used to treat myopia but have been applied for specific situations to treat post-LASIK ectasia[18] or keratoconus.[19] While the initial ICR FDA studies were promising,[20] the procedure never gained widespread acceptance because of the inability to treat astigmatism, difficulty in duplicating the initial FDA results, competition from LASIK, and the high explantation rate.

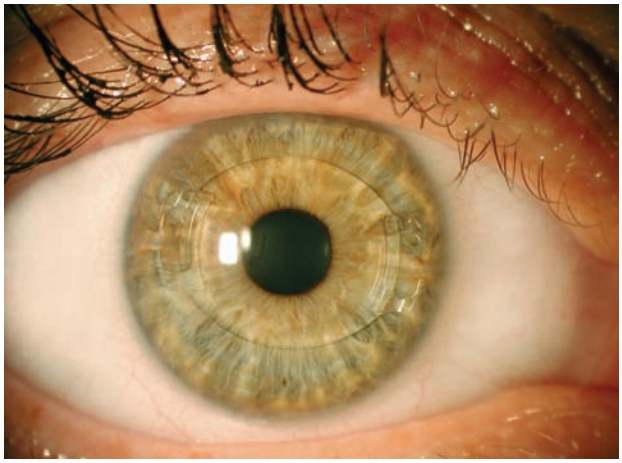
Phakic intraocular lenses (IOLs) and *refractive lensectomy (RL)* remain the main options for the correction of extreme ametropias. Advances in *phakic IOLs* include the Verisyse™ lens (Abbott Medical Optics Inc., Santa Ana, CA), also known as the Artisan® lens outside of the United States, that clips onto the iris stroma in the anterior chamber (Fig. 5.2). The U.S. FDA clinical trials have shown that the Verisyse phakic IOL provides excellent refractive outcomes, with endothelial cell loss within a mean of 5.0% over 3 years, or 1.8% per year, and few complications.[21] Another phakic IOL that is currently awaiting FDA approval is the Alcon (Fort Worth, TX) angle-supported Acrysof CACHÉ lens (Fig. 5.3).[22] The Visian ICL (implantable collamer lens, Staar Surgical, Monrovia, CA) is implanted behind the iris in the posterior chamber and was U.S. FDA approved in 2005 (Fig. 5.4).[23,24]

RL, also known as *clear lens extraction (CLE)* for myopia, has benefited from the availability of low diopter power IOLs; however, concerns about the increased risk of retinal detachment remain.[25] RL for hyperopia has used piggyback IOLs for eyes requiring heavy corrections[26]; however, high-power customized foldable IOLs (e.g., up to 60.0 D CT Xtreme D, from Carl Zeiss Canada Ltd., Toronto, Ontario, not yet FDA approved) may make this less necessary in the future.

Multifocal, accommodating, and diffractive IOLs such as the ReZoom, previously Array (AMO, Santa Ana, CA), Crystalens, previously AT-45 (Eyeonics, Aliso Viejo, CA), and the ReSTOR IOL (Alcon Laboratories, Fort Worth, TX) have been under development for over two decades. Several modifications have been made to improve distance, intermediate, and near vision compared with their predecessors. Unfortunately, these modifications have also resulted in unwanted side effects such as glare and halos, decreased contrast sensitivity in multifocal lenses, and inconsistent near-vision results in accommodating IOLs. Careful patient selection is crucial for successful results.[27]

A

B



C

FIGURE 5.2 Verisyse Artisan® **(A)** and Artiflex® **(B)** and **(C)** anterior chamber iris-claw lens (permission for figure reproduction granted from OPHTEC Inc.).

Femtosecond laser cataract surgery has recently arisen in the forefront of refractive cataract surgery. There are four platforms approved by the FDA at the time of preparing this manuscript, including the LensAR (LensAR Inc., Winter Park, FL), LenSx (Alcon Laboratories, Fort Worth, TX), Catalys Precision Laser System (OptiMedica Corp., Sunnyvale, CA), and the VICTUS Laser System (Bausch & Lomb/Technolas

FIGURE 5.3 Acrysof® Cachet™ angle-supported phakic intraocular lens (permission for figure reproduction granted from Alcon Inc.).

Perfect Vision, Munich, Germany). Various functions "depending on the machine" have received U.S. FDA approval (corneal incisions, astigmatic keratotomies, capsulorhexis, nucleus fragmentation or softening). The LenSx laser was the first to receive FDA approval and in initial studies, femtosecond laser lens fragmentation on grade 3 and 4 cataracts resulted in a 43% reduction in phacoemulsification power and a 51% decrease in effective phacoemulsification time.[28] In the initial series of procedures performed on human eyes, femtosecond laser capsulotomy and lens fragmentation was complete with no operative complications.[28] When compared with manual capsulorhexis for IOL implantation, femtosecond laser capsulotomy formation improved the predictability of the effective lens position.[29] Much additional study is underway to determine if femtosecond laser–assisted cataract surgery will significantly improve the refractive outcomes of cataract surgery.

Radial keratotomy (RK) is no longer performed,[30] as other refractive procedures offer a more predictable and stable outcome. For RK, a diamond knife was used to create radial incisions in the cornea.

LTK is no longer performed for low hyperopia, and the bankruptcy of the laser manufacturer officially ended its tenure. For LTK, peripheral thermal burns were applied to the peripheral cornea for the correction of small degrees of hyperopia.

LASIK, PRK, LASEK, and epi-LASIK are the main methods for the treatment of astigmatism. Astigmatic keratotomy and limbal relaxing incisions are generally used in conjunction with

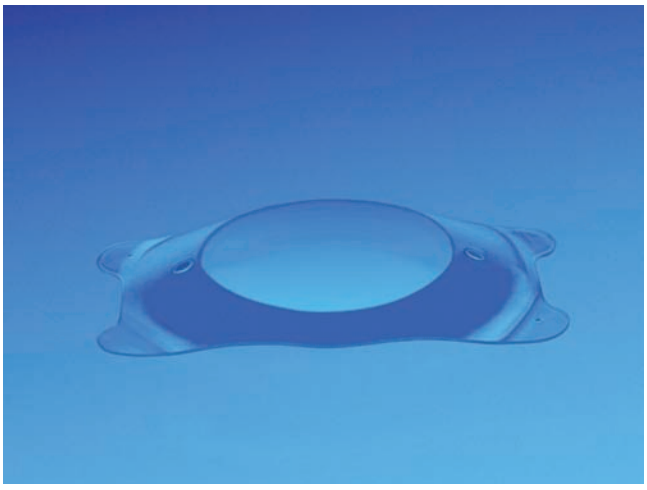


FIGURE 5.4 STAAR® Visian implantable collamer lens (permission to reproduce figure granted from STAAR surgical).

other intraocular procedures to partially reduce astigmatism. The limits for the treatment of astigmatism by PRK, LASEK, or LASIK have been expanded by utilizing the cross-cylinder ablation or bitoric ablation technique originally proposed by Vinciguerra et al.[31] Toric pseudophakic and phakic IOLs are also available for the treatment of astigmatism associated with lens implantation.[32]

U.S. Food and Drug Administration Studies: Advantages and Challenges

Apart from the Prospective Evaluation of Radial Keratotomy (PERK) study of RK,[33] there have been no large-scale multicenter trials to evaluate the different techniques and technologies of refractive surgery as compared with the comprehensive studies performed for the other ophthalmic subspecialties. However, refractive procedures involve the use of new devices and therefore require the submission of detailed studies to the FDA, which are available on the FDA web site shortly after approval (http://www.fda.gov). The FDA submission criteria require that the data be submitted in a standardized format so that the results of different lasers, procedures, and devices can be compared.

While there are obvious advantages to using the FDA data for comparisons, in practice, there are some limitations also. First, excellent results in an FDA study do not always correlate with those in general practice. The most notable example of this discrepancy was with Intacs. The result of the FDA study for Intacs was outstanding; however, the results in the hands of most surgeons were disappointing, which led to the failure of Intacs as a viable option for the correction of myopia. Second, FDA studies are generally sponsored by the company seeking FDA approval and performed by physicians with close relationships with those companies and so at least some degree of bias could be involved. Finally, in some cases, FDA studies have been submitted years apart, so it is inappropriate to compare the results from one study submitted years before with another that used different and probably inferior technology. Despite these limitations, the FDA approval data provide an excellent comparison of the results of refractive procedures (see Table 5.1) as well as a good sample of the complications. This chapter includes not only a detailed analysis and comparison of the FDA data but also other independent studies in the literature to provide a balanced and more updated view of the results of the procedures.

The Evaluation of Refractive Surgery Results

The results of refractive surgery are generally reported as the percentage of eyes achieving 20/20 and 20/40 vision (efficacy) and the percentage of eyes achieving within ±0.5 D of emmetropia and ±1.0 D of emmetropia (predictability). The overall reduction in the degree of myopia and the stability of this number over the length of follow-up in the study are also reported, as is the percentage of eyes with complications.

The indices of efficacy and safety may provide the best assessment of visual improvement using the standard methods of visual assessment.[34] The efficacy index is the ratio of the preoperative best-corrected visual acuity (BCVA) divided by the postoperative UCVA, with both numbers in the decimal visual form. This value represents the result that patients truly wish to achieve—uncorrected vision at least as good as the corrected vision with their glasses or contact lenses. The safety index is the ratio of the preoperative BCVA divided by the postoperative BCVA, with both numbers in the decimal visual form. This provides an overall assessment of the changes in BCVA that allows an excellent evaluation of safety using standard vision testing. Unfortunately, these reporting methods have not been widely accepted; so, the efficacy and predictability indices will not be reported in this chapter.

Photorefractive Keratectomy

Myopia. The efficacy and the predictability of the FDA results for the various excimer lasers for PRK are found in Table 5.1. After 2000, the FDA submissions were made for LASIK results rather than for PRK results. It can be seen that the early results for PRK

TABLE 5.1 **FDA Data. FDA Results of the Various FDA Studies Reported on the FDA Web Site. Since All New Devices Require an FDA Study Review, a Tremendous Amount of Comparative Data can be Gathered**

Device	Approval range	Approval number	Approval date	Number of eyes	≥20/20	≥20/40	0.5 D	1.0 D	Loss of 2 lines BCVA	Loss > 2 lines BCVA
Conventional Myopic PRK										
Alcon Apex Plus	1–6 D myopia, 1–4 D astigmatism	P930034/S9	3/11/98	151	48.3	84.1	49	73.5	n/a	3.4
Alcon LadarVision	1–10 D myopia	P970043	11/2/98	417	69.7	95.9	77.5	92.6	1	0.5
Alcon LadarVision	1–10 D myopia with 4 D astigmatism	P970043	11/2/98	177	59.3	93.2	74.3	92	2.1	0
Bausch and Lomb 116	1.5–7.0 D myopia (results 3–4 D spherical)	P970056	9/28/99	33	42.4	81.8	48.5	87.9	0	3
Bausch and Lomb 116	1.5–7.0 D myopia with astigmatism (results 3–4 D spherical equivalent (SE))	P970056	9/28/99	35	45.7	77.5	48.6	80	0	5.7
LaserSight LSX	1–6 D myopia	P980008	11/12/99	265	55.5	87.5	58.5	81.5	n/a	0
Nidek EC5000	0.75–7 D myopia	P970053	12/17/98	441	65.5	94.8	68.6	90.2	2.2	0.3
Nidek EC5000	7–13 D myopia	P970053	12/17/98	145	45.5	80.7	42.8	68.3	2.5	3
Nidek EC5000	1–8 D myopia with 4 D astigmatism	P970053/S1	9/29/99	631	64.3	93.5	62.3	86.1	1.1	0.5
VISX Star and Star2	0–12 D myopia with 4 D astigmatism	P930016/S5	3/27/96	156	50.7	79.5	45.9	70.9	n/a	7.5
Conventional Hyperopic PRK										
VISX Star and Star2	1–6 hyperopia	P930016/S7	11/2/98	158	53.3	96	74.1	90.5	0	1
VISX Star, Star2, and Star3	0.5–5 hyperopia with 4 D astigmatism	P930016/S10	10/18/00	231	50.2	95.4	69.5	91.2	5.1	1.5
Conventional Hyperopic LASIK										
Alcon LadarVision (9 mo)	<6 D hyperopia with up to 6 D myopia astigmatism	P970043/S7	9/22/00	66	57.6	95.2	70.2	91.5	5.8	0

Bausch and Lomb 116	1–4 D hyperopia with 2 D astigmatism	P990027/S4	2/25/03	233	61.4	94.8	60	86.6	2.1	0.7
Meditec MEL 80 Excimer Laser System	Hyperopia ≤ 5 D with or without astigmatism > +0.5 D and ≤ +3 D	P060004/S1	3/28/11	160	61.9	97.5	73.8	92.5	2.5	1.9
NIDEK EC-5000 Excimer	0.5–5 D hyperopia with or without astigmatism 0.5–2.0D	P970053/S9	10/11/06	291	59.8	98.6	68.7	93.5	3.1	0.3
VISX S2 and S3	0.5–5 D hyperopia with 3 D and astigmatism	P930016/S12	4/27/01	113	54	99.1	70.7	94.7	3.8	0
Wavelight Allegretto	Hyperopia up to 6 D with astigmatism up to 5 D	P30008	10/10/03	212	67.5	95.3	72.3	90.4	n/a	1.5
Conventional Mixed Astigmatism LASIK										
Alcon LadarVision	Hyperopia < 6 D with myopic astigmatism < 6 D	P970043/S7	9/22/00	37	51.4	93.6	82	96	1.9	0
VISX S2 and S3	Mixed astigmatism up to 6 D (3-mo data)	P930016/S14	11/16/01	115	58.3	98.3	79.1	97.4	0	0.9
Custom Myopic LASIK										
Alcon LadarVision	myopia to 7 D with 0.5 D astigmatism	P970043/S10	10/18/02	139	79.9	91.4	74.8	95.7	0	0
Alcon LadarVision	Myopic astigmatism 0.5–4 D	P970043/S15	6/29/04	225	85.8	97.4	80.2	91.8	0	0
Bausch and Lomb 217Z	Myopia to 7 D with 3 D astigmatism	P990027/S6	10/10/03	117	90.1	99.1	71.3	92.4	0	0.4
Wavelight Allegretto Wave	Myopia to 7D with 3 D astigmatism	P020050/S4	7/26/06	166	93.4	99.4	94.6	98.2	9	0.6
VISX S4 Wavescan	Myopia to 6 D with 3 D astigmatism	P930016/S17	5/23/03	277	93.9	99.6	90.3	99.3	0	0
VISX S4 Wavescan	Monovision by the targeted retention of myopia to −1.25 to −2 D in nondominant eye of presbyopic myopes	P930016/S25	7/11/2007	158	84.8	98.7	89.6	99.3	1.9	0

(*continued*)

TABLE 5.1 (Continued)

Device	Approval range	Approval number	Approval date	Number of eyes	≥20/20	≥20/40	0.5 D	1.0 D	Loss of 2 lines BCVA	Loss > 2 lines BCVA
Custom Hyperopic LASIK										
VISX S4 Wavescan	Hyperopia up to 3 D and astigmatism up to 2 D	P930016/S17	12/14/04	131	61.8	95.4	58	88.5	0	0
Conductive Keratoplasty (CK)										
Keratec CK	Hyperopia from 0.75 to 3.25 D with < 0.75 D astigmatism	P10018	4/11/02	205	63	96	70	96	4	1
Keratec CK	Presbyopia (16 spots)	P10018/S5	2/6/04	81	56(J1)	90(J3)	82	97	0	2
Intacs										
Keravision Intacs	1–3 D myopia with < 0.5 D astigmatism	P980031	1/12/99	442	69	96	68	91	n/a	n/a
Phakic IOL										
Ophtec Verisyse	5–20 D of myopia with 2.5 D of astigmatism	P30028	2/5/04	581	33.2	86.7	72	94.5	n/a	0.344234079
Presbyopia										
AMO Array	Cataract—distance	P960028	9/5/97	400	39	91.5	n/a	n/a	n/a	n/a
AMO Array	Presbyopia—near	P960028	9/5/97	400	47.5	87.4	n/a	n/a	n/a	n/a
Alcon Restor	cataract—distance	P20040	3/21/05	110	29.2	92.7	n/a	n/a	n/a	n/a
Alcon Restor	presbyopia—near	P20040	3/21/05	110	30.9 (J1)	94.5 (J3)	n/a	n/a	n/a	n/a
Eyeonics Crystalens	cataract—distance	P30002	5/23/05	368	49.6	91.4	84.5	85.9	7.9	n/a
Eyeonics Crystalens	presbyopia—near	P30002	5/23/05	368	14.1 (J1)	89.1 (J3)	84.5	85.9	7.9	n/a

BCVA, best-corrected visual acuity; IOL, intraocular lens; LASIK, laser in situ keratomileusis; PRK, photorefractive keratectomy.

were modest, with only 40% to 60% of eyes achieving 20/20 UCVA. The high degree of loss of BCVA of two or more Snellen lines is of particular interest, ranging from 1% to 7%. There are few reports of the results of the use of modern excimer lasers and techniques for conventional PRK as most reports now focus on custom LASIK; however, the results have markedly improved, with 20/20 rates for conventional PRK as high as 92%.[35]

Hyperopia. Hyperopic PRK has received far less attention as compared with myopic PRK. This is because hyperopic patients make up a small proportion of the total number of refractive patients and are generally treated with LASIK rather than PRK because of concerns about regression of effect after hyperopic PRK. The FDA results for hyperopia on the VISX Star and Star2 are found in Table 5.1. An UCVA of 20/20 was achieved in about 50% of eyes, which is similar to the early myopic PRK results. Once again, there is a high loss of BCVA noted for the hyperopic PRK corrections. More recent reports on hyperopic PRK with conventional treatments have found modest results, with an UCVA of 20/40 achieved in only 81% of eyes.[36]

Mixed Astigmatism. Most reports for the treatment of mixed astigmatism have been with LASIK because of the popularity of LASIK and the concern about regression of astigmatic treatments after PRK. There have been no FDA approvals for the treatment of mixed astigmatism with PRK. One independent PRK study with the MEL 60 excimer laser of 75 eyes with mixed astigmatism found that the mean preoperative –4.20 D cylinder and +3.00 D spherical equivalent refraction decreased to –0.50 D cylinder and –0.50 D spherical equivalent refraction. An UCVA of 20/40 or better was achieved in 83% (62/75 eyes); 20/20 or better in 32% (24/75 eyes); and 13.3% (10/75 eyes) lost two or more lines of BCVA.[37] More recently, cross-cylinder or bitoric ablations and custom ablations have been used for the treatment of mixed astigmatism, which has improved the results for LASIK and would presumably benefit PRK as well.

Photorefractive Keratectomy Complications. The complications of PRK are commonly related to the healing of the stroma and the epithelium after the procedure but can also be related to the placement and the type of excimer laser treatment. Common PRK complications reported in the FDA studies are found in Table 5.2.

TABLE 5.2 The U.S. Food and Drug Administration Study of PRK with the Bausch and Lomb 116 Reported a Number of Complications that were Typical of the PRK Experience at that Time

PRK Complications with the Bausch and Lomb 116 ($n = 714$)	
Complications at 6 mo	(%)
Loss of ≥ 2 lines BCVA at 6 mo or later	7.4
BCVA worse than 20/40 at 6 mo or later	0.7
BCVA worse than 20/25 if 20/20 preoperatively	3.4
Haze ≥ trace with loss of >2 lines BCVA	0.6
Increased manifest refractive astigmatism	0.5
Postoperative IOP increase >10 mmHg	2.3
Postoperative IOP >25 mmHg	3.2
Complications at any visit	
Blepharitis	0.3
Blurry vision	0.7
Burning	1.7
Conjunctivitis	1.0
Epithelial defect	0.4
Corneal scarring	1.0
Dry eye	1.0
Foreign body sensation	4.1
Ghosting/double image	2.1
Glare	11.3
Halos	4.8
Haze	1.1
Iritis	4.1
Light sensitivity	2.4
Night driving	4.5
Pain	0.6
Patient discomfort	3.2
Recurrent erosion	0.4
Redness	0.8
Tearing	0.7
Undercorrection	0.7

BCVA, best-corrected visual acuity; IOP, intraocular pressure; PRK, photorefractive keratectomy.

Conventional Laser In Situ Keratomileusis

Myopia. The results from conventional myopic LASIK from the FDA are reported in Table 5.3. The percentage of eyes achieving 20/20 can be seen to vary widely, depending on the excimer laser used, from a low of 46.4% to a high of 88.2%. The percentage of eyes achieving 20/20 can be seen to drop as the level of myopia increases.

Hyperopia. The results of conventional hyperopic LASIK are found in Table 5.1. The higher rates of loss of BCVA in this group, with a loss of two lines of BCVA ranging from 2.1% to 5.8%, are the biggest cause for concern. The 20/20 and 20/40 rates are similar to those reported for myopic LASIK. One independent study of 43 eyes at 3 months postoperatively has reported that the Alcon LadarVision achieves better results for primary hyperopic LASIK as compared with the VISX Star S3, with an UCVA 20/20 rate of 63% versus 24% and an UCVA 20/40 rate of 84% versus 100%.[38]

Mixed Astigmatism. Only two lasers have been approved from the treatment of mixed astigmatism with conventional LASIK, the VISX, and the Alcon LadarVision. The FDA results for mixed astigmatism (Table 5.1) are comparable to the results for myopic and hyperopic LASIK.

Adverse Events/Complications. The complications reported in the Alcon LadarVision LASIK study would be similar to the complications experienced with the other lasers at this time (see Table 5.4).

Custom Laser In Situ Keratomileusis

Myopia. The FDA results for custom myopic LASIK show a vast improvement over those of conventional LASIK (Table 5.3). While there are slight differences among the results of the three systems, overall, they are remarkably similar. An UCVA of 20/20 was achieved in 79.9% to 93.9% of eyes. Another impressive result is the drop in the rate of loss of BCVA, with the highest level of 0.4% reported for a loss of more than two lines of BCVA. These BCVA loss rates are much better than those of conventional LASIK. A study comparing the custom results of the Alcon CustomCornea and the VISX CustomVue in 93 eyes found that an UCVA of 20/15 or better was achieved by 32% of CustomCornea eyes and 23% of VISX CustomVue eyes, while an UCVA of 20/20 or better was achieved by 98% of CustomCornea and 95% of CustomVue eyes.[39]

Hyperopia. At present, only the VISX laser has received FDA approval for custom hyperopic LASIK. The VISX custom hyperopic results demonstrate some improvement from the conventional hyperopic results; however, they do not achieve nearly the same efficacy and predictability of the custom myopic results (Table 5.1).

Mixed Astigmatism. While custom mixed astigmatism has recently been approved for the VISX S4 laser, these data have not been posted on the FDA web site.

Adverse Events/Complications. Interestingly, complications were uncommon in the FDA custom LASIK studies; in fact, the VISX CustomVue LASIK report listed no complications out of 277 eyes at 6 months. The improved technology and techniques of LASIK are probably responsible for this dramatic improvement in safety.

Conductive Keratoplasty

CK has been approved by the FDA for the treatment of both low hyperopia and presbyopia (Table 5.1). While the results of CK for the correction of hyperopia and presbyopia are very similar to the results of conventional hyperopic LASIK, there has been concern regarding the regression of the thermal keratoplasty effect. Figure 5.5 demonstrates the regression reported in the FDA study, with extrapolation of the regression over 4 years. The only complication in the 146 eyes at 6 months reported in the FDA trial was a decrease in BCVA by more than 10 letters due to irregular astigmatism. Most notably, there were no increases in astigmatism as were reported after FDA approval. A CK study of 38 eyes with an average of 30 months follow-up found that the UCVA was 20/20 or better in 52.5% and 20/40 or better in 89% of eyes and achieved within ±0.50 D of emmetropia in 68% and within ±1.00 D of emmetropia in 92%. No eye lost two or more Snellen lines or had an induced cylinder of

TABLE 5.3 **The FDA Study Results for Myopic LASIK Demonstrate that Success of LASIK Decreases with Increasing Levels of Myopia**

Uncorrected Vision ≥ 20/20 at 6 mo Postoperative per Preoperative Manifest Refractive Spherical Equivalent

	1.00–1.99 D	2.00–2.99 D	3.00–3.99 D	4.00–4.99 D	5.00–5.99 D	6.00–6.99 D	7.00 D and above
Autonomous	68.8% (*n* = 11)	53.8% (*n* = 14)	35.3% (*n* = 6)	45.8% (*n* = 11)	30.0% (*n* = 6)	37.5% (*n* = 3)	34.4% (*n* = 11)
B + L Technolas (3 mo)	85.7% (*n* = 21)	90.4% (*n* = 73)	83.8% (*n* = 80)	84.0% (*n* = 81)	84.2% (*n* = 57)	77.5% (*n* = 40)	90.0% (*n* = 10)
LaserSight (12 mo)	55.6% (*n* = 9)	51.5% (*n* = 33)	67.9% (*n* = 53)	45.7% (*n* = 46)	41.7% (*n* = 36)	32.1% (*n* = 109)	
Nidek	88.2% (*n* = 17)	61.2% (*n* = 152)		54.3% (*n* = 164)		38.1% (*n* = 425)	
Summit	46.4% (*n* = 28)	54.7% (*n* = 53)	41.7% (*n* = 48)	47.7% (*n* = 44)	50.0% (*n* = 52)	37.8% (*n* = 37)	32.0% (*n* = 147)
VISX	59.0% (*n* = 39)	51.7% (*n* = 58)	65.2% (*n* = 89)	64.3% (*n* = 84)	45.1% (*n* = 82)	51.1% (*n* = 94)	43.0% (*n* = 200)

Uncorrected Vision ≥ 20/40 at 6 mo Postoperative per Preoperative Manifest Refractive Spherical Equivalent

	1.00–1.99 D	2.00–2.99 D	3.00–3.99 D	4.00–4.99 D	5.00–5.99 D	6.00–6.99 D	7.00 D and above
Autonomous	100% (*n* = 16)	88.5% (*n* = 23)	100% (*n* = 17)	87.5% (*n* = 21)	70.0% (*n* = 14)	87.5% (*n* = 7)	84.4% (*n* = 27)
B + L Technolas (3 mo)	100% (*n* = 21)	100% (*n* = 21)	100% (*n* = 80)	98.8% (*n* = 81)	100% (*n* = 57)	97.5% (*n* = 40)	100% (*n* = 10)
LaserSight (12 mo)	100% (*n* = 9)	87.9% (*n* = 33)	90.6% (*n* = 53)	80.4% (*n* = 46)	77.8% (*n* = 36)	32.1% (*n* = 114)	
Nidek	94.1% (*n* = 17)	86.2% (*n* = 152)		86.6% (*n* = 164)		82.6% (*n* = 425)	
Summit	92.9% (*n* = 28)	94.3% (*n* = 53)	91.7% (*n* = 48)	95.5% (*n* = 44)	98.1% (*n* = 52)	86.5% (*n* = 37)	88.4% (*n* = 147)
VISX	97.4% (*n* = 39)	96.6% (*n* = 58)	98.9% (*n* = 89)	95.2% (*n* = 84)	96.3% (*n* = 82)	94.7% (*n* = 94)	91.5% (*n* = 200)

(*continued*)

TABLE 5.3 (Continued)

Manifest Refractive Spherical Equivalent within ±0.50 D of Intended at 6 mo Postoperative							
	1.00–1.99 D	2.00–2.99 D	3.00–3.99 D	4.00–4.99 D	5.00–5.99 D	6.00–6.99 D	7.00 D and above
Autonomous	93.8% (*n* = 15)	65.4% (*n* = 17)	75.0% (*n* = 18)	75.9% (*n* = 22)	61.9% (*n* = 13)	77.8% (*n* = 7)	60.0% (*n* = 21)
B + L Technolas (3 mo)	76.2% (*n* = 21)	89.6% (*n* = 77)	83.5% (*n* = 85)	86.9% (*n* = 84)	76.3% (*n* = 59)	73.2% (*n* = 41)	50.0% (*n* = 10)
LaserSight (12 mo)	88.9% (*n* = 9)	75.8% (*n* = 33)	63.6% (*n* = 55)	39.1% (*n* = 46)	50.0% (*n* = 38)	32.5% (*n* = 114)	
Nidek	64.7% (*n* = 17)	80.7% (*n* = 150)		67.5% (*n* = 163)		52.5% (*n* = 425)	
Summit	66.7% (*n* = 27)	78.8% (*n* = 52)	57.1% (*n* = 49)	76.5% (*n* = 51)	60.0% (*n* = 55)	66.7% (*n* = 39)	55.4% (*n* = 166)
VISX	87.9% (*n* = 33)	83.6% (*n* = 61)	86.8% (*n* = 91)	79.8% (*n* = 89)	65.9% (*n* = 91)	71.1% (*n* = 97)	61.8% (*n* = 212)

Source Document References: FDA "Summary of Safety and Effectiveness Data"	
Autonomous	PMA# P970043/S5: Table #11
B + L Technolas	PMA# 990027: Table #19
LaserSight (12 mo)	PMA# P980008: Tables #12 and #13
Nidek	PMA# P970053/S002: Table #12
Summit	PMA# P930034/S13: Tables #20 and #22
VISX	PMA# P990010: Tables #22 and #24

FDA web site: www.fda.gov/cdrh/LASIK/lasers.htm
FDA, Food and Drug Administration; LASIK, laser in situ keratomileusis.

TABLE 5.4 **The U.S. Food and Drug Administration Study of the Alcon LadarVision Laser in situ Keratomileusis (LASIK) Complications at 6 mo ($n = 324$) Represents the Typical Complications for LASIK at that Time**

Alcon LadarVision LASIK Complications at 6 mo ($n = 324$)	
Clinical findings at 6 mo	(%)
Rolled flap edge with corneal melt	0.3
Corneal abrasion	0.3
Corneal folds/striae	0
Corneal opacities	0.3
Double/ghost images	1.5
Epithelial ingrowth	1.5
Foreign body sensation	0.3
Interface debris	1.5
Superficial punctate keratitis	3.1
Subjective symptoms worse at 6 mo	
Blurring of vision	15.3
Burning	8.0
Double vision	6.3
Dryness	17.7
Excessive tearing	1.8
Foreign body sensation	5.3
Fluctuation of vision	20.7
Glare	18.6
Halos	20.7
Headache	2.7
Light sensitivity	21.4
Night driving difficulty	14.2
Pain	4.5
Quality of vision	5.2
Redness	5.4

2.00 D or greater.[40] CK has now been largely abandoned as a refractive procedure because of regression, although it is still sometimes used to correct presbyopia by the creation of "blended vision" in one eye.

Intacs

Intracorneal ring segments (Intacs) achieved good results in the FDA study that were better than those reported for conventional myopic LASIK (Table 5.1), but these results could not be duplicated by the average surgeon and the procedure has been abandoned except for the therapeutic use of Intacs for the treatment of keratoconus and post-LASIK ectasia.[41]

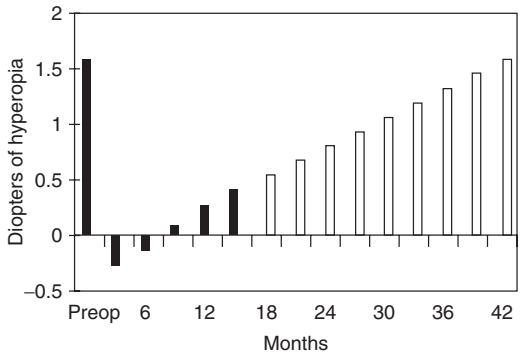


FIGURE 5.5 Extrapolation of the U.S. Food and Drug Administration data on conductive keratoplasty found that the small amount of regression reported initially in the study (*black bars*) would result in complete elimination of the effect after 48 months if the regressive trend continues (*white bars*).

Phakic Intraocular Lenses

Phakic IOLs are generally reserved for the treatment of extreme myopia or hyperopia in the pre-presbyopic age group (Fig. 5.1). While there are several phakic IOLs available worldwide, at present, only the Verisyse phakic IOL has received FDA approval, although approval for the Visian posterior chamber IOL is pending (Table 5.1). The results of efficacy and predictability for the spherical phakic IOLs are much poorer than those reported for both conventional and custom LASIK because of residual astigmatism and spherical error after implantation. Many of the eyes treated with phakic IOLs required a secondary enhancement procedure or "bioptics" to achieve results similar to those of primary LASIK.[42,43] Toric phakic IOLs that allow the treatment of high levels of ametropia and astigmatism are now available internationally, which will reduce the need for secondary enhancement procedures.

Conversely, myopic phakic IOL implantation is usually associated with an improvement in the BCVA (and therefore a high safety index), which is probably because of the reduction of minification that has not been noted with the correction of high ametropias with the corneal refractive procedures.

The myopic results with the anterior chamber angle–supported phakic IOL (Vivarte, Bausch & Lomb Surgical, Claremont, CA),[44,45] the iris-claw phakic IOL (Verisyse, previously Artisan, OPHTEC USA, Boca Raton, FL),[46] and the posterior chamber implantable contact lens (Visian, previously Intraocular Contact Lens or ICL, Staar Surgical, Monrovia, CA)[47,48] have been reported in various studies (see Table 5.5). Results for the less common phakic IOLs are scarce and are therefore not reported. The hyperopic phakic IOL results are also reported in Table 5.5 for each of the three main phakic IOLs.[49–51]

TABLE 5.5 The U.S. Food and Drug Administration Study of the Crystalens Found a Number of Complications Not Uncommon for Intraocular Surgery

Complications with the Crystalens (*n* = 324)	
	(%)
Endophthalmitis	0.3
Hyphema	0.3
Cystoid macular edema	3.7
Secondary surgery	0.6
Intraocular lens dislocation	0
Papillary block	0
Retinal detachment	0
Night vision symptoms (*n* = 130)	
Nighttime glare	
Mild	23.8
Moderate	13.8
Severe	5.4
Night driving difficulty	
Mild	17.4
Moderate	11.6
Severe	3.3
Halos	
Mild	20
Moderate	12.3
Severe	6.2

Phakic IOLs are associated with more risks than the corneal refractive procedures because phakic IOLs are intraocular procedures with greater surgical intervention in the eye (Table 5.5). The main risks of these procedures include pupil ovalization for angle-supported phakic IOLs,[44] endothelial cell loss for iris-claw phakic IOLs,[52] and anterior subcapsular cataracts for posterior chamber IOLs.[53] In the FDA study, the Verisyse IOL had an endothelial cell loss rate of 1.8% per year, which would lead to 39% of patients losing 50% of their corneal endothelial cells within 25 years of implantation.[54] A meta-analysis of three randomized controlled trials that included 228 eyes, comparing excimer laser and phakic IOLs for myopia between 6 and 20 D with up to 4.0 D of astigmatism, revealed interesting results. The phakic IOL group was less likely to lose 2 or more lines of best spectacle corrected visual acuity at 12 months (p = 0.001), and phakic IOL surgery scored more highly on patient satisfaction and preference questionnaires.[55]

Clear Lens Extraction/Refractive Lensectomy

CLE is a procedure generally reserved for extreme myopia or hyperopia (Fig. 5.1). Because CLE makes use of the IOLs generally used for cataract surgery for a refractive purpose, there is no FDA approval required as CLE uses existing technology. There is a paucity of studies involving CLE, which may be due to the lower number of eyes requiring CLE.

There is considerable controversy about the use of this technique for myopia because of the high rate of retinal detachment reported in long-term follow-up studies of high myopes.[56] The results of CLE for the treatment of high degrees of hyperopia have been equally successful as those for high myopia; however, the risk of retinal detachment does not appear to be as significant.[57]

The studies of CLE do not report detailed results regarding the efficacy of the procedure.

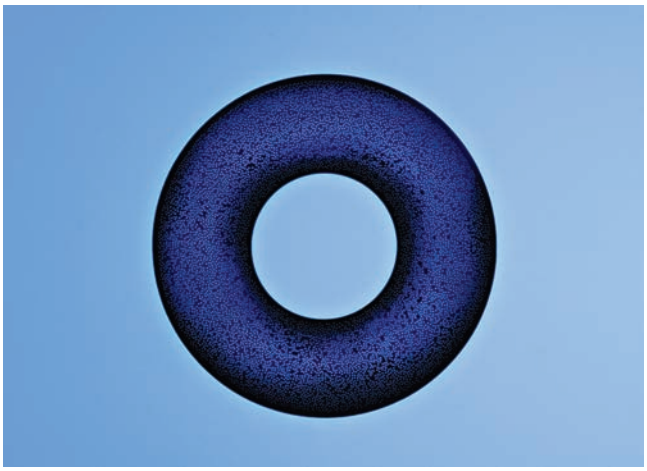


FIGURE 5.6 KAMRA™ corneal inlay for correction of presbyopia (permission to reproduce figure granted from AcuFocus, Inc.).

In terms of predictability, 1.0 D within emmetropia is achieved by 59% in myopic CLE[35] and 91.4% in hyperopic CLE.[57]

Presbyopia. Recently, several IOLs have been introduced for the treatment of cataracts and presbyopia. The FDA results for the AMO Array IOL, Alcon Restor IOL, and the Eyeonics Crystalens are found in Table 5.1. The AMO ReZoom IOL did not require a separate FDA study as it was a modification of the FDA-approved ARRAY multifocal IOL. The results for the presbyopic IOLs show an UCVA of 20/20 in 39% to 49.6% and an UCVA of 20/40 in 91.4% to 92.7% of eyes. These results are worse than those for the corneal refractive procedures because of the residual astigmatism and sphere. The predictability data were only provided for the Eyeonics IOL.

The distance corrected near visual acuity (DCNVA) may be the best assessment of the ability of the presbyopic IOLs to simultaneously correct distance and near vision. The DCNVA with the ARRAY was 43.8% at J1 and 86.6% at J3, the Restore was 30.2% at J1 and 92.1% J3, and the Crystalens was 0.8% at J1 and 88.4% at J3.[37] The DCNVA results demonstrate that while presbyopic IOLs improve the near vision, they do not provide full simultaneous correction of distance and near vision.

Another option for presbyopia management that is currently undergoing FDA studies for approval is the use of corneal inlays (Fig. 5.6) to be implanted in a patient's nondominant eye.[58]

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6 Glaucoma: Clinical Trials in Glaucoma Therapy

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Glaucoma, with its characteristic optic nerve pathology and associated visual field (VF) defects, results from a heterogeneous group of eye disorders. While many risk factors have been identified for the development and progression of glaucoma, intraocular pressure (IOP) takes center stage as the only significant modifiable risk factor, and glaucoma management currently hinges on IOP reduction. The clinical armamentarium used to achieve IOP reduction includes numerous medications as well as laser and incisional surgery. This chapter first reviews the pivotal clinical trials addressing the efficacy of lowering IOP in the treatment of glaucoma. Subsequent sections describe studies reporting on specific medical, laser, and surgical therapies for glaucoma.

I. INTRAOCULAR PRESSURE REDUCTION IN THE PREVENTION AND TREATMENT OF GLAUCOMA

Overview

The studies reviewed in this section have been instrumental in defining the modern management of glaucoma. These large, multicentered prospective studies demonstrated that lowering IOP is an effective treatment strategy. Specifically, the Ocular Hypertension Treatment Study (OHTS)[1–7] showed that lowering IOP can prevent the development of glaucoma in patients with ocular hypertension. The Early Manifest Glaucoma Trial (EMGT)[8–14] and the Collaborative Normal-Tension Glaucoma Study (CNTGS)[15–20] both demonstrated that lowering IOP decreases the risk of glaucoma progression. Finally, although the Advanced Glaucoma Intervention Study (AGIS)[21–35] was designed to compare surgical versus laser therapies in advanced glaucoma patients, this study is discussed in this section because of its importance in demonstrating the relationship between IOP control and the risk of progression in advanced glaucoma.

Ocular Hypertension Treatment Study

Results published 2002

The OHTS was a multicenter, randomized, controlled clinical trial (RCT) assessing the risk of conversion from ocular hypertension to primary open-angle glaucoma (POAG) in patients with medically lowered IOP compared to patients observed with no treatment.

Study Population

Enrolled patients had moderate-risk ocular hypertension without evidence of glaucomatous optic neuropathy.

Major Inclusion Criteria

- IOP in at least 1 eye ≥24 and ≤32 mmHg
- IOP in fellow eye ≥21 and ≤32 mmHg
- Normal and reliable Humphrey 30-2 Visual Filed VF (two consecutive)
- Normal optic discs in both eyes on clinical exam and stereo photos

Major Exclusion Criteria

- Best corrected visual acuity worse than 20/40
- Secondary causes of raised IOP including steroid use

- Narrow angles or angle closure
- Diabetic retinopathy
- Other diseases causing VF defects or optic neuropathies

Sample Size and Baseline Characteristics

1,637 subjects were recruited. Mean age was 55 years. Mean baseline IOP was 24.9 mmHg.

Intervention

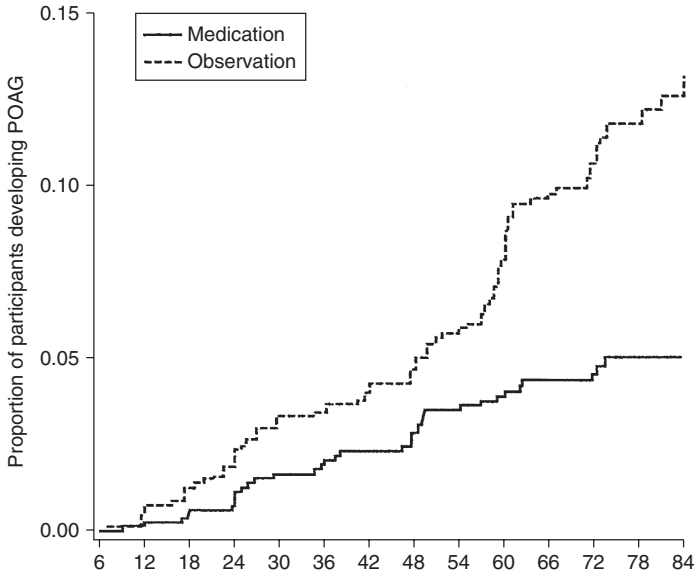
Patients were randomized to treatment using topical hypotensive medications (drug choice was at the discretion of the treating ophthalmologist; $n = 817$) or observation ($n = 819$). In the treatment arm, medications were added as needed to achieve an IOP that was both 20% below baseline and ≤24 mmHg. Follow-up was carried out every 6 months for a minimum of 5 years.

Outcome Measures

The primary endpoint was the conversion to POAG as defined by either a reproducible VF abnormality or reproducible optic disc cupping attributable to POAG. Adverse effects of treatment were also assessed.

Results

The cumulative probability of conversion to POAG was significantly lower in the treatment group versus the observation group during the course of the study (hazard ratio, 0.40; $p < 0.0001$; Fig. 6.1). Conversion to POAG



															Total
Observation Group															
At Risk	819	809	800	789	772	753	742	721	696	673	601	506	357	204	
POAG	1	5	6	10	5	3	4	9	4	24	3	9	1	5	**89**
Deaths	0	1	1	4	3	2	4	4	3	2	1	0	2	2	**29**
Inactive	9	3	4	3	11	6	13	12	12	10	4	2	0	0	**89**
Medication Group															
At Risk	817	797	787	775	759	751	739	731	708	690	648	536	372	210	
POAG	0	2	3	7	1	5	0	9	1	5	0	3	0	0	**36**
Deaths	2	2	5	3	1	0	2	3	1	0	3	2	1	1	**26**
Inactive	18	6	4	6	6	7	6	11	10	4	4	2	0	0	**84**

FIGURE 6.1 Kaplan-Meier plot of the cumulative probability of developing primary open-angle glaucoma (POAG) of the randomized group. The participants at risk were those who had not developed POAG at the beginning of each 6-month period. The number of participants classified as developing POAG is given for each interval. Participants who did not develop POAG and withdrew before the end of the study or who died are censored from the interval of their last completed visit. Reprinted with permission from *Arch Ophthalmol.* 2002;120:707.

at 5 years was 4.4% in the treatment group versus 9.5% in the observation group.

Baseline Factors Associated with Conversion to Primary Open-Angle Glaucoma

Baseline factors predictive of the development of POAG by both univariate and multivariate analysis included advanced age, higher IOP, greater pattern standard deviation, thinner central corneal thickness (CCT), and larger vertical cup-to-disc ratio. A subgroup analysis of the 25% of participants that self-identified as being African American found a higher rate of conversion to POAG in both study arms. The median follow-up for this subgroup was 78 months, with conversion to POAG occurring in 8.4% in the treatment group and 16.1% in the observation group. However, race was not an independent predictor in multivariate analysis. This was explained by African American participants having larger baseline vertical cup-to-disc ratios and thinner CCTs, which when adjusted for in the multivariate model made race nonpredictive. CCT showed a striking predictive effect on the development of POAG (multivariate hazard ratio [HR] = 1.71 per 40 μm thinner). The OHTS also highlighted the compounded risk associated with decreasing CCT and increasing baseline IOP. For example, 36% of participants in the observation group with CCT ≤ 555 μm and baseline IOP > 25.75 mmHg developed POAG within 5 years (Fig. 6.2).

Clinical Implications

The OHTS demonstrated that IOP reduction reduces the risk of conversion from ocular hypertension to POAG. However, the total number of patients developing glaucoma was quite small (9.5% in the untreated group at 5 years). This resulted in a large number needed to treat (NNT) of 20 to prevent one patient from developing early POAG. This study also highlighted some important risk factors that are predictive of conversion to POAG, such as thin CCT (especially when combined with higher

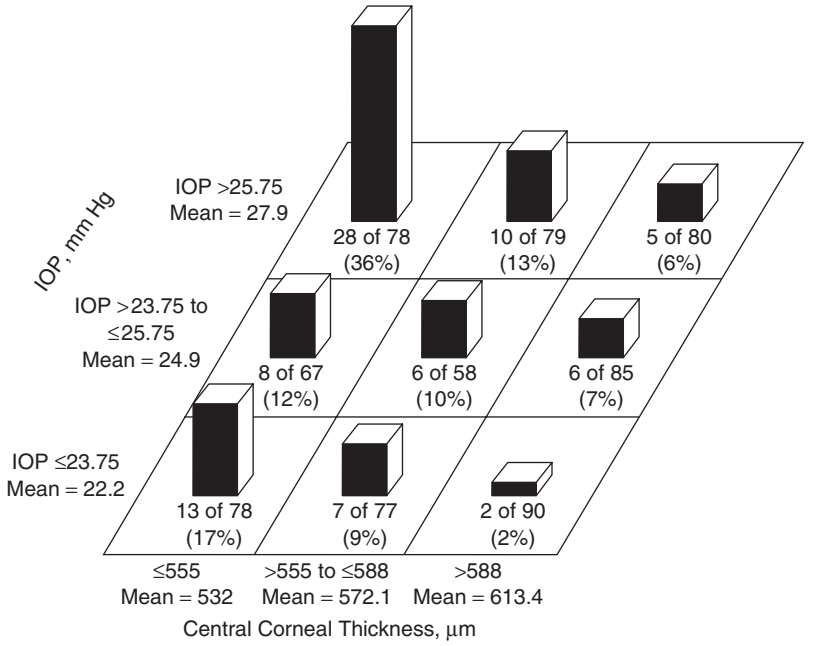


FIGURE 6.2 The percentage of participants in the observation group who developed primary open-angle glaucoma (median follow-up 72 months) grouped by baseline intraocular pressure (IOP) of ≤23.75, >23.75 to 25.75, and >25.75 mmHg and by CCT measurements of 555, >555 to 588, and >588 μm. These percentages are not adjusted for length of follow-up. Reprinted with permission from Arch Ophthalmol. 2002;120:718.

baseline IOP). Hence, using these predictive factors and risk calculations now allows clinicians to more accurately predict risk in individual patients in order to refine treatment decisions. Notably, while the OHTS found that increased pattern standard deviation and cup-to-disc ratio were predictive factors of conversion to POAG, patients with these findings at baseline may have already had early glaucoma. This would not be expected to alter the main findings of this trial, but could affect its generalizability.

Early Manifest Glaucoma Trial

Results published 2002

The EMGT was a multicenter, randomized, unmasked, controlled clinical trial designed to determine if lowering IOP in newly diagnosed glaucoma patients decreases the risk of disease progression.

Study Population

The EMGT enrolled patients with early-stage OAG. In order to identify patients with glaucoma that had not yet received treatment for their disease, a screening program was undertaken at multiple sites in Sweden, ultimately screening over 44,000 people to accrue an appropriate number of patients for the study.

Major Inclusion Criteria

- Newly diagnosed, untreated OAG
- Diagnosis based on repeatable VF defects in at least one eye compatible with glaucoma (based on the Glaucoma Hemifield Test), not explained by other causes
- Included POAG, normal-tension glaucoma, and exfoliative glaucoma

Major Exclusion Criteria

- Advanced VF defects (mean deviation [MD] worse than –16 dB), or threat to fixation
- Mean IOP > 30 mmHg or any IOP > 35 mmHg

Sample Size and Baseline Characteristics

A total of 255 patients were included in the study. The mean age was 68 years and 66% were females. Average IOP was 20.6 mmHg and median VF MD was –4 dB; 25 patients (10%) had pseudoexfoliation.

Intervention

Patients were randomized to treatment with topical betaxolol plus a single session of 360° argon laser trabeculoplasty (ALT; $n = 129$) or to observation ($n = 126$). There was no specific target IOP in this study; however, the protocol did specify the addition of latanoprost if IOP exceeded 25 mmHg in the treatment group. Follow-up was carried out every 3 months for a minimum of 4 years.

Outcome Measures

Progression of glaucoma was the primary outcome—defined as VF progression (at least three progressing test points in the same location in three consecutive VF tests compared to baseline) or optic disc changes (identified by flicker chronoscopy and confirmed by nonflicker side-by-side photo comparisons).

Results

In the treatment group, the mean IOP was reduced from 20.6 to 15.5 mmHg (25% reduction) and the reduction was maintained throughout the study period. IOP was not significantly changed in the observation group. The median follow-up times were 66 and 69 months for the treatment and control groups, respectively. Progression of glaucoma was more common in the control patients, occurring in 62% of patients (78/126) compared to 45% (58/129) of treated patients ($p = 0.007$). Figure 6.3 shows progression over time in all study patients and demonstrates an early separation between study arms that was maintained throughout. Median time to progression (Kaplan-Meier cumulative survival) was 48 months in controls compared to 66 months in treated patients, indicating a delay in progression with treatment. All except one patient that met the criteria for progression did so based on VF criteria (with or without optic disc changes).

Baseline Factors Associated with Progression

Baseline factors associated with progression in multivariate analysis included older

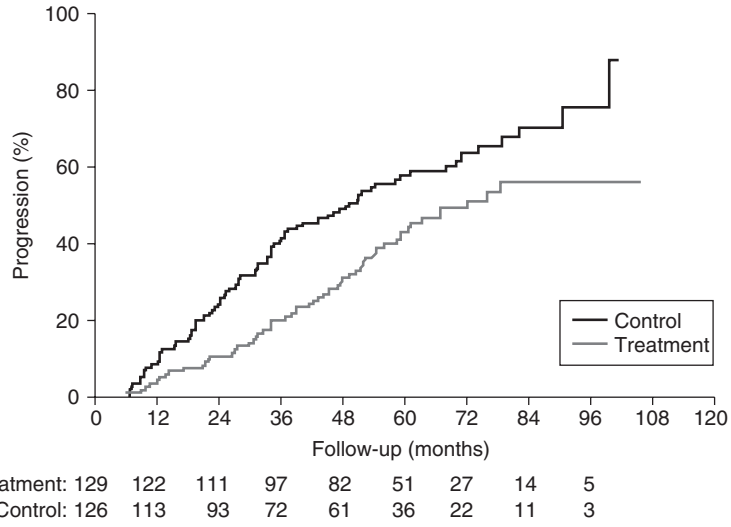


FIGURE 6.3 Progression across time in patients of the study group. The cumulative probability of patients with progression was larger in the control group than in the treatment group ($p = 0.007$). The number of patients at risk for progression of glaucoma in the treatment group and control group is shown below the *x*-axis. Reprinted with permission from *Arch Ophthalmol.* 2002;120:1272.

age (>67 years; HR 1.47), higher IOP (> 21 mmHg; HR 1.70), more negative MD (≤–4 dB; HR 1.58), and the presence of pseudoexfoliation (HR 2.22). Higher frequency of disc hemorrhages at follow-up visits was also associated with progression.

Clinical Implications

The EMGT was the first large RCT (and likely the last) in which patients with manifest glaucoma and elevated IOP could be randomized to observation alone. This study showed that a pressure reduction of 25% in newly diagnosed glaucoma patients decreases the risk of progression, with an NNT of approximately 6 (over approximately 6 years). The EMGT enrollment protocol, which consisted of a population screening program, yielded a study patient sample that was highly reflective of the underlying population with glaucoma. This, combined with the high patient retention and rigorous study protocol, supports the validity and generalizability of the results. While the high rate of glaucoma progression observed may have resulted from overly sensitive VF progression criteria, these criteria were necessary from an ethical standpoint in order to detect the earliest progression in the observation group. Because this effect was nondifferential, it would not be expected to influence the overall study conclusions.

In contrast to the OHTS, which identified conversion to POAG in the majority of patients based on optic disc changes,[3] the EMGT found progression by VF criteria in an overwhelming majority of the patients that progressed. This highlights differences between the studies in the relative sensitivity of the VF and optic nerve criteria used to define progression.

Collaborative Normal-Tension Glaucoma Study

Results published 1998

The CNTGS was a multicenter, randomized, controlled, unmasked trial designed to determine if lowering IOP decreases the risk of progression in normal-tension glaucoma.

Study Population

The target population for this study was patients with "normal-tension" glaucoma.

Major Inclusion Criteria

- Glaucomatous optic disc and VF abnormalities based on three reliable static-perimetry VFs
- Median untreated IOP (or IOP after a 4-week medication washout) ≤20 mmHg with no measurements >24 mmHg and not more than one measurement of 23 to 24 mmHg
- Evidence of disease progression, a VF defect threatening fixation, or an optic disc hemorrhage

Major Exclusion Criteria

- Use of a systemic beta-blocker or clonidine
- Presence of a nonglaucomatous condition causing VF defects
- Previous laser or intraocular surgery
- Visual acuity less than 20/30

Sample Size and Baseline Characteristics

A total of 230 patients were enrolled in the evaluation for eligibility phase of the study; 145 eyes of 145 patients ultimately met the criteria for randomization. The mean baseline IOPs were 16.1 and 16.9 mmHg in the observation and treatment groups, respectively. The mean age of patients was 66 years.

Intervention

Patients were randomized to observation (n = 79) or a 30% IOP reduction (n = 61) using medical or surgical intervention, at the discretion of the treating clinician. Treatment was augmented as required in the latter group to maintain a 30% reduction from baseline throughout the study period, except in those undergoing filtration surgery, where a 20% IOP reduction was accepted in order to limit the number of procedures a patient would undergo. Patients were followed every 3 months for the first year and every 6 months thereafter. If the endpoint of disease progression was reached, therapeutic constraints were lifted and patients were treated at the discretion of the treating clinician.

Outcome Measures

The primary endpoint was disease progression as defined in the protocol by VF progression (scotoma deepening, expansion, or newly appearing) verified by two of three VFs done within 1 month, and two of three VFs done 3 months later, or optic disc change (stereophotographs agreed upon by two experts). An additional VF analysis was included, which defined progression as having occurred when four-of-five consecutive VFs showed deterioration relative to baseline ("four-of-five" criterion).

Results

During the study period, IOP was unchanged at 16.0 mmHg in the observation group and was reduced to an average of 10.6 mmHg in the treatment group (37% reduction). Using the primary VF endpoints, 35% of the control group and 12% of the treatment group progressed over 5 years (p = 0.0001). Using the "four-of-five" analysis of progression, the difference was smaller, however still significant, with 30% of the control group and 18% of the treatment group showing progression (p = 0.01). It is important to note that when an intent-to-treat analysis was performed, there was no significant difference in progression between the two groups, with 39% and 33% of the observation and treatment groups showing progression, respectively (p = 0.21; Fig. 6.4). However, after adjusting the VF data to account for cataract development, the difference in progression between the two groups in the intent-to-treat analysis became significant, with 27% and 13% of patients in the observation and treatment groups, respectively, showing progression at 5 years (p = 0.0018; Fig. 6.5). Indeed, cataract developed in 14% of the control group and 38% of the treatment group (p = 0.0011), which was attributable to the treatment patients who underwent glaucoma surgery.

Baseline Factors Associated with Progression

Female gender (adjusted risk ratio [RR] 1.85), history of migraine (adjusted RR 2.85), and baseline disc hemorrhage (adjusted RR 2.72) were positively associated with VF progression. Surprisingly, age and higher IOP were not predictive.

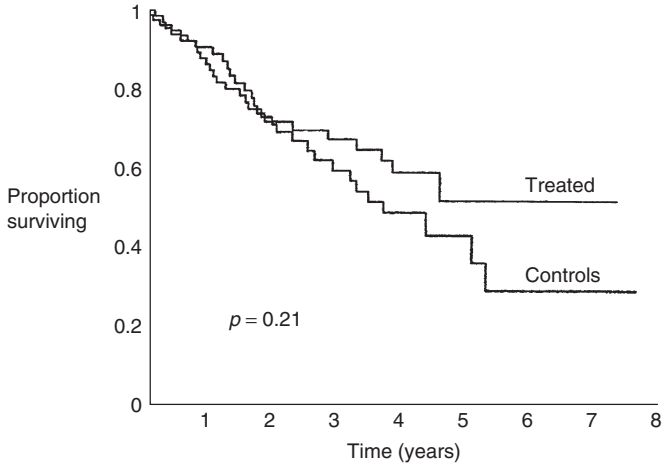


FIGURE 6.4 Survival curves of endpoints in untreated control subjects and treated patients from visual field baselines obtained at randomization using 4/5 defined endpoints. Reprinted with permission from *Am J Ophthalmol*. 1998;126:502.

Clinical Implications

The CNTGS, like the EMGT, was an important study as it compared IOP reduction to no treatment in a group of patients with manifest glaucoma. The CNTGS conclusively demonstrated that there is an IOP-dependent component of disease progression in many patients with IOPs in the statistically "normal" range.

The findings of the CNTGS indicate that treating patients with normal-tension glaucoma to achieve an IOP reduction of 30% delays progression of disease, with an NNT of approximately 7 over a 5-year period. However, it is important to highlight that many patients in the observation arm of the CNTGS did not progress. Further, 85 of 230 patients (37%) initially assessed as having glaucomatous discs

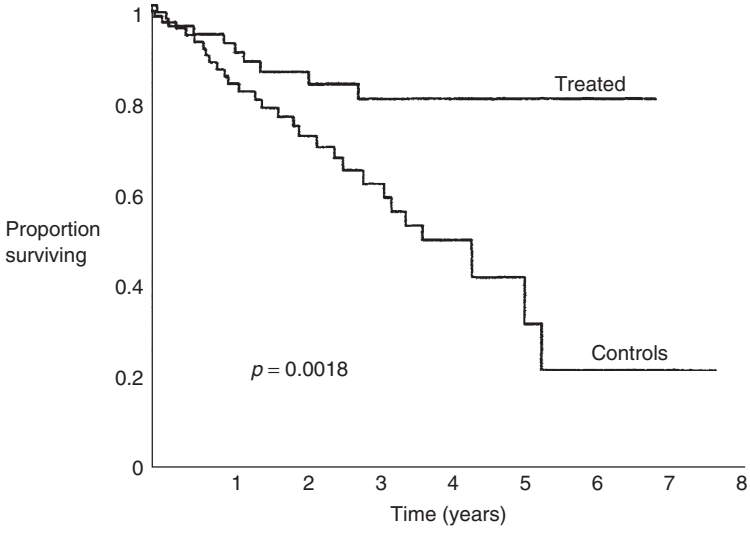


FIGURE 6.5 Survival curves of endpoints in untreated control subjects and treated patients from visual field baselines obtained at randomization using 4/5 defined endpoints with data on eyes developing cataracts, censored at the time of the diagnosis of the cataract. Reprinted with permission from *Am J Ophthalmol*. 1998;128:503.

and repeatable VF defects failed to show any change in VF and thus were never randomized. Hence, the NNT in standard clinical settings is, in reality, much higher. At the other end of the spectrum, several patients progressed in the treatment arm despite a 30% reduction in IOP, supporting the concept of IOP-independent mechanisms of disease progression in patients with normal-tension glaucoma. These findings highlight the importance of identifying patients at risk for progression to visual disability in order to tailor clinical management accordingly.

Advanced Glaucoma Intervention Study

Results published 1998 to 2004

The AGIS was a multicenter, randomized, unmasked clinical trial, designed to determine the optimal steps in the management of patients with advanced glaucoma for whom medical therapy has failed. Specifically, the AGIS investigated whether ALT or trabeculectomy should be the next treatment in such patients. While the AGIS was designed to evaluate the optimal sequence of interventional treatment, the study is covered in this section as it ultimately provided important general information regarding the relationship between IOP control and VF deterioration in patients with advanced glaucoma.

Study Population

The target population for this study was patients with "advanced" OAG no longer controlled by maximal medical therapy.

Major Inclusion Criteria

- Meeting the criteria for uncontrolled advanced OAG based on IOP, VF defect, and optic disc damage
- Phakic status
- Maximal medical therapy
- VA ≥ 20/80

Major Exclusion Criteria

- Secondary glaucoma
- Previous laser (except iridotomy) or incisional surgery
- Other eye pathology or VF defect not attributable to glaucoma

Sample Size and Baseline Characteristics

A total of 591 patients (789 eyes) were enrolled; 42% of the patients self-identified as white and 56% as black. The median age was 67 years, and the mean baseline IOP was 24.0 mmHg.

Intervention

Eyes were randomized to one of two treatment sequences:

- TAT sequence: step 1—trabeculectomy; step 2—ALT (if trabeculectomy failed); step 3—trabeculectomy (if ALT failed)
- ATT sequence: step 1—ALT; step 2—trabeculectomy (if ALT failed); step 3—trabeculectomy (if first trabeculectomy failed)

If both eyes of an individual were enrolled in the study, the first eye enrolled was randomized and the fellow eye assigned to the alternate treatment sequence. If eyes failed all three steps in their respective sequence, additional treatment was offered at the discretion of the treating clinician. Duration of follow-up was at least 4 years, with numerous analyses extending to longer periods.

Outcome Measures

The primary outcome assessed was visual function, including loss of VA or VF deterioration. VF defects were scored from 0 (no defect) to 20 (end stage) based on the number and depth of depressed test sites. Numerous AGIS publications report on additional outcomes including complications of surgery, cataract formation, bleb encapsulation, and filtration surgery failure.

Results

The AGIS reported primary results stratified by race. Overall, at the 10-year report, there was a trend toward more VF progression in the TAT sequence in the black subpopulation; however, this did not reach statistical significance. In contrast, the white subpopulation demonstrated greater VF loss with the ATT sequence, which became statistically significant at follow-up years 8 to 10. The proportion of eyes with decreased visual acuity was greater in the TAT sequence in both black

and white subpopulations in the early follow-up period but was not significantly different between the TAT and ATT groups from years 2 through 10.

While the objective of AGIS was to compare different sequences of interventional surgical management in advanced glaucoma, the most often quoted and arguably the most sustainably useful data generated from this study relate to IOP control and its relationship to VF progression. AGIS addressed this relationship through two analyses. First, a predictive analysis investigated whether IOP level during early follow-up was predictive of subsequent VF deterioration over the next 7 years. A total of 738 patients were divided into three groups based on their average IOP during the first 18 months of follow-up, and rates of subsequent VF deterioration among each group were compared. Figure 6.6 demonstrates the results of this predictive analysis and shows a considerable difference in the rate of VF progression dependent on early IOP levels. Second, an associative analysis (Fig. 6.7) was designed to determine the effect of elevated IOP measurement frequency on VF progression. Specifically, 586 eyes were divided into four groups defined by the percent of visits with an IOP less than 18 mmHg, and the rates of VF progression were compared. A striking relationship between IOP control and VF stability

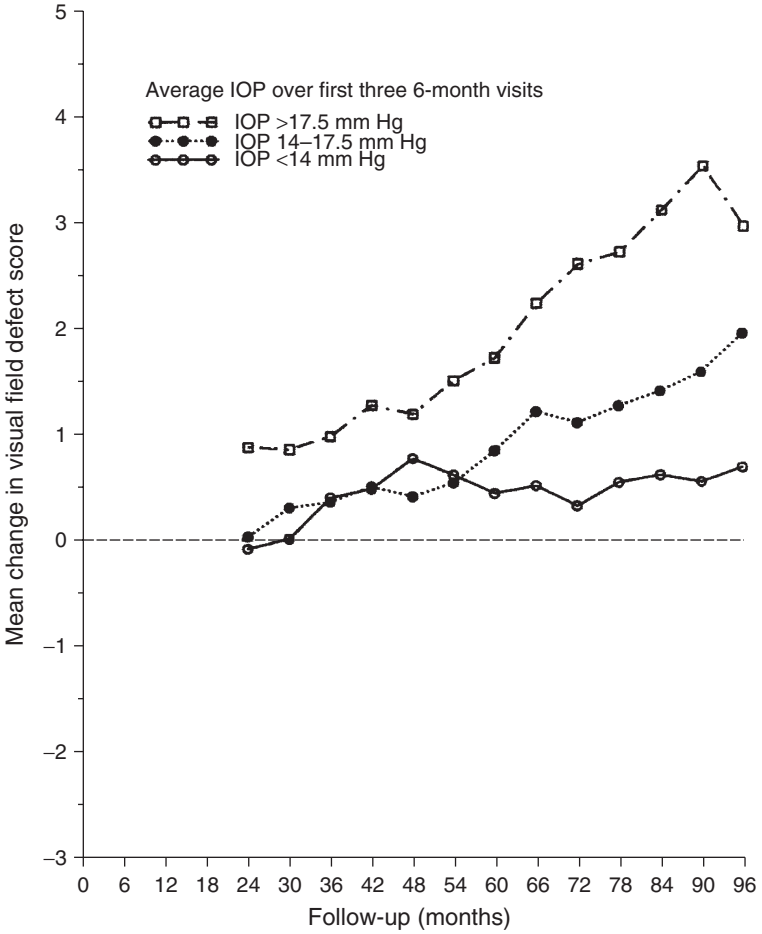


FIGURE 6.6 Predictive analysis. Mean change from baseline in visual field (VF) defect score by intraocular pressure classified according to average value over the first three 6-month visits. Reprinted with permission from *Am J Ophthalmol*. 2000;130:434.

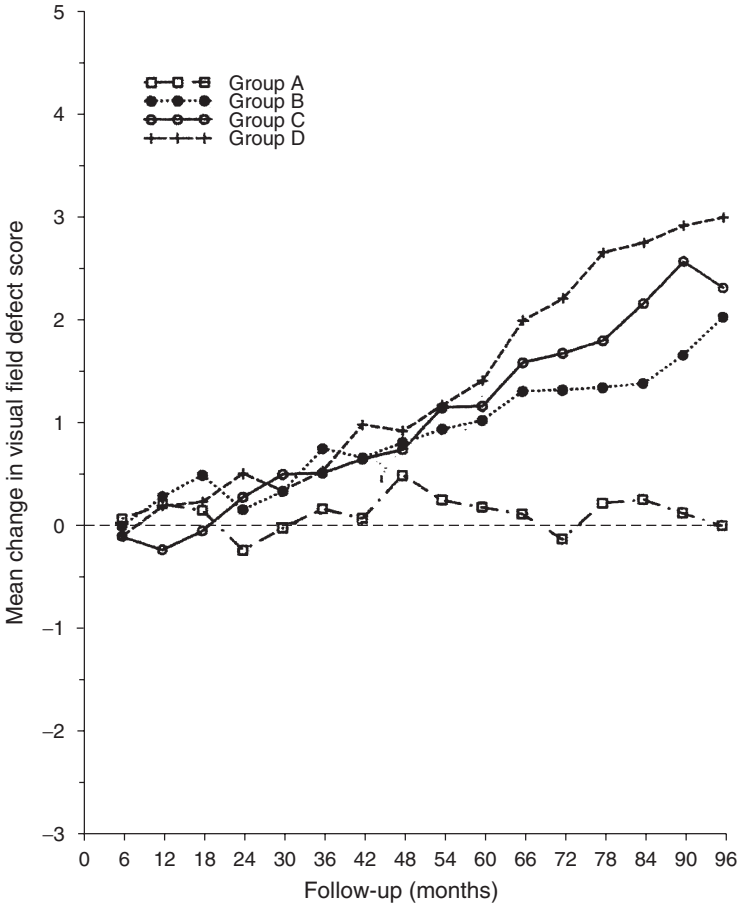


FIGURE 6.7 Associative analysis. Mean change in visual field (VF) defect score by percent of visits over 6 years at which an eye presented with intraocular pressure <18 mmHg (group A is 100%, group B is 75% to <100%, group C is 50% to <75%, and group D is 0% to <50%.). Reprinted with permission from *Am J Ophthalmol*. 2000;130:437.

was demonstrated, with patients who had an IOP less than 18 mmHg at all visits (group A, mean IOP of 12.3 mmHg) showing no change in mean VF score.

The AGIS also showed that the rate of cataract development was higher in the TAT sequence than in the ATT sequence (56% and 47%, respectively). Additionally, younger age and higher preintervention IOP were risk factors for both ALT and trabeculectomy failure, while diabetes and postoperative complications were associated with trabeculectomy failure. Male gender was found to be a risk factor for bleb encapsulation.

Clinical Implications

Strengths of AGIS include its large size, long follow-up period, racially heterogeneous patient population, and numerous subgroup analyses. Criticisms of AGIS include the lack of well-defined endpoints for treatment failure as well as the changing use of antimetabolites in filtration surgery during the study period. The types of medications available at the time of AGIS were also much more limited than today, reducing the generalizability of some of the findings.

While AGIS provided some clinically applicable data regarding ALT and trabeculectomy outcomes, the associative and predictive analy-

ses of IOP control and VF progression have become instrumental in generating IOP targets in advanced glaucoma. Specifically, the associative analysis demonstrated that IOPs consistently below 18 mmHg stabilize the VF in many patients. This subgroup had an average IOP of 12.3 mmHg, which has resulted in many clinicians choosing 12 mmHg as a target in very advanced POAG. However, it is important to note that while there was no change in mean VF score in this subgroup as a whole, individually some patients showed VF deterioration (14.4% had worse VF defect score at 7 years) despite never having an IOP above 18 mmHg. The overall stability of this subgroup's mean IOP score was due to a counterbalancing improvement in many patients' VFs.

II. MEDICAL MANAGEMENT OF GLAUCOMA

Overview

Despite the lack of recent breakthroughs, over the past two decades the medication options for lowering IOP have improved considerably. Modern topical hypotensive agents show greater IOP-lowering ability with improved side-effect profiles compared to older agents. The drug classes typically used in glaucoma practice include beta-blockers, alpha-agonists, carbonic anhydrase inhibitors, and prostaglandin analogs. There have been numerous clinical trials demonstrating the efficacy of these agents in lowering IOP—the surrogate outcome for most glaucoma medication clinical trials. Given the large number of agents and clinical trials in this area, this section presents important meta-analyses that synthesize some of these trials.

Intraocular Pressure Lowering Effects of All Commonly Used Drugs

Results published 2005

This meta-analysis reported on the IOP-lowering effects of the most commonly used glaucoma drugs, including beta-blockers, alpha-agonists, prostaglandin analogs, and carbonic anhydrase inhibitors, based on data from RCTs, primarily within populations of patients with POAG and ocular hypertension.[36]

Included Studies

A total of 28 eligible RCTs of sufficient quality were identified for inclusion in the meta-analysis.

Major Inclusion Criteria for Studies

- RCTs (either comparison of two drugs or drug vs. placebo)
- At least 85% of patients in study with POAG or ocular hypertension
- IOP as the study's primary endpoint

Outcome Measure

The outcome measure analyzed was the change in IOP from baseline to the 1-month follow-up visit. In studies where IOP at 1 month was not reported, the first measurement after 1 month was accepted up to a maximum of 6 months after drug initiation. Both peak and trough measurements were analyzed.

Results

Table 6.1 shows the mean change in IOP for each drug at peak and trough.

Clinical Implications

These results support the shift among many clinicians to utilizing prostaglandin analogs as first-line agents in medical monotherapy for POAG and ocular hypertension. However, the results underscore the efficacy of all of the listed drugs. Hence, an assessment of variables such as cost, likelihood of compliance, and side effects is also necessary in making rational therapeutic choices for individual patients.

Intraocular Pressure Lowering Effects of All Commonly Used Drugs in Normal-Tension Glaucoma

Results published 2009

This meta-analysis focused on RCTs evaluating commonly used glaucoma medications in the treatment of normal-tension glaucoma.[37]

TABLE 6.1 Relative Change in Intraocular Pressure in POAG and Ocular Hypertension

		Mean percent IOP reduction from baseline (95% confidence limits)	
Drug class	Generic name	Peak	Trough
Prostaglandin analogs	Bimatoprost	33 (35–33)	28 (29–27)
	Travoprost	31 (32–29)	29 (32–25)
	Latanoprost	31 (33–29)	28 (30–26)
Beta-blockers	Timolol	27 (29–25)	26 (28–25)
	Betaxolol	23 (25–22)	20 (23–17)
Alpha-agonists	Brimonidine	25 (28–22)	18 (21–14)
Carbonic anhydrase inhibitors	Dorzolamide	22 (24–20)	17 (19–15)
	Brinzolamide	17 (19–15)	17 (19–15)

Included Studies

A total of 15 eligible RCTs of sufficient quality were identified for inclusion in the meta-analysis.

Major Inclusion Criteria for Studies

- RCTs (either comparison of two drugs or drug vs. placebo)
- Patients diagnosed with normal-tension glaucoma
- IOP as the study's primary endpoint

Outcome Measure

The outcome measure analyzed was the change in IOP from baseline to the 1-month follow-up visit, or the closest time point, with a range from 0.5 to 3 months. Peak, trough, and diurnal IOP measurements were analyzed.

Results

Brimonidine showed the greatest IOP reduction at peak, but demonstrated a relatively small trough reduction, and therefore, the prostaglandin analogs demonstrated the greatest overall mean reduction at peak and trough of approximately 20%. Table 6.2 lists the agents in their respective classes and their IOP-lowering effect at peak and trough as reported in the meta-analysis.

Clinical Implications

These results suggest that the IOP-lowering capabilities of the commonly used glaucoma medications have a similar rank order in normal-tension glaucoma and POAG. However, all medications achieve a smaller percent decrease in IOP from baseline in normal-tension glaucoma than in POAG. This suggests that medical monotherapy will not be adequate in many patients with normal-tension glaucoma should a 30% IOP reduction target be required.

Intraocular Pressure Lowering Effects of Commonly Used Drugs when Combined with Prostaglandin Analogs

Results published 2010

Given the superior IOP-lowering effect and good safety profile of prostaglandin analogs, these drugs have become a common first-line therapy in the medical management of glaucoma. This meta-analysis was designed to estimate the efficacy and safety of the remaining three major drug classes when added to a prostaglandin analog.[38]

Included Studies

A total of 10 eligible RCTs of sufficient quality were identified for inclusion in the meta-analysis.

Major Inclusion Criteria for Studies

- Randomized, controlled, masked trial (either comparison of two drugs or drug vs. placebo)

TABLE 6.2 Relative Change in Intraocular Pressure in Normal Pressure Glaucoma

		Mean percent IOP reduction from baseline (95% confidence limits)	
Drug class	Generic name	Peak	Trough
Prostaglandin analogs	Bimatoprost	21 (16–25)	18 (14–22)
	Latanoprost	20 (17–24)	20 (18–23)
Beta-blockers	Timolol	15 (12–18)	18 (8–27)
	Betaxolol	12 (1–23)	Not reported
Alpha-agonists	Brimonidine	24 (17–31)	11 (7–14)
Carbonic anhydrase inhibitors	Dorzolamide	14 (8–9)	12 (–7 to 31)
	Brinzolamide	13 (6–20)	Not reported

IOP, intraocular pressure.

- At least 80% of patients in trial with OAG (and elevated IOP) or ocular hypertension
- Minimum duration of therapy with adjunctive agent of 10 days

Outcome Measures

The primary outcome analyzed was the mean IOP reduction from baseline (while receiving a prostaglandin analog) following initiation of the adjunctive therapy. Peak, intermediate, and trough IOP-lowering effects were defined as occurring 1 to 4, more than 4 and less than 9, and 9 to 12 hours after the adjunctive drug, respectively. The frequency of adverse events and discontinuation of the study drug were also assessed.

Results

All three classes of ocular hypotensives significantly lowered IOP from baseline, with mean IOP reductions at peak of 2.51, 2.68, and 3.16 mmHg for beta-blockers, carbonic anhydrase inhibitors, and alpha-agonists, respectively. Among the drug classes, there were no statistically significant differences in IOP-lowering effect at peak measurement. However, intermediate and trough measurements showed a statistically greater IOP reduction with beta-blockers (intermediate = 2.97 mmHg; trough = 3.92 mmHg) and carbonic anhydrase inhibitors (intermediate = 2.96 mmHg; trough = 2.98 mmHg) compared to alpha-agonists (intermediate = 1.98 mmHg; trough = 2.01 mmHg). Treatment-related adverse events resulting in discontinuation occurred in 0.40%, 2.34%, and 5.40% of subjects receiving beta-blockers, carbonic anhydrase inhibitors, and alpha-agonists, respectively.

Clinical Implications

The addition of a second topical hypotensive agent to a prostaglandin analog appears to be effective in further reducing IOP with all three classes of commonly used drugs. The effect appears to be approximately equal at peak measurement (with a trend toward alpha-agonist superiority); however, alpha-agonists appear to be somewhat inferior to the other two classes when measured at trough and intermediate time points. Additionally, in this meta-analysis, alpha-agonists had a higher rate of discontinuation due to adverse events.

III. LASER THERAPY IN OPEN-ANGLE GLAUCOMA

Overview

Laser trabeculoplasty has become an important treatment modality in the management of OAG. This treatment not only avoids problems related to medication compliance and side effects but also offers an additional step in the glaucoma treatment algorithm.

However, the optimal type of laser therapy and its position in the treatment algorithm remain controversial.

In general, trials of procedural interventions are more difficult to conduct than studies of drug therapies, and this is reflected in the relatively small number of high-quality studies of laser trabeculoplasty. The Glaucoma Laser Trial (GLT)[39–45] was a landmark trial that demonstrated the efficacy of ALT and its role as a potential first-line treatment in POAG. Since the GLT, selective laser trabeculoplasty (SLT) has been developed as an alternative to ALT and has gained popularity with many clinicians because it offers similar efficacy to ALT with less structural damage to trabecular meshwork (and therefore theoretically greater repeatability) and is somewhat technically easier to administer. While numerous retrospective and small prospective studies exist in this area, we present the larger RCTs comparing SLT to ALT,[46] and those comparing SLT and ALT to medical therapy.[39–45,47,48]

The Glaucoma Laser Trial

Results published 1990

The GLT was a multicenter, unmasked, RCT comparing the efficacy and safety of ALT versus medication as first-line therapy for POAG.

Study Population

The GLT enrolled patients with newly diagnosed POAG embarking on glaucoma therapy.

Major Inclusion Criteria

- Newly diagnosed POAG as evidenced by IOP ≥ 22 mmHg in both eyes plus glaucomatous VF defects in at least one eye; or IOP ≥ 27 mmHg in one eye and IOP ≥ 31 mmHg in the other eye and a cup/disc ratio difference of ≥0.3; or IOP ≥ 31 mmHg in both eyes and a cup/disc ratio of ≥0.8 in at least one eye.
- Inter-eye IOP ratio ≤1.5
- VA ≥ 20/70

Major Exclusion Criteria

- No history of glaucoma treatment within 6 months or any use of glaucoma medication for >14 days
- Secondary OAG
- Previous intraocular or laser surgery
- Severe VF defects, threatening fixation

Sample Size and Baseline Characteristics

A total of 271 patients were randomized in the GLT. Mean age of patients was 60 years and mean baseline IOP was 27 mmHg. The patient population was racially heterogeneous with 46%, 44%, and 10% self-identifying as white, black, and Hispanic, respectively.

Intervention

One eye of each patient was randomly selected to receive ALT or medication as the initial treatment modality. The contralateral eye subsequently received the alternative treatment. ALT was initially administered to 180° of the trabecular meshwork, with a second ALT treatment performed 4 weeks later on the remaining 180° of meshwork. Medically treated eyes commenced timolol 0.5% the evening that the first ALT session occurred in the contralateral eye. Patients were initially examined weekly and then every 3 months, with a median follow-up of 7 years and maximum of 9 years in the GLT follow-up study.

Target IOP was set at <22 mmHg or at least a 20% reduction from baseline IOP. This reference IOP could be changed by the attending ophthalmologist if VF progression occurred. Patients were stepped up to the next medical agent (i.e., initiation of timolol for the ALT-first eyes or advanced to the next drug class for the medicine-first eyes) as per a stepwise protocol (Table 6.3) if IOP was deemed above target at follow-up visits.

Outcome Measures

The primary outcome measure was the number of medications needed to control IOP. Secondary outcomes included overall IOP control and any deterioration in VF, optic disc or visual acuity. Adverse events were also noted, including early IOP spikes following ALT.

Results

ALT-treated eyes demonstrated a mean decrease in IOP of 9 mmHg (33%), while

TABLE 6.3 Stepwise Protocol for Medications in the Glaucoma Laser Trial

Step 1—Timolol 0.5% bid
Step 2—Dipivefrin 0.1% bid
Step 3—Low-dose pilocarpine qid
Step 4—High-dose pilocarpine qid
Step 5—Timolol 0.5% bid plus high-dose pilocarpine qid
Step 6—Dipivefrin 0.1% bid with high-dose pilocarpine qid
Step 7—Release from stepped regimen/treatment as per treating ophthalmologist

timolol-treated eyes had a mean decrease of 7 mmHg (26%). Thereafter, during the first 2 years, ALT-first eyes continued to have an average IOP that was 2 mmHg lower than the medication-first eyes. At the 2-year follow-up point, 44% of the ALT-first eyes continued to have adequate IOP control with ALT alone, whereas 30% of the medication-first eyes were controlled by timolol alone ($p < 0.001$); 89% of the ALT-first eyes and 66% of the medication-first eyes were controlled within the therapeutic medication regimen ($p < 0.001$). Not surprisingly, significantly more medication-first eyes required two or more agents to control IOP when compared to ALT-first eyes.

By the 3.5-year follow-up point, each of the measures of VF status (number of abnormal test locations, percentage of eyes with confirmed VF deterioration, and confirmed localized improvement) indicated a slightly better status for eyes treated with ALT first compared to medications first. Immediate postoperative IOP spikes occurred quite frequently in the GLT study. At 1-hour post-ALT, 14% of the eyes had an IOP between 6 and 10 mmHg above the prelaser level and a further 7% had an IOP > 10 mmHg above baseline.

Clinical Implications

The GLT demonstrated that primary treatment with ALT generally results in slightly greater IOP reduction than timolol, with fewer medical agents needed to control IOP. However, systemic absorption of timolol may lower IOP in the contralateral eye and may have altered the observed IOP in the ALT-first eyes. Further, the rate of initial IOP spikes with ALT suggests that this treatment modality may not be suitable for patients with advanced VF defects threatening fixation.

The applicability of results from the GLT is somewhat limited by the subsequent introduction of new, more efficacious glaucoma medications and SLT. Additionally, the finding that more patients showed VF improvement than progression, along with the IOP-based eligibility criteria, suggests that some study patients may not have had glaucoma, making it difficult to interpret the long-term VF progression results.

Selective Laser Trabeculoplasty versus Argon Laser Trabeculoplasty

Results published 2006

This was a single-center, RCT comparing the efficacy of SLT to that of ALT in patients with OAG uncontrolled on maximal medical therapy.[46]

Study Population

This study enrolled patients with OAG and IOP above target.

Major Inclusion Criteria

- OAG (including pseudoexfoliation and pigment dispersion)
- IOP ≥ 16 mmHg and on maximal medical therapy or having had a previous failed 180° or 360° ALT (>6 months previously)

Major Exclusion Criteria

- VF defect within 10° of fixation
- Previous incisional glaucoma surgery
- Corneal disease precluding accurate IOP measurement or trabecular meshwork visualization

Sample Size and Baseline Characteristics

A total of 152 patients (176 eyes) were enrolled. Average age of the patients was 70 years, and baseline IOP of the group was approximately 24 mmHg using a mean of 2.5 medications.

The percentages of eyes with POAG, pseudoexfoliation, and pigment dispersion were 58%, 30%, and 7%, respectively.

Intervention

Patients were randomized to SLT (n = 89) or ALT (n = 87) administered to 180° of the trabecular meshwork. Follow-up visits were carried out at 1 week and 1, 3, 6, and 12 months postlaser treatment. Patients were maintained on their prelaser glaucoma medications throughout the follow-up period, with further treatment added as deemed clinically necessary.

Outcome Measures

The primary outcome measure was the reduction in IOP at 12 months postlaser. Survival analysis defined success as a 20% IOP reduction from baseline with no additional glaucoma drugs or surgery required. Secondary outcomes included IOP measures at other time points, visual acuity, and anterior chamber reaction.

Results

ALT and SLT were equally efficacious, with mean IOP reductions at 12 months of 6.04 mmHg (26% reduction) in the ALT group and 5.86 mmHg (25% reduction) in the SLT group. No differences in IOP reduction were seen at any of the time points measured, and no difference in survival, as defined as a 20% IOP reduction with no additional glaucoma medicines or surgery, was observed. Adverse event rates were not different between groups, with three ALT patients and four SLT patients experiencing early postlaser IOP spikes (>6 mmHg).

In a companion observational study,[49] the authors analyzed baseline factors predictive of SLT success and found that patients who achieved success (≥20% IOP reduction) had significantly higher baseline IOP. Interestingly, the type of OAG (POAG, pseudoexfoliation, or pigment dispersion) and the amount of trabecular meshwork pigmentation were not predictive of success.

Clinical Implications

This study verified the comparable efficacy and safety of SLT and ALT. The broad inclusion criteria adopted by the investigators (including several different types of OAG, patients on glaucoma medications, and previous laser failures) allow wide generalizability and clinical applicability.

Selective Laser Trabeculoplasty versus Latanoprost in Controlling Intraocular Pressure

Results published 2005

This was a two-site, RCT comparing the efficacy of SLT to that of medical monotherapy with latanoprost in patients with OAG and ocular hypertension.[47]

Study Population

This study enrolled patients with OAG and IOP above target.

Major Inclusion Criteria

- OAG (primary or secondary) or ocular hypertension

Major Exclusion Criteria

- Previous laser or surgical glaucoma interventions
- Previous anterior segment surgery

Sample Size and Baseline Characteristics

A total of 167 patients (167 eyes) were enrolled in the study (85 with ocular hypertension and 82 with OAG). Mean age was 63 years and mean IOP was 29.3 mmHg.

Intervention

Patients were randomized to receive latanoprost 0.005% (n = 39), 90° SLT (n = 35), 180° SLT (n = 49), or 360° SLT (n = 44). Patients previously on medical glaucoma therapy required a minimum of 5 weeks washout prior to enrollment in the study.

Outcome Measures

The primary outcome measure was the percentage of eyes achieving success (defined in two ways: i) ≥20% IOP reduction from baseline, ii) ≥30% IOP reduction from baseline). Secondary measures included adverse event rates such as postlaser IOP spikes.

Results

The percentage of eyes achieving ≥20% and ≥30% IOP reduction at 12 months was 90% and 78% for latanoprost; 34% and 11% for 90° SLT; 65% and 48% for 180° SLT; and 82% and 59% for 360° SLT. These success rates demonstrated a statistically significant superiority of latanoprost versus 90° and 180° SLT; however, the differences between latanoprost and 360° SLT did not reach statistical significance.

The rates of transient adverse events increased with increasing extent of laser therapy, with 39% reporting discomfort/pain, 50% developing transient uveitis, and 27% sustaining a postlaser IOP spike of ≥5 mmHg in the 360° SLT group. There were no sight-threatening adverse events.

Clinical Implications

This study provided clinically relevant data because it compared SLT to the most efficacious class of medical therapy and found latanoprost to be superior to 90° and 180° SLT. While the study did not demonstrate a statistically significant difference in success at 1 year between latanoprost and 360° SLT, there was a trend for latanoprost to be superior, and importantly, the study had low power to detect a clinically relevant difference.

IV. SURGICAL MANAGEMENT OF GLAUCOMA

Overview

Incisional surgery remains an essential component of glaucoma management. With its excellent IOP-lowering capability, trabeculectomy remains the central filtration surgical procedure for OAG. This section examines the evidence for trabeculectomy and its position in the OAG treatment algorithm. Specifically, we describe the Collaborative Initial Glaucoma Treatment Study (CIGTS),[50–57] a landmark clinical trial comparing trabeculectomy to medical therapy as primary treatment. Additionally, data regarding the adjunctive use of antimetabolites in trabeculectomy from the Fluorouracil Filtering Surgery Study (FFSS)[58–62] and a trial comparing the two most commonly used antimetabolites, 5-fluorouracil (5-FU) and mitomycin C (MMC), are presented.[63,64]

Beyond trabeculectomy, many additional surgical glaucoma procedures have been developed including aqueous shunt implantation, nonpenetrating filtration surgery, endoscopic cyclophotocoagulation, and the implantation of various devices such as the iStent and Express shunt. While high-level evidence is lacking for many of these procedures, aqueous shunt implantation has been compared to trabeculectomy in the Tube Versus Trabeculectomy (TVT) trial,[65–71] and specific aqueous shunts have been compared in the Ahmed Baerveldt Comparison (ABC)[72,73] and Ahmed Versus Baerveldt (AVB)[74,75] studies.

Collaborative Initial Glaucoma Treatment Study

Results published 2001

Traditionally, filtration surgery was undertaken in eyes that had failed medical and laser therapy. However, numerous small studies suggested that early surgical intervention could be highly effective, indicating that surgery may be more effective in eyes that have not been subjected to long-term topical medications and their potential conjunctiva-altering properties. Additionally, chronic medical therapy for glaucoma presents significant compliance and quality-of-life issues, which may be circumvented with a single surgical procedure. Hence, CIGTS was a prospective, multicenter, RCT developed to compare initial medical treatment versus surgical treatment for newly diagnosed OAG.

Study Population

Patients enrolled in CIGTS had newly diagnosed, untreated OAG.

Major Inclusion Criteria

- Diagnosis of OAG (POAG, pseudoexfoliation, and pigmentary glaucoma)
- Qualifying IOP ≥ 20 mmHg plus a VF with at least three depressed contiguous points and a Glaucoma Hemifield Test result of "outside normal limits" plus an optic disc appearance compatible with glaucoma; or

IOP 20 to 26 mmHg plus a VF with at least two contiguous depressed points plus glaucomatous disc damage; or IOP ≥ 27 mmHg with glaucomatous optic disc damage (no required VF changes)
- VA ≥ 20/40

Major Exclusion Criteria

- Cumulative lifetime use of glaucoma eye drops exceeding 14 days
- Advanced VF defect (CIGTS VF score exceeding 16.0)
- Previous ocular surgery
- Ocular disease precluding IOP and VF assessment
- Likely to require cataract surgery within 1 year of randomization

Sample Size and Baseline Characteristics

A total of 607 patients were enrolled in the study. The majority of patients were aged 50 to 64 years and had POAG. Most patients qualified for inclusion with an IOP ≥ 20 mmHg plus VF defect.

Intervention

Patients were randomized to initial surgical (n = 300) or medical (n = 307) treatment. In the surgical arm, the study eye underwent trabeculectomy (and/or 5-FU at the surgeon's discretion) within 14 days of randomization. If trabeculectomy failed, the next steps in the treatment algorithm were ALT, followed by medications, followed by repeat trabeculectomy with 5-FU, followed by medications. In the medical arm, patients received a sequence of medications usually beginning with a topical beta-blocker followed by escalating combinations of topical therapy. If further treatment was required, patients received ALT followed by trabeculectomy, followed by more medication, followed by trabeculectomy with 5-FU. Intervention failure had to be met prior to initiation of further treatment steps.

Failure was initially defined as not meeting target IOP or progression on VF (VF reference score increase of ≥3.0 points on three consecutive tests). Target IOP was established based on reference IOP and reference VF score and calculated using the following formula: Target IOP = (1 – [reference IOP + VF score]/100) × reference IOP. If IOP was ≥1 mmHg over target on two consecutive visits, IOP-related intervention failure was declared and advancement in treatment algorithm instituted.

This definition of IOP-related failure was adjusted in 1996 because of concern that the original definition was resulting in overly aggressive advancement in the treatment sequence. The revision permitted greater tolerance for IOPs that were above target, depending on the extent of VF loss in the central region. Patients were followed every 6 months (after an initial period of more frequent follow-up) for 4 to 5 years.

Outcome Measures

The primary outcome was VF progression. Total VF scores were assigned based on the number and depth of depressed points and the number of adjacent depressed points. Other outcome measures assessed included IOP, VA, and health-related quality of life.

Results

IOP reduction was significant in both groups; however, surgery achieved a greater initial reduction, with this difference maintained through 5 years of follow-up (Fig. 6.8). Mean IOP among those receiving initial surgery decreased from a baseline of 27 to 15 mmHg (44% reduction), whereas mean IOP in the medically treated group decreased from 28 to 18 mmHg (36% reduction).

Despite the differences in IOP reduction between groups, over 60 months of follow-up, there was no significant difference in the CIGTS VF score between the two groups, with both showing minimal change. At the 8-year follow-up, the percentage of patients showing substantial VF worsening from baseline (–3 dB or more) was 21.3% in the surgery group and 25.5% in the medically treated group, which was not statistically different. Figure 6.9 shows the overall VF trends as well as the percentage of participants with substantial vision loss over the treatment period.

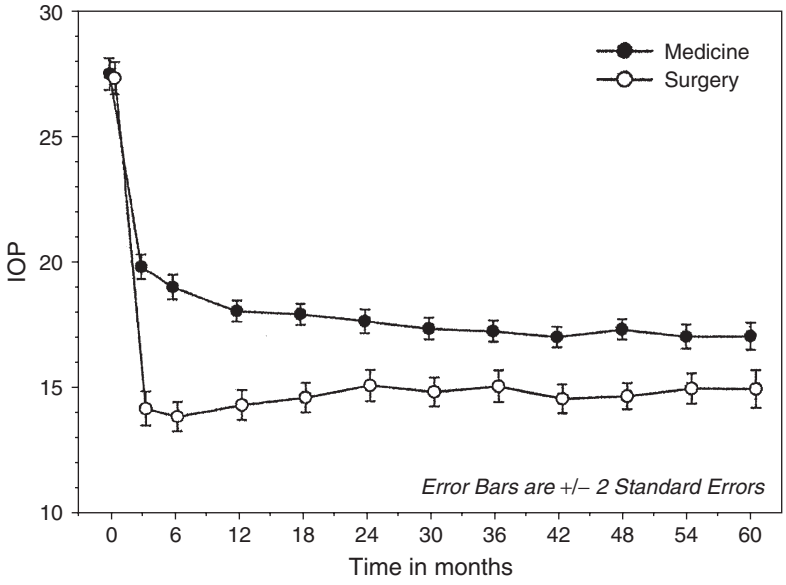


FIGURE 6.8 Intraocular pressure by time and the treatment group. Reprinted with permission from *Ophthalmology*. 2001;108:1949.

On average, surgery resulted in a 3-letter loss of VA, whereas there was no significant change in VA in the medically treated group in the first year. This initial decrease in VA in the trabeculectomy group was largely due to cataract formation. However, by the 4-year follow-up point, there was no significant difference in VA between the two groups as the surgery-first patients received treatment for their cataracts.

Health-related quality-of-life assessment demonstrated an increased incidence of local eye symptoms initially in the surgical group. However, symptom impact glaucoma scores were not significantly different between groups over 5 years of follow-up. In the surgery group, there was a 12% intraoperative complication rate, most commonly anterior chamber bleeding and conjunctival buttonhole. Early postoperative complications occurred in 50% of the eyes and included shallow or flat anterior chamber (13%), encapsulated bleb (12%), ptosis (12%), choroidal detachment (11%), and hyphema (10%). There were three suprachoroidal hemorrhages and no cases of endophthalmitis.

Baseline Factors Associated with Progression

Available data through 9 years of follow-up showed some interesting interactions between initial treatment modality and baseline VF MD, as well as diabetes status. Specifically, subjects with more severe VF loss at baseline (–10 dB or more) showed less VF loss over time if treated surgically (1.03 dB on average better MD in the surgical group at 7 years); 17% of the patients initially enrolled in CIGTS were diabetic and they were significantly better off over extended follow-up if treated with medicine first, showing on average 0.76 dB less VF loss compared to the surgery-first group at 9 years.

Clinical Implications

CIGTS highlighted the potential utility of using individualized target IOPs based on a formula that accounts for baseline extent of glaucomatous damage as well as pretreatment IOP. CIGTS also showed that despite a greater IOP reduction with initial surgery, surgical and medical management were equally efficacious in reducing the risk of progression. These results reassure clinicians that medical management is an appropriate first-line modality

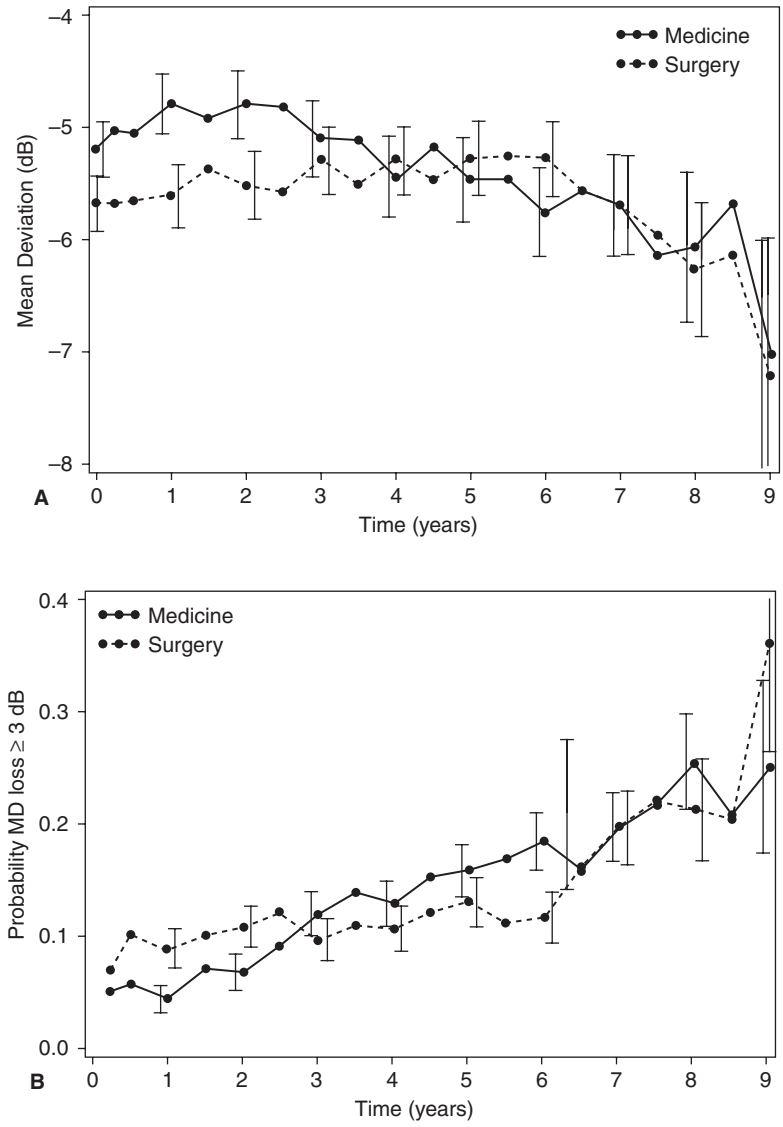


FIGURE 6.9 (A) Graph showing the mean deviation (MD) by time and treatment group. Error bars are ±1 standard error and are slightly offset to show the bar for each treatment more clearly. **(B)** Graph showing the percentage of participants with a decrease (worsening) of MD from baseline of 3 dB or more by time and treatment group. Reprinted with permission from *Ophthalmology.* 2009;116:202.

in the treatment of OAG as it achieves similar visual function results while avoiding possible complications inherent in surgical options. The corollary is that CIGTS confirmed that trabeculectomy is also a reasonable initial therapy. It is also important to note that newer, more potent IOP-lowering topical agents (prostaglandin analogs) were not available during CIGTS. Because CIGTS results may underestimate the efficacy of medications, the results may not be entirely generalizable to current practice.

Fluorouracil Filtering Surgery Study

Results published 1989 to 1996

Following its initial description, trabeculectomy was adopted as the gold-standard filtering

surgery for OAG because of its superior safety profile compared to previous full-thickness filtering surgeries. However, the IOP-lowering capability of trabeculectomy may be significantly reduced by fibrosis and scarring. The FFSS was a prospective, multicenter, RCT comparing the efficacy and safety of trabeculectomy with and without 5-FU.

Study Population

Patients enrolled had uncontrolled glaucoma and were deemed at risk for failure with standard trabeculectomy (e.g., aphakic, pseudophakic, or phakic eyes with previous failed filtering surgery).

Major Inclusion Criteria

- Uncontrolled IOP (>21 mmHg) on maximally tolerated medical therapy
- Previous intraocular surgery (cataract extraction or failed trabeculectomy)

Major Exclusion Criteria

- Previous 5-FU treatment (systemic or to study eye)
- Anterior segment neovascularization
- No light perception vision

Sample Size and Baseline Characteristics

A total of 213 patients were enrolled in the study. Mean age was 62 years and mean baseline IOP was 35 mmHg; 76% of the patients had undergone previous cataract extraction, and 24% had undergone previous failed filtering surgery.

Intervention

All patients in the study underwent standard trabeculectomy with a limbus-based conjunctival flap. Eyes were excluded from randomization if any intraoperative complications occurred or if, on the first postoperative day, a wound leak or previously unrecognized conjunctival buttonhole was identified. Eligible eyes were then randomized to either trabeculectomy alone (n = 108) or trabeculectomy augmented with postoperative 5-FU (n = 105). The latter group subsequently received 5.0 mg (0.5 ml) subconjunctival injections of 5-FU twice daily on postoperative days 1 to 7 and once daily on postoperative days 8 to 14. Both groups received frequent postoperative steroid drops. All patients were examined daily for 14 days after surgery and monthly thereafter.

Outcome Measures

The primary outcome measure was failure of treatment, defined as IOP > 21 mmHg at the 1-year postoperative visit, or reoperation to lower IOP during the first year. Further outcome measures included IOP, visual acuity, and complications.

Results

Treatment failure rates through the 1-year follow-up were 27% and 50% in the 5-FU-augmented trabeculectomy and standard trabeculectomy groups, respectively (p = 0.0007). During the first six postoperative days, mean IOP was similar in the two treatment groups; however, by day 7, the standard trabeculectomy group had a mean IOP 2 mmHg higher than the 5-FU group, and by day 14, the mean IOPs were 9 and 18 mmHg in the 5-FU and standard trabeculectomy groups, respectively. Finally, by the 1-year follow-up point, among patients who did not require further surgery, 66% of the 5-FU group and 36% of the standard trabeculectomy group required no additional medical therapy.

Epithelial toxicity issues including epithelial defects occurred more frequently in the 5-FU group during the postoperative 5-FU injection period, such that 46% of patients did not receive their entire scheduled 21 injections. In the first postoperative year, wound leaks and bleb rupture were more common in the 5-FU group.

At the final 5-year follow-up, the 5-FU group continued to demonstrate higher success, with 49% of patients maintaining adequate IOP control without further surgery, compared to 26% of the standard trabeculectomy patients. The 5-FU group continued to show a higher rate of bleb leak (nine patients) compared to the standard trabeculectomy group (two patients) over the 5 years.

Clinical Implications

The FFSS was an important study comparing two surgical techniques that demonstrated

the efficacy of postoperative 5-FU in trabeculectomy surgery. This validated the use of adjuvant antimetabolites in filtering surgery as an effective way to achieve long-term success. Since the FFSS, concerns over significant epithelial toxicity with 5-FU and its cumbersome application (numerous postoperative injections) have led many glaucoma surgeons to favor intraoperative use of antimetabolites and the use of the more potent antimetabolite MMC.

5-Fluorouracil versus Mitomycin C in Trabeculectomy Surgery

Results published 2002 and 2009

Numerous small studies have been conducted comparing intraoperative 5-FU to MMC in trabeculectomy; however, most have been short term or underpowered. One moderately sized RCT recently reported long-term results.[63,64] This was a prospective, single-center, masked, RCT comparing intraoperative 5-FU to MMC in primary trabeculectomy.

Study Population

Patients enrolled had inadequate IOP control despite maximally tolerated medical therapy.

Major Inclusion Criteria

- Medically uncontrolled glaucoma (OAG or chronic angle closure)

Major Exclusion Criteria

- Previous intraocular surgery (except laser trabeculoplasty)

Sample Size and Baseline Characteristics

A total of 103 patients (115 eyes) were enrolled. Mean age was 65 years and the majority had POAG.

Intervention

Eyes were randomized to intraoperative 5-FU (50 mg/ml for 5 minutes; $n = 57$) or MMC (0.2 mg/ml for 2 minutes; $n = 58$), and a standard limbus-based conjunctival flap was used.

Outcome Measures

The primary outcome measure was reduction in IOP. Failure was defined as IOP > 21 mmHg or not reduced by 20% from preoperative IOP on two consecutive visits; IOP < 6 mmHg on two consecutive visits; or additional surgery required to reduce IOP (excluding bleb revision). Secondary measures included IOP, VA, number of glaucoma medications, postoperative interventions, and complications.

Results

At the 12-month postoperative time point, there was no significant difference in failure or number of complications, though there was a trend suggesting more complications in the MMC group. At 5 years, cumulative survival was 76% in the 5-FU group and 66% in the MMC group. This was not a statistically significant difference. The most common complication and reason for failure was bleb leak, which occurred equally in each group at about 4% per year.

Clinical Implications

This study suggests that success and complication rates are similar with 5-FU and MMC used as adjunctive antifibrotic agent during primary trabeculectomy. This result may not be generalizable to the higher concentrations or longer duration of MMC exposure often used clinically. Further, the results may not be generalizable to secondary or other trabeculectomy cases with complex features.

Tube versus Trabeculectomy Study

Five-year results published 2012

Over recent years, aqueous shunt surgery has gained in popularity among glaucoma surgeons. Initially used mainly for refractory glaucomas and patients with multiple risk factors for trabeculectomy failure, aqueous shunts have steadily been utilized for wider indications because of the concern over long-term bleb complications with trabeculectomy. The TVT study was a prospective, multicenter, RCT comparing trabeculectomy with Baerveldt glaucoma drainage implant surgery.

Study Population

Patients enrolled had uncontrolled glaucoma and a history of previous intraocular surgery.

Major Inclusion Criteria

- Inadequately controlled IOP ≥ 18 mmHg and ≤40 mmHg on maximal tolerated medical therapy
- Previous trabeculectomy, cataract extraction with intraocular lens implantations, or both

Major Exclusion Criteria

- No Light Perception (NLP) vision
- Aphakia
- Iridocorneal endothelial syndrome, epithelial or fibrous downgrowth
- Chronic or recurrent uveitis
- Severe posterior blepharitis
- Conjunctival scarring precluding trabeculectomy

Sample Size and Baseline Characteristics

A total of 212 patients were enrolled, with a mean age of 71 years and a mean baseline IOP of 25 mmHg on an average of 3.1 glaucoma medications; 81% of patients had POAG, with smaller numbers having chronic angle closure glaucoma (8%), pseudoexfoliation (4%), pigmentary (1%), and other types of glaucoma (6%). Seventy-five percent of the eyes were pseudophakic and 56% of eyes had undergone previous trabeculectomy.

Intervention

Patients were randomized to aqueous shunt implantation ($n = 107$) or trabeculectomy with MMC ($n = 105$). For the aqueous shunt group, a Baerveldt 350 mm^2 implant was placed in the superotemporal quadrant. The plate was placed under or over the superior and lateral recti muscles depending on the surgeon's preference. The aqueous shunt was occluded to temporarily restrict aqueous flow to prevent postoperative hypotony, and surgeons were given the option to fenestrate the aqueous shunt for early IOP reduction. The trabeculectomy group underwent a superior trabeculectomy with fornix- or limbus-based conjunctival flap and received 0.4 mg/ml MMC subconjunctival application for 4 minutes. Patients were followed frequently in the postoperative period and then every 6 months up to 2 years and subsequently yearly through 5 years.

Outcome Measures

Primary outcome measures included IOP and complication rates. Failure was defined as one of the following: IOP > 21 mmHg or less than a 20% reduction from baseline on two consecutive visits after the initial 3 months; IOP ≤ 5 mmHg on two consecutive visits after the initial 3 months; additional glaucoma surgery required; or loss of light perception vision. Complete success was defined as not reaching failure criteria and requiring no supplemental medication, whereas qualified success was defined as not reaching failure criteria but requiring supplemental medication. Other outcome measures included visual acuity, VF, and quality of life.

Results

Figure 6.10 demonstrates cumulative probabilities of failure of 29.8% and 46.9% in the aqueous shunt and trabeculectomy groups, respectively, at 5 years ($p = 0.002$, trabeculectomy vs. aqueous shunt hazard ratio 2.15). Persistent hypotony was an important cause of failure in the trabeculectomy group, whereas this was a rare cause in the aqueous shunt group. At the 5-year follow-up point, mean IOP (excluding subjects requiring further surgical intervention) was 14.4 mmHg on 1.4 medications in the aqueous shunt group and 12.6 mmHg on 1.2 medications in the trabeculectomy group, which was not significantly different (Fig. 6.11). Initial IOP reduction was greatest in the trabeculectomy group; however, at all time points after 3 months, there was no significant difference between the two groups' mean IOPs. The aqueous shunt group required significantly more medications for the first 2 years, but by year 3 and beyond, there was no significant difference in the mean number of medications.

Early postoperative complications (onset ≤ 1 month) were more common in the trabeculectomy group (37% of patients) compared to the aqueous shunt group (22% of patients), largely attributable to the greater number of wound leaks in the trabeculectomy

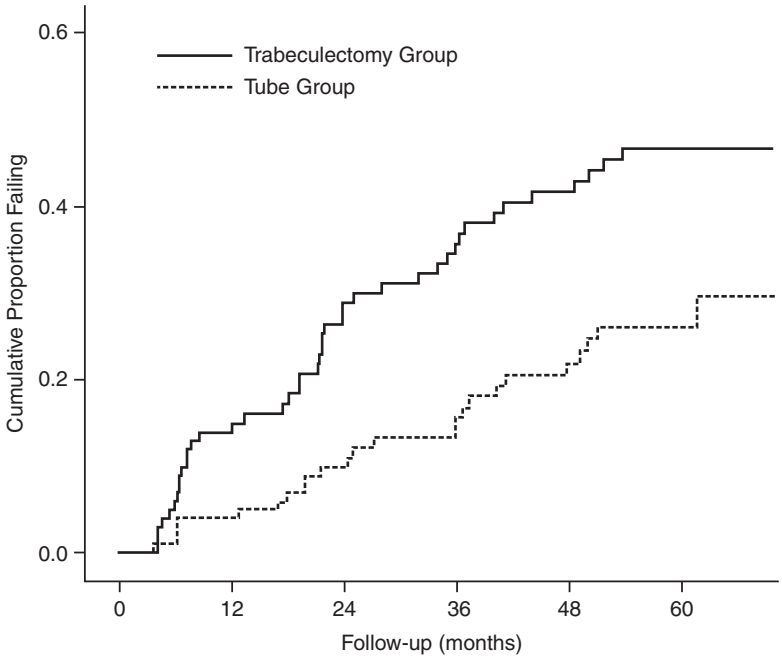


FIGURE 6.10 Kaplan-Meier plots of the probability of failure in the Tube Versus Trabeculectomy Study. Reprinted with permission from *Am J Ophthalmol*. 2012;153:794.

group (11%) compared to the aqueous shunt group (1%). There was no significant difference in the overall rate of late (>1 month) postoperative complications between the two groups; however, bleb leak occurred more often in the trabeculectomy group (6%) than in the aqueous shunt group (0%). New-onset diplopia secondary to motility disturbances was reported in 5% of patients at 1 year in the aqueous shunt group and in no patients in the trabeculectomy group. Importantly, there was no significant difference in the incidence of complications resulting in vision loss and/or reoperation between the treatment groups,

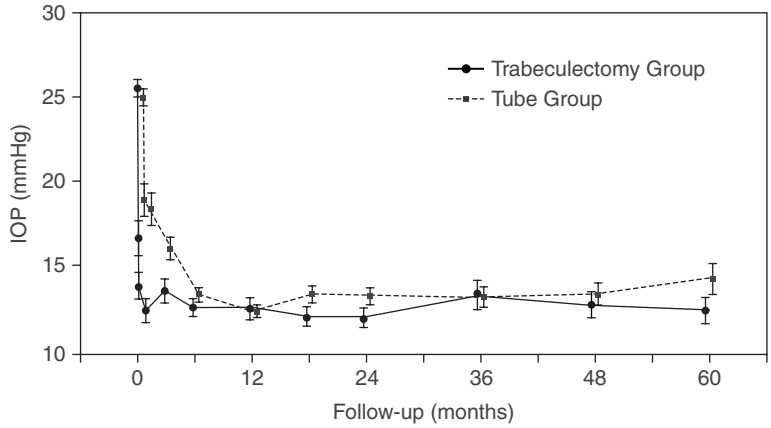


FIGURE 6.11 Intraocular pressure (IOP) at baseline and follow-up in the Tube Versus Trabeculectomy Study. Data are presented as mean ± standard error of the mean and are censored after a reoperation for glaucoma. Reprinted with permission from *Am J Ophthalmol*. 2012;153:792.

reaching 22% and 20% in the aqueous shunt and trabeculectomy groups, respectively.

Clinical Implications

The TVT provided evidence to support a broader indication profile for aqueous shunt surgery beyond just end-stage refractory glaucomas. At 5 years, aqueous shunt surgery appears to be as effective as trabeculectomy at reducing IOP in eyes with previous intraocular surgery, with fewer postoperative complications and lower probability of failure. However, it is important to note that the rate of serious complications resulting in vision loss and/or reoperation was the same in both treatment groups. Additionally, closer scrutiny of the reasons for reoperations shows that the most common operative procedure in the trabeculectomy group was bleb revision (five patients), a comparatively benign outcome compared to the need for penetrating keratoplasty in six aqueous shunt patients. Further, the high concentration of MMC and long duration of exposure may have led to the high rate of leaks in the trabeculectomy group. Consequently, the results may not be generalizable to lower doses of MMC. Given the significantly greater cost and increased surgical complexity of aqueous shunt implantation, the TVT results suggest that while aqueous shunts will gain expanded indications, trabeculectomy will continue to play an important role in glaucoma management.

Comparison of Ahmed and Baerveldt Aqueous Shunt Implants

Results published 2011

The ABC[72,73] and the AVB[74,75] studies recently reported 1-year results comparing these two aqueous shunts. For comparison, these independent studies are presented together. Both were prospective, multicentered, RCTs comparing the Ahmed FP7 implant to the Baerveldt 350 mm^2 implant in patients with uncontrolled glaucoma.

Study Population

Both the ABC and AVB enrolled patients with uncontrolled IOP resulting from refractory POAG with previous failed trabeculectomy, or secondary glaucomas, such as neovascular and uveitic glaucoma, without previous trabeculectomy.

Major Inclusion Criteria

- Inadequately controlled IOP despite maximal therapy
- Additionally, the ABC study specified further the following:
  - IOP ≥ 18
  - Previous intraocular surgery or secondary glaucoma known to have a high trabeculectomy failure rate

Major Exclusion Criteria

- Aqueous shunt implantation surgery planned in combination with other procedures
- Additionally, the ABC study specified further the following:
  - Previous cyclodestructive procedure or aqueous shunt

Sample Size and Baseline Characteristics

The baseline characteristics were very similar in the two studies. The ABC study enrolled 276 patients with a mean age of 64 years and a mean IOP of 31.5 mmHg on a mean of 3.4 medications. The AVB study enrolled slightly fewer patients at 238. The mean age was 66 years and the mean IOP was 31.4 mmHg on a mean of 3.1 medications. Overall, 40% to 50% of the patients had a diagnosis of POAG, while neovascular glaucoma made up the second largest category at 21% to 29%.

Intervention

Standardized implantation protocols for each aqueous shunt were used in each study (slightly different techniques were employed in each study). Patients were followed closely in the immediate postoperative period, and then at 3 months, 6 months, and 1 year, with further ongoing follow-up planned.

Outcome Measures

The primary outcome in both studies was failure, determined by similar composite criteria incorporating IOP, medication use,

visual acuity, complications of surgery, and subsequent interventions required. The ABC study used an upper IOP limit of 21 mmHg to define failure, whereas the AVB study used 18 mmHg. Other criteria for failure were similar. Complete success was defined as not reaching failure criteria and not requiring glaucoma medications, whereas qualified success was defined as not reaching failure criteria but requiring glaucoma medications. Secondary outcome measures included IOP, number of medications used, complications, visual acuity, and interventions required.

Results

The cumulative probability of failure at 1 year in the ABC study was 16.4% in the Ahmed group and 14% in the Baerveldt group ($p = 0.52$). The most common reason for failure in both groups was inadequately reduced IOP. When an alternate upper IOP limit of 14 mmHg was used in the failure criteria, a significant difference emerged between the two groups, with a cumulative probability of failure of 38.6% in the Ahmed group compared to 24.0% in the Baerveldt group ($p = 0.008$). Not surprisingly, given the stricter failure criteria used, the AVB study demonstrated a higher failure rate than the ABC study, with the cumulative probability of failure reaching 43% and 28% in the Ahmed and Baerveldt groups, respectively ($p = 0.049$).

Overall, early postoperative complications were more common in the Baerveldt group in both studies, reaching statistical significance in the ABC study. Serious complications associated with vision loss or requiring reoperation were more common with the Baerveldt implant in the ABC study. Further, postoperative interventions were more common in the Baerveldt group in the AVB study.

Clinical Implications

The ABC and AVB trials showed that both devices are capable of reducing IOP. While the Baerveldt implant appears to be slightly more efficacious in achieving very low IOP, this comes at the cost of a somewhat higher complication rate. It is important to note that to date, these studies have only reported 1-year results. Both studies plan longer term follow-up reports, which will provide a more thorough assessment of each device's efficacy.

Conclusion

The studies reviewed in this chapter provide a basis for evidence-based care of glaucoma patients. These studies have strengths and weaknesses that must be considered when evaluating their applicability to individual patients. Moreover, there are many clinical situations for which large trials do not exist, and lower levels of evidence may need to be accepted with the recognition that definitive evidence is lacking. Hence, while much progress has been made in the field of glaucoma care, many questions remain, and innovative discoveries will be needed to address the burden caused by this disease.

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7A Diabetic Retinopathy: Prevention and Screening

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I. DIABETES CONTROL AND COMPLICATIONS TRIAL

Introduction

Long-term microvascular and neurologic complications cause considerable morbidity and mortality in patients with insulin-dependent diabetes mellitus. These complications develop over a period of years, and in the 1960s, there was evidence to suggest that the underlying cause is chronic elevation of blood glucose. Subsequently, there was controversy as to whether improved control of blood glucose would reduce the chronic complications of diabetes, including diabetic retinopathy.[1–7] If such a relationship existed, and if improved control of blood glucose could be achieved, then there was potential benefit in pursuing effective treatment strategies to reduce blood glucose levels. However, the effects of such intervention might not become apparent for years, and maintaining blood glucose concentrations as close to the normal range as possible (normoglycemia) had associated costs and potential complications. To address these questions of considerable public health importance, a prospective, multicenter, randomized, controlled clinical trial was needed.

Background and Study Questions

The Diabetes Control and Complications Trial (DCCT) was established in the 1980s to determine whether improved control of blood glucose levels would reduce the frequency and severity of diabetic retinopathy and other chronic complications of diabetes.[8] Improved control of blood glucose was termed *intensive control*, with the goal of achieving normoglycemia.

Patients Included in the Study

A total of 1,441 patients with type 1 diabetes, aged between 13 and 39, with no retinopathy and a duration of diabetes of 1 to 5 years (the primary-prevention cohort, 726 patients) or mild to moderate nonproliferative retinopathy and a duration of diabetes of 1 to 15 years (the secondary-intervention cohort, 715 patients) were enrolled.

Intervention and Outcome Measures

Patients were randomly assigned to intensive or conventional insulin therapy. Intensive therapy consisted of the use of an external insulin pump (continuous subcutaneous insulin infusion) or three or more daily insulin injections and guided by four or more blood glucose tests daily (doses adjusted on the basis of self-monitoring). Conventional therapy involved one or two daily insulin injections and once-daily monitoring. Outcome measures included the appearance and progression of retinopathy using the Early Treatment Diabetic Retinopathy Study (ETDRS) retinopathy severity scale and systemic findings related to nephropathy and neuropathy.

Major Findings

At a mean follow-up of 6.5 years (range 3.5 to 9 years) in the primary-prevention cohort,

intensive therapy reduced the risk of developing retinopathy by 76% compared with conventional therapy. In the secondary-intervention cohort, intensive therapy slowed the progression of retinopathy by 54% and reduced the development of severe nonproliferative or proliferative retinopathy by 47%. In both cohorts, intensive therapy reduced the occurrence of microalbuminuria and albuminuria, and clinical neuropathy.[9–11]

Cumulative 8.5-year rates of progression of retinopathy by three or more steps at two consecutive visits were 12% with intensive treatment as compared to 54% with conventional treatment in the primary-prevention cohort and 17% as compared to 49% in the secondary-intervention cohort. Once progression occurred, subsequent recovery was at least two times more likely with intensive treatment than with conventional treatment.[12]

The level of glycemic exposure (HbA_{1c}) measured at eligibility screening and the duration of insulin-dependent diabetes were the dominant baseline predictors of the risk of progression.[13] The intensive treatment group achieved a median HbA_{1c} of 7.2% versus 9.1% in the conventional treatment group. Mean blood glucose was 155 mg/dl in the intensive treatment group and 230 mg/dl in the conventional group.

The major adverse event associated with intensive therapy was a two- to three-fold increase in severe hypoglycemia.[9] At the 6- and 12-month visits, a small adverse effect of intensive treatment occurred, termed *early worsening of retinopathy*. Worsening was defined as any of the following: progression of retinopathy ≥3 steps, the development of soft exudates and/or intraretinal microvascular abnormalities, or the development of clinically important retinopathy (clinically significant diabetic macular edema [CSDME], severe nonproliferative diabetic retinopathy [NPDR], retinal neovascularization elsewhere [NVE], or neovascularization of the optic disc [NVD]). Worsening was considered early if it occurred between baseline and the 12-month follow-up visit. Early worsening was noted in 13% of patients undergoing intensive treatment and in 8% undergoing conventional treatment. Risk factors were higher HbA_{1c} level at screening, and reduction in this level during the first 6 months of the study (but not related to rate of reduction).[14] Early worsening was followed by a beneficial effect that increased with follow-up duration,[12] and the long-term benefits of intensive treatment greatly outweighed the risks of early worsening.

Implications for Clinical Practice

The DCCT demonstrated the powerful impact of glycemic control on the microvascular complications of diabetes mellitus. In patients with insulin-dependent diabetes who met the inclusion criteria, intensive insulin therapy as administered in this trial effectively delayed the onset and slowed the progression of diabetic retinopathy, nephropathy, and neuropathy.

The DCCT concluded that the beneficial effect of intensive treatment in slowing the progression of retinopathy was very substantial, increased with time, was consistent across all outcome measures assessed, and was present across the spectrum of retinopathy severity included in the study.

However, intensive therapy did not prevent retinopathy completely, and it was associated with early worsening in some patients with long-standing poor glycemic control (elevated HbA_{1c}), especially if retinopathy was at or beyond the moderate nonproliferative stage. In such patients, examination prior to initiation of intensive treatment and at frequent (3- to 4-month) intervals for the first year was recommended. In patients with elevated HbA_{1c} whose retinopathy was approaching high risk, prompt photocoagulation was recommended if intensive treatment was to be initiated.[14] The magnitude, but not the rapidity, of the reduction in HbA_{1c} during the first 6 months of intensive treatment was an important risk factor for early worsening.

Despite this, intensive treatment had a remarkable beneficial effect that began after 3 years of therapy on all levels of retinopathy that were studied.[15] The reduction in risk observed in the DCCT translated into reduced need for laser treatment and reduced risk of visual loss, and the DCCT

recommendation was to implement intensive treatment as early as possible in as many insulin-dependent diabetic patients as was safely possible.

The Epidemiology of Diabetes Interventions and Complications (EDIC) study assessed whether the benefits demonstrated in the DCCT persisted after the end of the DCCT. This study concluded that the benefits associated with intensive treatment extended well beyond the period of intensive implementation. The recommendation was that once intensive treatment is initiated in patients with insulin-dependent diabetes, it should be maintained thereafter, aiming for a target HbA_{1c} level of 7.0% or less (normal 3.0% to 6.0%) and a fasting blood glucose level of 110 mg/dl or less.[16]

Unanswered Questions

The DCCT demonstrated a substantial beneficial effect of intensive insulin therapy in slowing the progression of retinopathy. Although this treatment effect increased during the follow-up period, its relation to long-term functional outcome can only be estimated.

Inclusion criteria for the DCCT were the absence of retinopathy or the presence of mild to moderate nonproliferative retinopathy, while patients with more advanced levels of retinopathy were excluded from the study. When early worsening occurred in the study patients, it was not associated with any cases of serious visual loss. It is possible, however, that patients with severe nonproliferative or proliferative diabetic retinopathy may experience early worsening that is clinically relevant when intensive treatment is initiated. Although increased surveillance and a lower threshold for photocoagulation are recommended for these patients when intensive treatment is initiated, the early effects of intensive treatment are unknown.[12]

Furthermore, the disease process appears to have considerable momentum, as evidenced by the number of years of intensive therapy required before a treatment effect manifests. In patients with advanced retinopathy, although the long-term effects are unknown, it is unlikely that intensive treatment alone can halt the progression.[15]

II. UNITED KINGDOM PROSPECTIVE DIABETES STUDY

Introduction

Type 2 diabetes accounts for approximately 90% of all cases of diabetes worldwide.[17,18] We are currently in the midst of a global epidemic of type 2 diabetes, although the burden is felt disproportionately by non-European populations. It is a multifactorial disease with complex interactions between genetic and environmental factors that result in the common endpoints of insulin resistance, defective insulin secretion, and increased hepatic production of glucose.[19] Older age, nonwhite race, obesity, physical inactivity, poor diet, stress, Westernization, and urbanization are all risk factors.[17] Type 2 diabetes is one of the world's most important public health issues, and ophthalmologists play an integral role in diagnosing the disease, and preventing and treating retinal microvascular complications.

Background and Study Questions

Type 1 and type 2 diabetes are clinically and pathogenically distinct entities. Therefore, data from clinical trials examining type 1 diabetes cannot be fully extrapolated to patients with type 2 diabetes. The DCCT was arguably the most important clinical trial in diabetes research, but it only examined patients with type 1 diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) was organized in order to fulfill the need to examine the effects of intensive glycemic control in patients with type 2 diabetes. Three prior trials existed at the time, but they were limited in sample size, and results were equivocal.[20–22]

Patients Included in the Study

The UKPDS recruited over 7,600 potential subjects and included 5,102 patients with newly diagnosed type 2 diabetes from

23 medical centers in the United Kingdom between 1977 and 1991. All patients were white. Patients were followed for an average of 10 years, and over 20 million data items were collected to produce one of the largest epidemiologic databases for diabetes research.

Intervention and Outcome Measures

Subjects were either randomized to intensive glycemic control defined as fasting plasma glucose <108 mg/dl using a combination of chlorpropamide, glyburide, metformin, and insulin, or to diet modification with the goal of fasting plasma glucose <270 mg/dl. When subjects in the diet-modification group could not attain the goal glycemic levels, they were crossed over to the intensive treatment group. When single agents failed, combinations were used, and metformin was used only in obese patients. Numerous substudies were embedded within the trial.[23] The retinopathy component of UKPDS relied on fundus photographs graded according to a modified Early Treatment of Diabetic Retinopathy Study (ETDRS) Severity Scale.[24] The UKPDS used four photographic fields (central macula, nasal macula, temporal macula, and optic disc), rather than the standard seven ETDRS fields.

Major Findings

The final results of the UKPDS were published in 1998.[25,26] Baseline examination of 2,964 patients revealed that the prevalence of any level of retinopathy at the time of diagnosis was 39% in men and 37% in women.[26] The overall degree of retinopathy was mild, with approximately one of five subjects having only isolated microaneurysms in one eye, with 97% of these patients having three or fewer microaneurysms. The few cases of severe retinopathy were seen more commonly in men. Male sex, elevated fasting plasma glucose, and systolic blood pressure (SBP) were independent risk factors for increasing retinopathy severity.

The median glycosylated hemoglobin levels over the subsequent 10 years were 7.0% in the intensive treatment group, compared to 7.9% in the conventional group (this 0.9% difference was half that seen in the DCCT, where the difference was 1.9%).[25] There was an overall 25% risk reduction of microvascular complications in the intensive treatment group. Most of the risk reduction was attributed to the decreased requirement of photocoagulation. Other endpoints such as amputation, renal failure, and unilateral blindness did not reach statistical significance. Cataract extraction occurred less frequently in the intensive treatment group. There were no differences in microvascular endpoints between the different diabetic medications.

Surrogate endpoints were measured every 3 years, and included two-step progression of diabetic retinopathy and visual acuity. After 6 years of follow-up, fewer subjects in the intensive group had a two-step deterioration in retinopathy, even after controlling for the need for photocoagulation. At 12 years, the risk reduction of two-step deterioration in retinopathy was 21%. In comparison, the DCCT had a 63% risk reduction.[9]

The UKPDS examined whether the presence of microaneurysms, in the absence of other lesions, has predictive value in the progression of diabetic retinopathy.[27] Of the 5,102 patients enrolled in the UKPDS, 3,569 had fundus photographs at the time of entry into the study. Of these patients, 2,424 also had fundus photographs at 6 years, and 1,809 of these had either no retinopathy or isolated microaneurysms at baseline. Spontaneous resolution of microaneurysms occurred at rates of 47.5%, 30.8%, and 16.7%, for eyes with 1, 3, or 5 or more microaneurysms, respectively, at 6 years. There was a correlation between the number of microaneurysms at the time of entry and subsequent worsening of retinopathy at 6 and 12 years. This would seem intuitive since longer duration of disease is likely to cause more severe retinopathy. However, the authors argue that the number of microaneurysms alone had predictive value, because the rate of progression between entry and 6 years is "very similar" to that between 3 and 9 years. Regression analysis was not performed.

Risk factors for the 6-year progression of diabetic retinopathy were examined in

1,919 patients with fundus photographs and complete clinical data at 6 years.[28] At baseline, 1,216 (63.4%) had no retinopathy. At 6 years, 22% of these patients had developed some level of retinopathy. The independent risk factors for the incidence of retinopathy were elevated glycosylated hemoglobin, elevated SBP, and interestingly, not smoking. In patients with existing retinopathy at baseline, 37% had a two-step or more progression of retinopathy according to a modified ETDRS retinopathy severity scale. The independent risk factors for progression of existing retinopathy were elevated glycosylated hemoglobin level, male sex, older age, and again, not smoking.

The Hypertension in Diabetes Study was an important component of the UKPDS that was introduced in 1987 to examine the effects of blood pressure control in the UKPDS cohort[29]; 1,148 patients with type 2 diabetes and hypertension, defined as SBP > 160 mmHg and/or diastolic blood pressure (DBP) > 90 mmHg if treatment naive for hypertension, or SBP > 150 mmHg and/or DBP > 85 mmHg if already receiving treatment, were enrolled. Patients were randomized to tight blood pressure control (SBP < 150 mmHg and DBP < 85 mmHg), or less tight control (SBP < 180 mmHg and DBP < 105 mmHg), using either an angiotensin-converting enzyme (ACE) inhibitor or a beta blocker.

Median follow-up in the Hypertension in Diabetes Study was 9.3 years. The mean blood pressure of the tight control group over the 9 years was 144/82 and 154/87 for the less tightly controlled group ($P < 0.0001$). The tightly controlled group had fewer microaneurysms, hard exudates, and cotton-wool spots at 4.5 and 7.5 years. There was also a 34% risk reduction for a two-step or more deterioration in the ETDRS retinopathy severity scale ($P = 0.0004$), 35% risk reduction for requiring photocoagulation ($P = 0.023$), and a 47% risk reduction in losing 3 lines or more of visual acuity ($P = 0.004$). These effects were seen in both patients with no retinopathy at baseline (primary prevention), and those with existing retinopathy (secondary prevention). However, the differences in blood pressure between the two groups disappeared within 2 years of termination of the trial, and the risk reductions for all major endpoints were lost. This indicated that benefits of previous blood pressure control are not sustained unless tight control is maintained.[30]

Implications for Clinical Practice

The UKPDS showed that tight glycemic control and blood pressure control are both essential in preventing the incidence and progression of diabetic retinopathy in patients with type 2 diabetes. Glycemic control was by then a well-established means to prevent microvascular complications, but the UKPDS had a significant role in establishing blood pressure control as an effective co-strategy.

The exact mechanisms of how hypertension worsens the course of diabetic retinopathy are still in investigation. However, it appears that the shear force applied by elevated blood pressures against retinal vasculature with impaired autoregulation appears to play a role in exacerbating the microvascular insults caused by hyperglycemia.[29]

Unanswered Questions

The UKPDS was one of the largest clinical trials in medicine and provided many insights into diabetes care, but there were several limitations to its design. It was noted after the trial commenced that achieving intensive treatment with monotherapies was difficult. One of the initial goals of the study was to compare the efficacies of the different medications, but this was not possible due to most patients requiring more than one medication. Furthermore, approximately 80% of the patients in the control group could not maintain fasting plasma glucose levels <270 mg/dl, and were crossed over into the treatment arm.[31] Such crossovers diluted the treatment and control groups, resulting in only modest reductions in glycosylated hemoglobin levels.

The methodologies and endpoints regarding diabetic retinopathy in the UKPDS also had several differences with other major population-based studies described in this chapter. For example, the UKPDS used four-field fundus photography for grading purposes, rather

than the standard seven-field ETDRS retinal photography. This may have decreased the sensitivity in grading retinopathy.

The emphasis on the number of microaneurysms was a unique but likely relevant endpoint, since all of the patients were newly diagnosed patients with minimal retinopathy. However, it remains unclear whether the number of microaneurysms can truly predict the progression of disease, independent of other risk factors such as glycemic indices and as this study showed, hypertension.

The presentation of visual acuity and anatomic outcomes was also less comprehensive compared to other studies. For example, the UKPDS provided limited data regarding the prevalence and progressive incidence of visual impairment and blindness. Also, data specific to macular edema, the most common cause of visual loss in diabetic retinopathy, was often lost in the general category of subjects who required photocoagulation (lumped together with panretinal photocoagulation for neovascular disease).

Lastly, the UKPDS was carried out in white populations in the United Kingdom, where the access to and delivery of medical care differs greatly from the United States. The data from the UKPDS provides insightful information regarding the epidemiology and risk factors for diabetic retinopathy in patients with type 2 diabetes, but care should be taken when applying the results to other populations and individual patients.

III. WISCONSIN EPIDEMIOLOGIC STUDY OF DIABETIC RETINOPATHY

Introduction

In the 1970s, there was limited data concerning the epidemiology of diabetic retinopathy. Information on the prevalence and severity of retinopathy in a large cohort of diabetic patients was needed to plan a well-coordinated approach to this important public health problem. To recommend the guidelines for ophthalmologic care, patients with a broad distribution of retinopathy severity needed to be examined and followed up, and patients with risk factors for developing visual loss from diabetic retinopathy needed to be identified. Such data would also be helpful in planning future clinical trials to better define etiologic relationships and to assess the effects of new treatments.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) was established to address these issues. The WESDR was a cross-sectional and longitudinal study designed to provide data on the prevalence, severity, incidence, and progression of diabetic retinopathy in a geographically defined population of diabetic patients. It was the largest and most comprehensive epidemiologic study of diabetic retinopathy.

Background and Study Questions

Established in the late 1970s, the WESDR sought (a) to describe the prevalence and severity of diabetic retinopathy and its component lesions, and to determine the frequency of visual impairment in a total population of patients with diabetes who were under physicians' care in a defined geographic region, and (b) to determine the relationships between risk factors, prevalence, and severity of diabetic retinopathy in these patients.

Patients Included in the Study

The patient population described in the WESDR was obtained in the following manner: in an 11-county area in southern Wisconsin, 452 primary care physicians (99% of total) provided charts of all diabetic patients they had seen over a 1-year period. Approximately 10,000 charts were identified and reviewed, and a sample of approximately 3,000 patients was selected for examination.

Intervention and Outcome Measures

Patients were examined in the early 1980s to determine the prevalence and severity of diabetic retinopathy and associated risk variables. The WESDR cohort was reexamined periodically thereafter to determine the

incidence and progression of visual impairment and retinopathy. Both the younger- and older-onset groups were reexamined 4 and 10 years later, but only the younger-onset group was reexamined at the 14-year follow-up due to the high death rate among older-onset patients.

Outcome measures included visual acuity using the ETDRS protocol: visual impairment, grouped into four levels (no impairment: >20/40; mild impairment: 20/40 to 20/63; moderate impairment: 20/80 to 20/160; blind: ≤20/200); the relative contribution of diabetic retinopathy in eyes with impaired vision; the severity and progression of diabetic retinopathy using a modification of the Airlie House classification scheme that specifies nine levels[32]; the presence of macular edema; and metabolic control as determined by glycosylated hemoglobin and protein levels in the urine.

Major Findings

Fifteen percent of patients were diagnosed with diabetes before 30 years of age and were taking insulin (younger-onset group), while 85% were diagnosed at 30 years of age or older (older-onset group). The older-onset patients had their diagnosis confirmed by a random or postprandial serum glucose level of at least 200 mg/dl or a fasting level of at least 140 mg/dl, and approximately 50% of these patients were taking insulin.

Visual impairment (visual acuity in the better eye ≤ 20/40) increased with increasing age. Legal blindness (visual acuity in the better eye ≤ 20/200) was related to the duration of diabetes in both the younger- and older-onset groups. In the younger-onset group, legal blindness was present in 3.6% of patients, and diabetes was at least partly responsible in 86% of such patients. In the older-onset group, legal blindness was present in 1.6%, and diabetes was a cause in 33%.[33]

In the younger-onset group, the prevalence of diabetic retinopathy was 17% in patients with diabetes <5 years and 98% for those with diabetes for ≥15 years. Proliferative retinopathy was present in 23%. Retinopathy severity was related to longer duration of diabetes and higher levels of glycosylated hemoglobin.[34] In the older-onset group, the prevalence of retinopathy was 29% in patients with diabetes for <5 years and 78% in those with diabetes ≥15 years. Proliferative disease was present in 9%. Retinopathy severity was related to longer duration of diabetes, younger age at diagnosis, higher glycosylated hemoglobin levels, higher SBP, and the use of insulin.[35]

In the younger-onset group, the prevalence of macular edema varied from 0% in those with diabetes for <5 years to 29% in those with diabetes for ≥20 years. In the older-onset group, prevalence rates of macular edema varied from 3% in those with diabetes <5 years to 28% in those with diabetes ≥20 years. Macular edema was associated with longer duration of diabetes, higher glycosylated hemoglobin level, and the presence of proteinuria.[36]

In the younger-onset group, the prevalence rate was 14% for panretinal photocoagulation and 4% for focal laser, and in the older-onset group, the rates were 4% and 3%, respectively. At the time of the WESDR, focal treatment for macular edema had not been proven to be efficacious.[37]

At the 4-year follow-up examination, the rates of blindness were 1.5% in younger-onset patients, 3.2% in the older-onset insulin users, and 2.7% in the older-onset nonusers of insulin. The rate of blindness increased with increasing age, increasing retinopathy severity, and lower baseline visual acuity in all three groups.[38] The 4-year incidence of retinopathy (59%, 47%, and 34%) and the progression to proliferative disease (11%, 7%, and 2%) were highest in the younger-onset group, intermediate in the older-onset insulin user group, and lowest in the older-onset insulin nonuser group, respectively (see Table 7A.1).[39,40]

At the 10-year follow-up examination, the incidence of blindness was 1.8% in the younger-onset patients, 4.0% in the older-onset insulin users, and 4.8% in the older-onset nonusers of insulin.[41] The 10-year incidence of retinopathy (89%, 79%, and 67%) and the progression to proliferative disease (30%, 24%, and 10%) were highest in the younger-onset group, intermediate in the older-onset insulin user group, and lowest in the older-onset insulin nonuser group, respectively (Table 7A.1).[42]

TABLE 7A.1 **Rate of Blindness, Incidence of Retinopathy, and Progression to Proliferative Disease at the 4- and 10-Year Follow-Up Examinations for Younger-Onset Patients, Older-Onset Insulin Users, and Older-Onset Nonusers of Insulin in the Wisconsin Epidemiologic Study of Diabetic Retinopathy**

	4-year follow-up examination			10-year follow-up examination		
	Younger-onset Patients (%)	Older-onset patients taking insulin (%)	Older-onset patients not taking insulin (%)	Younger-onset patients (%)	Older-onset patients taking insulin (%)	Older-onset patients not taking insulin (%)
Rate of blindness	1.5	3.2	2.7	1.8	4.0	4.8
Incidence of retinopathy	59	47	34	89	79	67
Progression to proliferative disease	11	7	2	30	24	10

At the 14-year follow-up examination, the incidence of blindness was 2.4%, the rate of progression to proliferative disease was 37%, and the incidence of macular edema was 26%. Visual loss (doubling of the visual angle) was associated with older age, longer duration of diabetes, higher glycosylated hemoglobin, higher SBP and DBP, the presence of proteinuria, more pack-years smoked, the presence of macular edema, and more severe retinopathy.[43,44]

At the 25-year follow-up examination, the cumulative incidence of blindness was 3%,[45] progression of diabetic retinopathy was 83%,[46] progression to proliferative retinopathy was 42%,[46] and cumulative incidence of macular edema was 29%.[47] Multivariate analyses determined that the risk factors for doubling of the visual angle were presence of cataract, history of glaucoma, higher glycosylated hemoglobin, and proteinuria.[45]

There was a strong association between glycosylated hemoglobin levels and multiple outcomes. At both the 4- and 10-year follow-up visits, for all three groups (younger-onset, older-onset insulin users, older-onset nonusers of insulin), there was a statistically significant relationship between glycosylated hemoglobin and the incidence of retinopathy, progression of retinopathy, and progression to proliferative retinopathy. At the 10-year follow-up visit, this relationship also existed for macular edema in the younger- and older-onset groups and for visual loss in the younger-onset group and the older-onset insulin user group.[48,49] At the 14- and 25- year follow-up visits, glycosylated hemoglobin level was associated with doubling of the visual angle.[43,45]

An important relationship also existed between hypertension and the incidence and progression of diabetic retinopathy. Elevation of both SBP and DBP was associated with an increased risk of developing proliferative retinopathy in the younger-onset and older-onset insulin user groups.[50]

Dyslipidemia, particularly in patients with diabetes with poor glycemic control, is characterized by increased levels of cholesterol, low-density lipoproteins (LDLs), and triglycerides, and by decreased levels of high-density lipoproteins (HDLs). In patients who used insulin, there was a significant trend of increasing severity of retinopathy and retinal hard exudates with increasing cholesterol levels.[51]

Nephropathy is a common microvascular complication of diabetes, and proteinuria was measured in the WESDR. Gross proteinuria was found to be a risk factor for proliferative retinopathy in younger-onset patients.[52]

All-cause and cause-specific mortality was determined from death certificates in the WESDR. The presence of more severe

retinopathy or visual impairment in patients with diabetes was a risk indicator for all-cause, stroke, and ischemic heart disease mortality.[53]

Implications for Clinical Practice

The WESDR provided data on the prevalence and severity of diabetic retinopathy, the frequency of visual impairment, and the relationships of risk factors in a geographically defined population of patients with diabetes. Before the WESDR, most information about the prevalence, severity, incidence, and progression of diabetic retinopathy had been derived from specific groups of patients presenting to specific clinics, where patients with severe disease may be overrepresented. This study was unique in that a large cohort with a broad distribution of retinopathy severity was examined at baseline and reexamined 4, 10, 14, and 25 years later.

Longitudinal data from the WESDR has proven valuable in the design of clinical trials that evaluate interventions to prevent incidence of new events or progression of existing lesions. Reliable incidence rates of visual impairment have had important public health uses, such as projecting needs for services and costs, defining etiologic relationships, and assessing the effect of treatment. In addition, information obtained in the WSEDR has helped define current guidelines for care in patients with diabetes. For example, ophthalmologic evaluation for detection of vision-threatening retinopathy is not indicated in patients who are younger than 12 years since proliferative disease is rare in that age group. Thereafter, patients should be under ophthalmologic observation depending on the duration of diabetes and the severity of retinopathy detected. Although the progression from no retinopathy to proliferative disease is low in the first few years after diagnosis in younger-onset patients, the disease shows continued progression with increasing duration. In older-onset patients, proliferative disease is observed after a shorter duration of diabetes, and continued progression occurs with increasing duration. Periodic, lifelong ophthalmologic care is therefore absolutely essential for all patients with diabetes.

In addition to providing data of considerable importance from a public health standpoint, the WESDR has provided clinically useful information for individuals with diabetes. The WESDR demonstrated that several modifiable risk factors are associated with diabetic retinopathy and visual loss. The need for improved glycemic control, at any level of hyperglycemia and at any time during the course of diabetes, and improved control of blood pressure cannot be overemphasized, while control of cholesterol and cessation of smoking are additional recommendations. For patients with diabetes, risk factor modification can have substantial impact on the vision-threatening complications.

Unanswered Questions

In the WESDR, almost all patients with diabetes in an 11-county area in southern Wisconsin who were seen by their primary care physicians during a 1-year period were identified. A sample of these patients was available for ophthalmologic examination. These patients, by definition, demonstrated a level of compliance that may not be representative of the entire diabetic population. In addition, the racial composition of this group may not reflect the demographics of the population as a whole. Since the manifestations of diabetes are related to many factors including compliance and race, the findings of the WESDR may be applicable only to certain patient populations.

Patients were initially examined in the early 1980s, a time when many of the currently accepted treatments for diabetic retinopathy had not yet been proven effective. Some of the findings of the WESDR, therefore, may not be applicable today because of the 25-year evolution of the standard of care. Ironically, it was the WESDR that helped establish the current standard of care by substantially increasing the available epidemiologic data and by identifying modifiable risk factors for diabetic retinopathy.

The WESDR remains one of the most valuable epidemiologic studies ever conducted, as data obtained in the WESDR helped define

screening guidelines for ophthalmologic care and identify risk factors for retinopathy and visual loss. This study has provided important public health data and clinically useful information for individuals with diabetes.

IV. BEAVER DAM EYE STUDY

Background and Study Questions

In adult individuals, the majority of newly diagnosed cases of diabetes are noninsulin dependent (type 2). In the 1980s, there were conflicting data regarding the prevalence of diabetic retinopathy at the time of diagnosis of noninsulin-dependent diabetes mellitus (NIDDM), with some studies suggesting that retinopathy is relatively rare, whereas others suggested that retinopathy may appear at or shortly after the time of diagnosis.

To address this and other issues related to diabetic eye disease, the Beaver Dam Eye Study was established. It sought to evaluate the prevalence of diabetic retinopathy in people aged between 43 and 86 with previously diagnosed and newly discovered NIDDM who lived in a defined geographic area. It also sought to determine if relationships existed between older-onset diabetes and cataract, glaucoma, and age-related macular degeneration.

Patients Included in Study

The patient population described in the Beaver Dam Eye Study was obtained in the following manner: a census of the residents of Beaver Dam, Wisconsin, was performed in the late 1980s to identify individuals aged between 43 and 84. Almost 6,000 people were identified, and 4,926 (83%) of these were examined. Some people (4.5%) permitted only an interview.

Patients whose diabetes was diagnosed before 30 years of age were excluded from analysis because of the small sample size and because they typically were insulin dependent.

The remaining NIDDM patients ($n = 416$) were divided into one group with newly discovered NIDDM ($n = 49$) and three groups with previously diagnosed diabetes at 30 years of age or after: insulin users ($n = 79$), those using oral hypoglycemic agents and/or diet ($n = 271$), and those using a combination of oral hypoglycemic agents and insulin ($n = 17$).

Intervention and Outcome Measures

Patients were examined over a 30-month period in the late 1980s to determine the prevalence and severity of diabetic retinopathy in adults with newly discovered and previously diagnosed diabetes.[54] Additional data obtained included standardized grading of lens opacities to determine the prevalence of cataract in older-onset patients with diabetes[55]; standardized grading of optic discs and cups, measurement of intraocular pressure, and visual field testing to evaluate the relationship of open-angle glaucoma to older-onset diabetes[56]; and standardized grading for lesions associated with age-related maculopathy to examine the association among hyperglycemia, diabetes status, and age-related maculopathy in older-onset diabetics.[57]

The Beaver Dam Eye Study cohort was reexamined 5 and 10 years later to evaluate the change in visual acuity over this period. Of the surviving patients who had participated in the baseline examination, 81% participated in the 5-year follow-up examination,[58] and of these, 83% participated in the 10-year follow-up.[59] Since the longitudinal data did not specifically address changes in patients with diabetes, the results are not covered in this review.

Major Findings

The prevalence of retinopathy was lowest in people with newly discovered NIDDM (10%), intermediate in those who were using oral hypoglycemic agents and/or diet (30%) or oral hypoglycemic agents combined with insulin (35%), and highest in insulin users (70%). Proliferative retinopathy was present in <1% of nonusers of insulin and in 6% of insulin users. In the newly diagnosed group, none had proliferative retinopathy and 2% had macular edema.[54]

Older-onset diabetes was associated with increased frequency of a specific age-related

lens change, cortical opacity, and increased frequency of cataract surgery.[55]

Rates of persons meeting optic disc, visual field, and intraocular pressure criteria for definite glaucoma were more common in the older-onset diabetes group than in the group without diabetes.[56]

The data also suggested that diabetes was not related to early age-related maculopathy or geographic atrophy.[57]

Implications for Clinical Practice

These data suggest that asymptomatic individuals discovered to have NIDDM during epidemiologic studies may not need immediate ophthalmoscopic examination at the time of their diagnosis because they have a relatively low risk of visual loss from diabetic retinopathy at that time. In the Beaver Dam Eye Study, it was unusual to discover either proliferative retinopathy or macular edema in the newly diagnosed group. However, the initial ophthalmoscopic examination may represent an opportunity to educate newly diagnosed patients about the importance of controlling modifiable risk factors and the importance of periodic ophthalmologic examination.

Since the presence of cataract and open-angle glaucoma was found to be increased in older-onset diabetes, patients should be educated and periodically followed up for these conditions as well.

Unanswered Questions

Differences in the reported prevalence of diabetic retinopathy in people with newly discovered NIDDM may be due to variations in the time between onset and detection of diabetes. Because the prevalence of retinopathy increases with increasing duration of hyperglycemia, retinopathy is more likely to be found in patients who have a longer interval between the onset of diabetes and its discovery. This interval may depend on a variety of factors including the availability of and access to medical care, and the health care-seeking behavior of the specific group. The patient population studied in the Beaver Dam Eye Study was, by definition, relatively compliant and this may not represent the behavior patterns of other groups.

V. BLUE MOUNTAINS EYE STUDY

Background and Study Questions

To better understand visual impairment and ocular disease among a representative older community in a geographically defined area, the Blue Mountains Eye Study was established. It sought (a) to estimate the prevalence and severity of diabetic retinopathy among persons with both previously diagnosed and undiagnosed diabetes and (b) to examine systemic and ocular associations (cataract and glaucoma) with diabetic retinopathy.

Patients Included in the Study

The patient population described in the Blue Mountains Eye Study was obtained in the following manner: a census of the residents of an urban area west of Sydney, Australia was performed in the early 1990s to identify individuals born before 1943 (aged 49 years or older). Approximately 4,000 people were identified, and 3,654 (88%) of them were examined. Some patients permitted only an interview.

The population examined included 6% ($n = 217$) with a history of diabetes, including 21% ($n = 46$) who were treated with insulin, 46% ($n = 99$) treated with oral hypoglycemic agents, and 33% ($n = 72$) treated with diet only. An additional 1% ($n = 39$) was found to have undiagnosed diabetes, with a fasting blood glucose of 7.8 mmol/L or more.

Intervention and Outcome Measures

Patients were examined over a 2-year period in the early 1990s to determine the prevalence and severity of diabetic retinopathy in those with newly discovered and previously diagnosed diabetes.[60] Additional data obtained included standardized grading of lens opacities to determine the prevalence of cataract in a defined older diabetic population[61] and

standardized grading of optic discs, applanation tonometry, and automated perimetry to evaluate the relationship of open-angle glaucoma to diabetes.[62]

The Blue Mountains Eye Study cohort was reexamined 5 years later to evaluate the change in visual acuity over this period. Of the surviving patients who had participated in the baseline examination, 75% participated in the 5-year follow-up examination. The 5-year incidence of diabetic retinopathy among the 139 patients with diabetes diagnosed at baseline was 22%.[63] Retinopathy progression was noted in 26% of participants with retinopathy at baseline. New proliferative retinopathy was found in only 4% of individuals with baseline nonproliferative retinopathy. The risk factors associated with retinopathy progression were elevated fasting glucose and longer diabetes duration.

Major Findings

Diabetes was present in 7% of the population. Signs of diabetic retinopathy were found in 2.3% of the overall study population (32% of those with known or newly diagnosed diabetes). The prevalence was 1.7% in patients younger than 60 years of age, 2.4% in patients aged between 60 and 69 years, 2.7% in patients aged between 70 to 79 years, and 2.3% in patients 80 years of age or older. Higher blood glucose was related to the finding of moderate-to-severe retinopathy compared to milder retinopathy.[60]

The presence, severity, and progression of diabetic retinopathy were strongly related to the known duration of diabetes. Retinopathy was found in 21% of those with diabetes diagnosed for <1 year versus 68% in patients with a diabetes history for 20 years or longer.[60]

In the newly diagnosed cases, retinopathy was prevalent in 16%. No cases of proliferative retinopathy or macular edema were found in this group.[60]

In the Blue Mountains Eye Study, the presence of posterior subcapsular cataract and past cataract surgery were associated with diabetes.[61]

In addition, the prevalence of glaucoma and ocular hypertension were increased in patients with diabetes compared with those without diabetes. In many cases, glaucoma was diagnosed before diabetes.[62]

Implications for Clinical Practice

The Blue Mountains Eye Study provided an estimate of diabetic retinopathy prevalence in a representative Australian population aged 49 years or more. Systemic and ocular associations were also explored.

This study estimated the prevalence and severity of diabetic retinopathy in people with undiagnosed noninsulin-dependent diabetes, detected from fasting blood glucose measurements. The failure to find any cases of vision-threatening retinopathy among the newly diagnosed group suggests that for such patients, ophthalmologic examinations can be scheduled on a routine basis, unless visual symptoms are present. However, the clinical diagnosis of diabetes provides an opportunity to emphasize the importance of blood glucose control and the need for periodic ophthalmologic examinations.[60]

For patients with known diabetes, the results of the Blue Mountains Eye Study and the Beaver Dam Eye Study are similar. A slightly lower rate for the prevalence of any retinopathy was found in the current study (32%) as compared with the Beaver Dam study (37%), but the rates for signs of proliferative retinopathy (1.6% in Blue Mountains vs. 1.8% for Beaver Dam) and macular edema (4.3% in Blue Mountains vs. 3.9% in Beaver Dam) were very similar.[54,60]

Since the presence of cataract and open-angle glaucoma was found to be increased in diabetes, patients should be educated and periodically followed for these conditions as well.

Unanswered Questions

The Blue Mountains Eye Study found a higher overall retinopathy prevalence for patients with newly diagnosed diabetes (16%) compared with the Beaver Dam Eye Study (10%). This difference could reflect the different criterion used to detect undiagnosed diabetes (elevated fasting blood glucose in

the Blue Mountains Study vs. nonfasting glycosylated hemoglobin in the Beaver Dam Study), differences in access to health care, and the different probabilities of early diagnosis between the two communities.[54,60]

VI. LOS ANGELES LATINO EYE STUDY

Background and Study Questions

The Latino population is the largest minority group in the United States, comprising 12.5% of the US population in the 2000 census. Latinos are individuals who are born into or have descended from a Spanish-speaking community, regardless of the race. In the United States, they are a heterogeneous group, with the majority of Mexican ancestry (66%). Latinos are a racial/ethnic population with unique ocular disease characteristics, yet there have been relatively few epidemiologic studies in the Latino population.[64]

To study the prevalence of eye disease and to determine both modifiable and nonmodifiable risk indicators that may be associated with these ocular diseases among Latinos, the Los Angeles Latino Eye Study (LALES) was established. It had five specific aims: (a) to determine the age-specific prevalence of blindness, visual impairment, and ocular disease among Latinos 40 years or older; (b) to determine what proportion of the prevalence of blindness and visual impairment can be attributed to refractive error, lens opacities, glaucoma, diabetic retinopathy, and age-related maculopathy; (c) to evaluate the importance of suggested risk factors and the degree to which these factors may be associated with visual impairment and the prevalence of each ocular disease; (d) to determine the impact of blindness, visual impairment, and presence of ocular disease and comorbid medical conditions on self-reported visual impairment and health-related quality of life; and (e) to evaluate utilization of eye care and general health-care services.[64]

Patients Included in the Study

The patient population described in the LALES was obtained in the following manner: a census of the residents of an area of Los Angeles County, California was used to identify Latino individuals aged 40 years or older. Almost 8,000 people were identified, and 6,357 (82%) of these were examined. Some patients (7%) permitted only an interview.[64]

Intervention and Outcome Measures

Patients were examined from 2000 to 2003 to determine the prevalence and severity of diabetic retinopathy in those with newly discovered and previously diagnosed diabetes. Additional data obtained included standardized grading of lens opacities, evaluation for open-angle glaucoma, and measurements of quality of life and health-care utilization.[64]

Primary outcome variables included prevalence of visual impairment, blindness, cataract, glaucoma, diabetic retinopathy, and age-related macular degeneration. Secondary outcomes included risk factors associated with eye disease, health-related quality of life, and vision-related quality of life.[64]

Major Findings

Diabetes was present in 20% of the population. Retinopathy was present in 47% of patients with diabetes, and proliferative retinopathy was present in 6%. Macular edema was observed in 10% of patients; 60% (6% of total diabetic population) had clinically significant macular edema; 8% of diabetics had either proliferative diabetic retinopathy with high-risk characteristics or clinically significant macular edema requiring laser treatment.[65]

Twenty percent of the patients with diabetes were newly diagnosed, and retinopathy was noted in 23% of these. Proliferative retinopathy was present in <1% and macular edema was present in 2.4% of newly diagnosed patients.[65] The rate of visual impairment was 6% in those with diabetes as compared with 2% in those without diabetes.[65]

The risk factors associated with any diabetic retinopathy were being male, higher glycosylated hemoglobin, longer duration

of diabetes, higher SBP, and being on insulin treatment.[66] The latter three factors were also associated with proliferative diabetic retinopathy. Greater severity of diabetic retinopathy was associated with lower general and vision-specific health-related quality of life.[67]

In the 4-year follow-up examination, having diabetes was determined to be an independent risk factor for developing new visual impairment and monocular blindness.[68] The 4-year incidence of diabetic retinopathy, macular edema, and clinically significant macular edema were 34%, 5.4%, and 7.2%, respectively.[69] Progression from nonproliferative retinopathy to proliferative retinopathy and high-risk proliferative retinopathy occurred in 5.3% and 1.9%, respectively. Progression of retinopathy from baseline was found in 38.9 %. The incidence of new retinopathy was associated with longer duration of diabetes and younger age, and macular edema was associated with longer duration of diabetes.

Implications for Clinical Practice

Data from the LALES suggests that the prevalence and incidence of diabetic retinopathy are high among Latinos of primarily Mexican ancestry. The increase in prevalence and incidence of retinopathy with longer duration of diabetes emphasizes the importance of early diagnosis and management in Latinos. Since Latinos are the largest minority group and the fastest growing segment of the US population, these results have important public health implications.[65]

Unanswered Questions

Given that visual loss from diabetic retinopathy can be reduced with strict glycemic control and laser treatment, there will be an increased need for care and the implementation of culturally appropriate screening and prevention programs directed at Latinos.[65] Data on the risk factors for the incidence of diabetic retinopathy are forthcoming, and longer-term incidence studies are being planned.

VII. ACTION TO CONTROL CARDIOVASCULAR RISK IN DIABETES EYE STUDY

Background and Study Questions

Poor glycemic control and hypertension had been established risk factors for diabetic retinopathy and its progression. In addition, the WESDR[51] and the ETDRS[70] studies also found that dyslipidemia was associated with more hard exudates and vision loss. However, at the time, there were no randomized intervention trials to examine the effect of treating dyslipidemia on diabetic retinopathy. Furthermore, while the DCCT and United Kingdom Prospective Diabetes Study Group[25] examined patients with type 1 diabetes and newly diagnosed type 2 diabetes, little was known about the treatment effects of patients with long-standing type 2 diabetes.

In order to address these issues, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was organized. It was a large multicenter randomized controlled clinical trial to determine whether intensive glycemic control, intensive hypertension therapy, and using fibrates to lower serum triglycerides and increase high-density lipoproteins (HDL) in addition to the use of statins for LDL, would have an effect on patients with established type 2 diabetes.[71]

The ACCORD-EYE trial was the main microvascular outcome of the ACCORD study, in which the following primary questions were asked[71]: (a) Would targeting glycosylated hemoglobin to <6.0% reduce the development and progression of diabetic retinopathy compared to 7.0% to 7.9%? (b) In patients with type 2 diabetes whose LDL levels were decreased with statins, would the addition of fibrates to lower triglycerides and increase HDL decrease the development and progression of diabetic retinopathy? (c) Would targeting SBP to <120 mmHg compared to <140 mmHg decrease the development and progression of diabetic retinopathy?

Patients Included in the Study

10,251 subjects from 77 clinical sites in the United States and Canada were recruited

to participate in the ACCORD study.[72] The ACCORD study began in 2001, and ACCORD-EYE was added in 2003. All ACCORD participants were eligible for the ACCORD-EYE study, except for those with proliferative diabetic retinopathy treated with laser and/or vitrectomy at baseline. Of 3,472 patients eligible for follow-up, 2,856 (82%) had both baseline and 4-year follow-up ophthalmic examinations.

Intervention and Outcome Measures

The 10,251 ACCORD participants were randomized to undergo intensive glycemic control (target glycosylated hemoglobin <6.0%) or standard therapy (target 7.0% to 7.9%). Of these participants, 5,518 with dyslipidemia were randomized to receive simvastatin with either fenofibrate or placebo. The remaining 4,733 were randomized to intensive blood pressure control (<120 mmHg systolic) or standard therapy (<140 mmHg systolic).

The primary outcome of the ACCORD-EYE study was the composite endpoint of either progression of diabetic retinopathy as defined as an increase of three or more steps on the ETDRS Severity Scale for Persons, or development of proliferative diabetic retinopathy requiring photocoagulation or vitrectomy at 4 years.[71]

Major Findings

Diabetic retinopathy progressed in 7.3% with intensive glycemic control, compared to 10.4% with standard treatment ($P = 0.003$).[72] The respective rates of moderate vision loss were 23.8% and 26.3%. There was an increased death rate in the intensive group (5.0% compared to 4.0%), which necessitated early termination of this segment of the study.

LDL was equally decreased in both lipid treatment groups, while triglycerides were reduced more and HDL marginally increased in the fenofibrate group. Diabetic retinopathy progressed in 6.5% with fenofibrate compared to 10.2% with placebo ($P = 0.006$). There was no difference in visual outcomes.

The median SBP was 137 mmHg at baseline, which was decreased to 117 mmHg in the intensive group and 133 mmHg in the standard therapy group. The rates of diabetic retinopathy progression were 10.4% with intensive blood pressure control compared to 8.8% with standard treatment ($P = 0.29$).

Implications for Clinical Practice

The ACCORD-EYE study demonstrated that intensive glycemic control and multifactorial lipid control can slow the progression of diabetic retinopathy, but may not have significant effects on moderate vision loss. Interestingly, intensive blood pressure control did not confer an advantage over standard therapy. This was the first large study to address the effects of intensive treatment of patients with greater cardiovascular risk and longer-standing type 2 diabetes, which are the scenarios most commonly faced in actual clinical practice.

Unanswered Questions

The two main concerns about the parent ACCORD study was that intensive blood pressure and combination lipid therapies did not reduce cardiovascular events, and that intensive glycemic control resulted in increased mortality. From the ACCORD-EYE subgroup, while intensive glycemic and lipid control were associated with slower progression of diabetic retinopathy, this did not translate into improved visual outcomes. Longer follow-up studies and further subgroup analyses using redefined endpoints may be necessary to explain such outcomes.

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7B Diabetic Macular Edema: Clinical Trials

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I. DIABETIC MACULAR EDEMA

Early Treatment Diabetic Retinopathy Study

Introduction

In the 1960s, diabetic retinopathy was a growing public health problem and an important cause of blindness, chiefly because of proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME). The Diabetic Retinopathy Study (DRS) was successfully completed in the 1970s, and it served as the foundation for additional prospective, multicenter, randomized clinical trials. The DRS (discussed in detail in the section on Proliferative Diabetic Retinopathy) conclusively demonstrated that scatter panretinal photocoagulation (PRP) was effective in the treatment of PDR, and the remarkable benefit associated with treatment had important public health implications. Whereas the DRS results offered tremendous hope for patients with PDR, DME remained a significant clinical challenge, as macular edema was the leading cause of moderate visual loss in diabetic patients. It was in this historical context that the Early Treatment Diabetic Retinopathy Study (ETDRS) was organized.

Background

The ETDRS was established to address important questions related to diabetic retinopathy. Conducted in the 1980s, the ETDRS was even larger in scope and size than the recently completed DRS.

Before the ETDRS, there was no consensus regarding the optimal management of DME. Several small trials reported encouraging results using photocoagulation; however, it was suggested that treatment benefit might be limited to certain subgroups, such as eyes with focal rather than diffuse fluorescein leakage, or eyes with intact rather than damaged perifoveal capillaries.[1–4] One study involving macular photocoagulation sometimes used scatter treatment also, suggesting that scatter treatment itself might be beneficial for macular edema.[2] Questions regarding the roles of focal macular photocoagulation and scatter PRP in the treatment of DME remained unanswered. The ETDRS was designed to address these questions, as well as questions involving the use of scatter PRP in the treatment of earlier stages of retinopathy (mild to severe nonproliferative diabetic retinopathy [NPDR] and early PDR) and the use of aspirin.

The ETDRS sought to determine answers to three questions: whether focal photocoagulation was effective in the treatment of DME, when scatter PRP should be initiated to be most effective in the management of diabetic retinopathy, and whether aspirin was effective in altering the course of diabetic retinopathy. Each of these study questions is addressed separately. The management of DME is addressed in the subsequent text, and the other two arms of the ETDRS are reviewed in Chapter 7C.

Study Question

Is focal photocoagulation beneficial in the management of DME?

Patients Included in the Study

A total of 3,711 patients, with or without macular edema and mild-to-severe NPDR or early PDR (less than high risk), were enrolled.

Visual acuity (VA) criteria were 20/40 or better for eyes without macular edema and 20/200 or better for those with macular edema. Eyes with macular edema were analyzed separately as one arm of the study.

Macular edema was defined as retinal thickening or hard exudates at or within one-disc diameter of the center of the macula.[4,5] Clinically significant diabetic macular edema (CSDME) is defined in the following text. Definitions of mild, moderate, and severe NPDR as well as early PDR are included in the section discussing the early scatter treatment arm of the ETDRS (Chapter 7C).

Intervention and Outcome Measures

Eyes with macular edema were randomized to the immediate photocoagulation (focal and/or scatter) arm or the no treatment arm.

Specifically, eyes were divided among those without macular edema, those with macular edema and less severe retinopathy (mild or moderate NPDR), and those with macular edema and more severe retinopathy (severe NPDR or early PDR). One eye of each patient was randomized to deferral of treatment, and one eye to early photocoagulation using different combinations of scatter panretinal and macular focal photocoagulation (see Fig. 7B.1A–C). If an eye assigned to treatment deferral developed high-risk proliferative retinopathy, then scatter panretinal laser was initiated as per the DRS recommendations.

In eyes with macular edema and less severe retinopathy, those assigned to early photocoagulation received one of the four combinations: immediate focal and delayed mild scatter photocoagulation, immediate focal and delayed full scatter photocoagulation, immediate mild scatter and delayed focal photocoagulation, or immediate full scatter and delayed focal photocoagulation (Fig. 7B.1B).[4] In eyes with macular edema and more severe retinopathy, those assigned to early photocoagulation received one of the four combinations: immediate mild scatter and immediate focal photocoagulation, immediate mild scatter and delayed focal photocoagulation, immediate full scatter and immediate focal photocoagulation, or immediate full scatter and delayed focal photocoagulation (Fig. 7B.1C).[4,6]

Focal photocoagulation (also called focal/grid) was performed using a combination of direct focal treatment to microaneurysms (Fig. 7B.2) and/or grid photocoagulation to areas of diffuse fluorescein leakage or capillary nonperfusion (Fig. 7B.3). Focal photocoagulation consisted of treatment to all focal points of leakage located between 500 μm and two disc diameters (3,000 μm) from the center of the macula. Fifty- to one hundred-micrometer spots at 0.05 to 0.1-second duration were used. Focal lesions located between 300 and 500 μm from the center were treated only if the VA was 20/40 or worse and if the treating ophthalmologist did not believe that treatment would destroy the remaining perifoveal capillary network (see Table 7B.1). Grid photocoagulation consisted of 50 to 200 μm spots at 0.05 to 0.1 second duration, placed at least 500 μm from the center of the macula and no closer than 500 μm from the edge of the optic disc. The argon blue-green wavelength was used initially, but the green wavelength was used later (Table 7B.1).[4–6]

Outcome measures included moderate visual loss, defined as a loss of 15 or more letters (three lines on the ETDRS VA chart) from baseline, which is equivalent to a doubling of the visual angle (for example, a decrease from 20/25 to 20/50 or from 20/50 to 20/100).

Major Findings

In patients with macular edema, the ETDRS identified features that were associated with a particularly high risk of visual loss, termed CSDME. CSDME was defined by the ETDRS as any one of the following: (a) retinal thickening at or within 500 μm of the center of the macula; (b) hard exudates at or within 500 μm of the center of the macula, if associated with adjacent retinal thickening; (c) a zone or zones of retinal thickening one-disc area or larger in size, any part of which is within one-disc diameter of the center of the macula (see Table 7B.2)[6] CSDME was assessed by stereo-contact lens biomicroscopy and stereo photography.

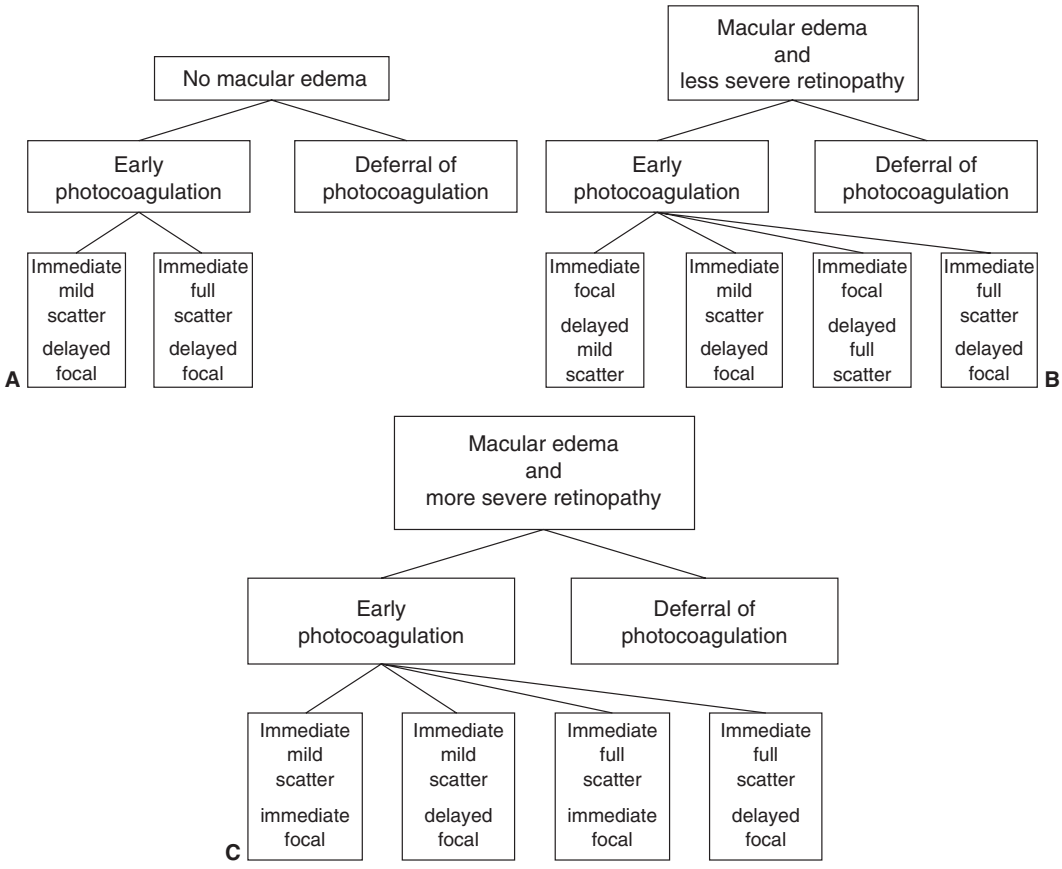

FIGURE 7B.1 **(A)** Early Treatment Diabetic Retinopathy Study (ETDRS) photocoagulation treatment scheme for eyes without macular edema and moderate-to-severe nonproliferative or early proliferative retinopathy. Eyes were assigned randomly to early photocoagulation or deferral of photocoagulation. Eyes assigned to early photocoagulation were further assigned randomly to either mild or full scatter (panretinal) photocoagulation. (From Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline characteristics. ETDRS Report No 7. *Ophthalmology*. 1991;98:741–756.) **(B)** ETDRS photocoagulation treatment scheme for eyes with macular edema and less severe retinopathy (mild-to-moderate nonproliferative retinopathy). Eyes were assigned randomly to early photocoagulation or to deferral of photocoagulation. Eyes assigned to early photocoagulation were further assigned randomly to either mild or full scatter (panretinal) photocoagulation, and to either immediate focal or delayed focal treatment. For eyes assigned to immediate focal treatment, the assigned scatter treatment was not applied initially, but only if severe nonproliferative retinopathy or worse developed during follow-up. (From Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline characteristics. ETDRS Report No 7. *Ophthalmology*. 1991;98:741–756.) **(C)** ETDRS photocoagulation treatment scheme for eyes with macular edema and more severe retinopathy. Eyes were assigned randomly to early photocoagulation or to deferral of photocoagulation. Eyes assigned to early photocoagulation were further assigned randomly to either mild or full scatter (panretinal) photocoagulation, and to either immediate focal or delayed focal treatment for at least 4 months. (From Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline characteristics. ETDRS Report No 7. *Ophthalmology*. 1991;98:741–756.)

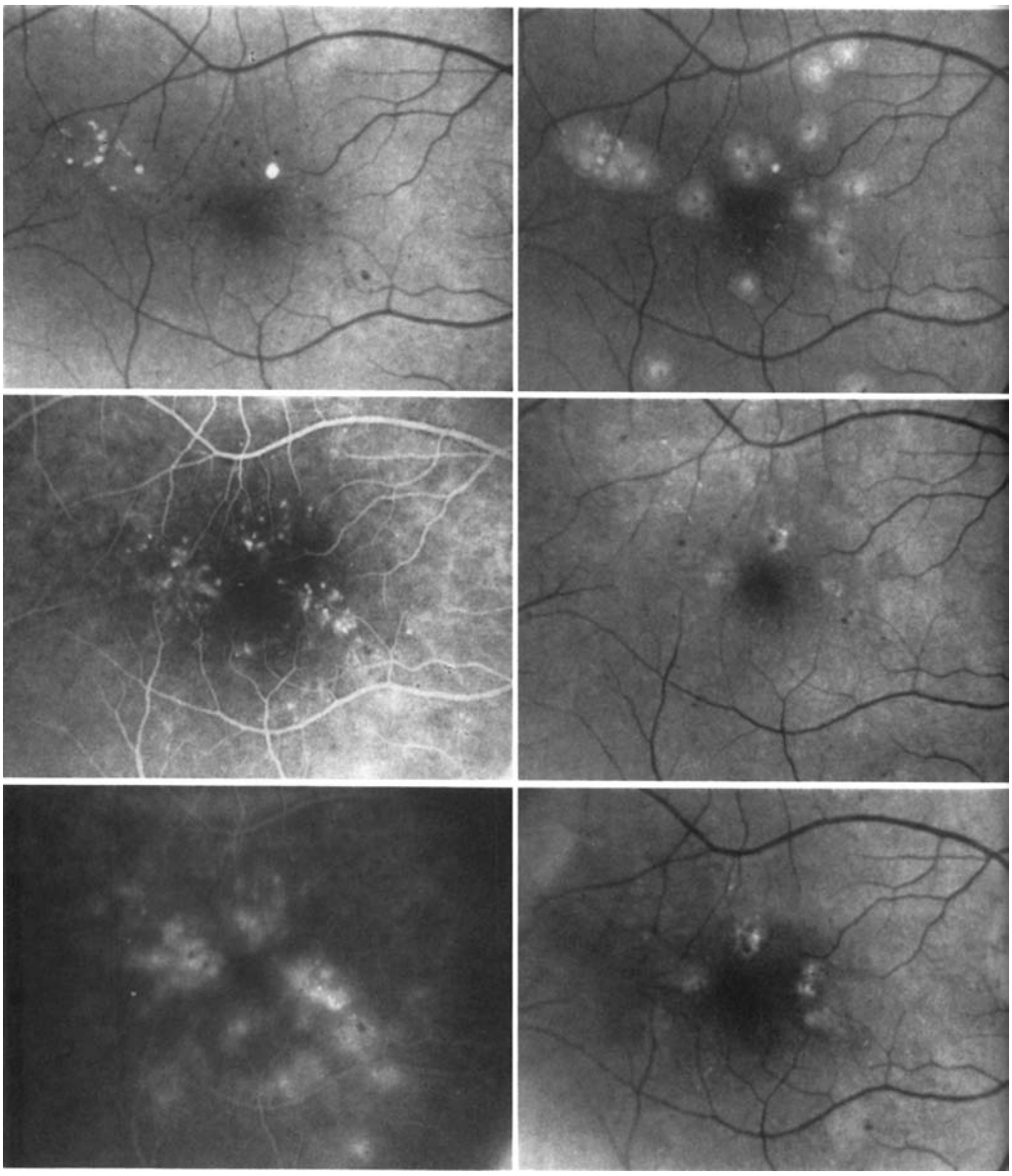

FIGURE 7B.2 Focal treatment of microaneurysms. The right eye of a 69-year-old woman with diabetes of 22 years' duration. *Top left*: At baseline visit, definite retinal thickening could be seen (with stereoscopic examination) nasal to the center of the macula and above it, probably involving the center. A few small microaneurysms and hard exudates are visible in the thickened area. Visual acuity was 20/30. *Center left:* Mid-phase angiogram shows microaneurysms surrounding the center of the macula most within 1,000 μm of the center and some within 500 μm. *Bottom left:* Late-phase angiogram shows leakage from the microaneurysms. *Top right:* Posttreatment photograph shows mild-to-moderate intensity focal treatment of most of the microaneurysms. The microaneurysms closest to the center have not been treated. *Center right:* One year after treatment, the center of the macula appears flat. Hard exudates and microaneurysms have decreased. Visual acuity was 20/50. *Bottom right:* Between the 1- and 2-year visits, additional focal photocoagulation was applied. At the 2-year visit, the center of the macula appears flat and no microaneurysms or hard exudates can be seen. Visual acuity was 20/25. (From Early Treatment Diabetic Retinopathy Study Research Group. Treatment technique and clinical guidelines for photocoagulation of diabetic macular edema. ETDRS Report No 2. *Ophthalmology*. 1987;94:761–774.)

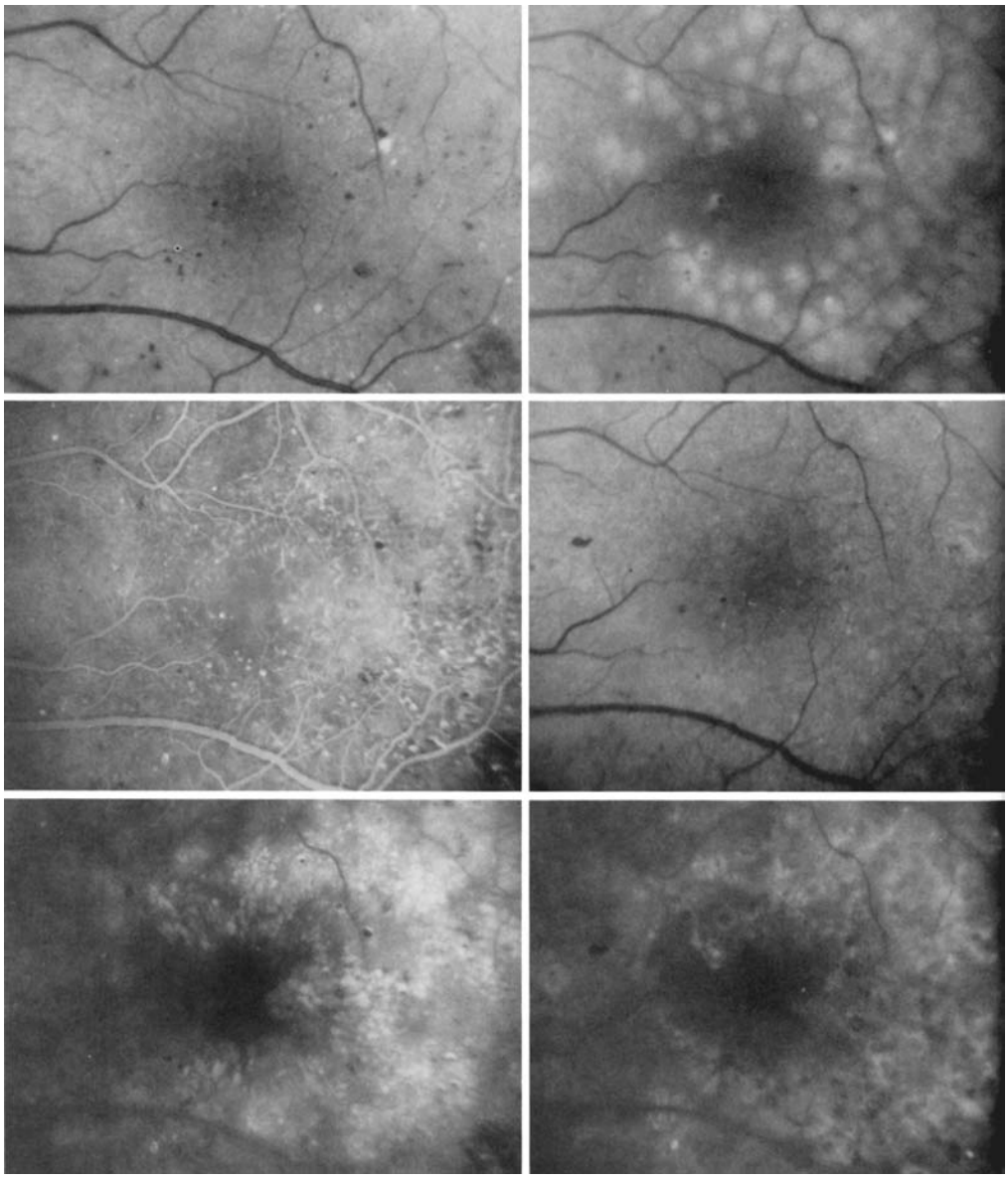

FIGURE 7B.3 Focal treatment of microaneurysms combined with a grid patter to areas of diffuse fluorescein leakage and capillary dropout. The left eye of a 49-year-old man with diabetes of 22 years' duration. *Top left:* The pretreatment photograph shows extensive retinal thickening with a few scattered microaneurysms and small hard exudates temporal to the center of the macula. Retinal thickening at the center is mild. Visual acuity was 20/40. *Center left:* Mid-phase angiogram shows moderate capillary dilation above and temporal to the center of the macula, with mild perifoveal capillary dropout. Scattered microaneurysms are also present. *Bottom left:* Late-phase angiogram shows extensive small cystoid spaces above, below, and temporal to the center of the macula. Some of the large microaneurysms fill only partially with fluorescein. *Top right:* Posttreatment photograph shows focal burns to microaneurysms and a grid pattern of burns above, below, and temporal to the macula. *Center right:* Four months later, microaneurysms and hard exudates have decreased. Retinal thickening is less and no longer involves the center of the macula. Visual acuity was 20/25. *Bottom right:* Late-phase angiogram shows treatment scars but most of the microaneurysms and cystoid spaces have disappeared. (From Early Treatment Diabetic Retinopathy Study Research Group. Treatment technique and clinical guidelines for photocoagulation of diabetic macular edema. ETDRS Report No 2. *Ophthalmology*. 1987;94:761–774.)

TABLE 7B.1 Specific Techniques for Scatter (Panretinal) and Focal Photocoagulation in the Early Treatment Diabetic Retinopathy Study

Scatter parameters	Full	Mild
Burn characteristics		
Size	500 μm (at retina)	500 μm (at retina)
Exposure	0.1 s	0.1 s
Intensity	Moderate	Moderate
Number	1,200–1,600	400–650
Placement	1/2 burn apart >2 disc diameters from fovea out to equator	≥1 burn apart >2 disc diameters from fovea out to equator
Number of episodes	≥2	1
Lesion treated directly	Patches of NVE <2 disc areas	Patches of NVE <2 disc areas
Indications for follow-up treatment	Recurrent or new NVE or high-risk proliferative retinopathy	Recurrent or new NVE or high-risk proliferative retinopathy
Focal parameters	**Direct**	**Grid**
Burn characteristics		
Size	50–100 μm	<200 μm (at retina)
Exposure	0.05–0.1 s	0.05–0.1 s
Intensity	Sufficient to whiten or darken large microaneurysms	Mild
Number	Sufficient to satisfactorily treat all focal leaks	Sufficient to cover areas of diffuse leakage and nonperfusion
Placement	500–3,000 μm from center of fovea	Spaced greater than one burn width apart 500–3,000 μm from center of fovea
Number of episodes	1	1
Indications for follow-up treatment	Presence of CSDME and treatable lesions at ≥4 mo	Presence of CSDME and treatable lesions at ≥4 mo

CSDME, clinically significant diabetic macular edema; NVE, neovascularization elsewhere.
From Early Treatment Diabetic Retinopathy Study Research Group. Early treatment diabetic retinopathy study design and baseline characteristics. ETDRS report no 7. *Ophthalmology* 1991;98:741–756.

TABLE 7B.2 Definition of Clinically Significant Diabetic Macular Edema

Clinically Significant Diabetic Macular Edema—any one of the following:

1. Retinal thickening at or within 500 μm of the center of the macula
2. Hard exudates at or within 500 μm of the center of the macula, if associated with adjacent retinal thickening
3. A zone or zones of retinal thickening of one-disc area or larger, any part of which is within one-disc diameter of the center of the macula

Eyes with macular edema demonstrated a considerable benefit from early focal photocoagulation, as treatment reduced the risk of moderate visual loss by approximately 50% (12% risk of moderate visual loss for treated eyes vs. 24% untreated at 3 years). In eyes with CSDME, these differences were even greater. Of eyes with CSDME, a majority had central foveal involvement, and these eyes demonstrated the most benefit from treatment (13% risk of moderate visual loss for treated eyes vs. 33% untreated at 3 years). In these eyes, early focal treatment was associated with a decrease in retinal thickening at the center of the macula. In eyes with CSDME but without central

foveal involvement, treatment resulted in a lesser, but significant, benefit (6% for treated eyes vs. 16% untreated at 2 years). In contrast, in eyes with macular edema that did not meet the definition of CSDME, there was no benefit associated with treatment (see Fig. 7B.4).[5–7]

The beneficial response to early focal treatment was most apparent in eyes with CSDME and worse VA at baseline (<20/40) as compared to those with better baseline acuity (20/25 to 20/40, 20/20 or better), but a treatment effect was demonstrated even in those with good initial VA (see Fig. 7B.5).[7] Despite the reduced risk of visual loss with treatment, visual improvement was rare in the ETDRS (improvement of 15 letters occurred in <3%). Therefore, the ETDRS recommendation was to consider prompt focal treatment for eyes with CSDME, regardless of VA, to prevent visual loss.[6]

The ETDRS documented treatment-related side effects, which included a small,

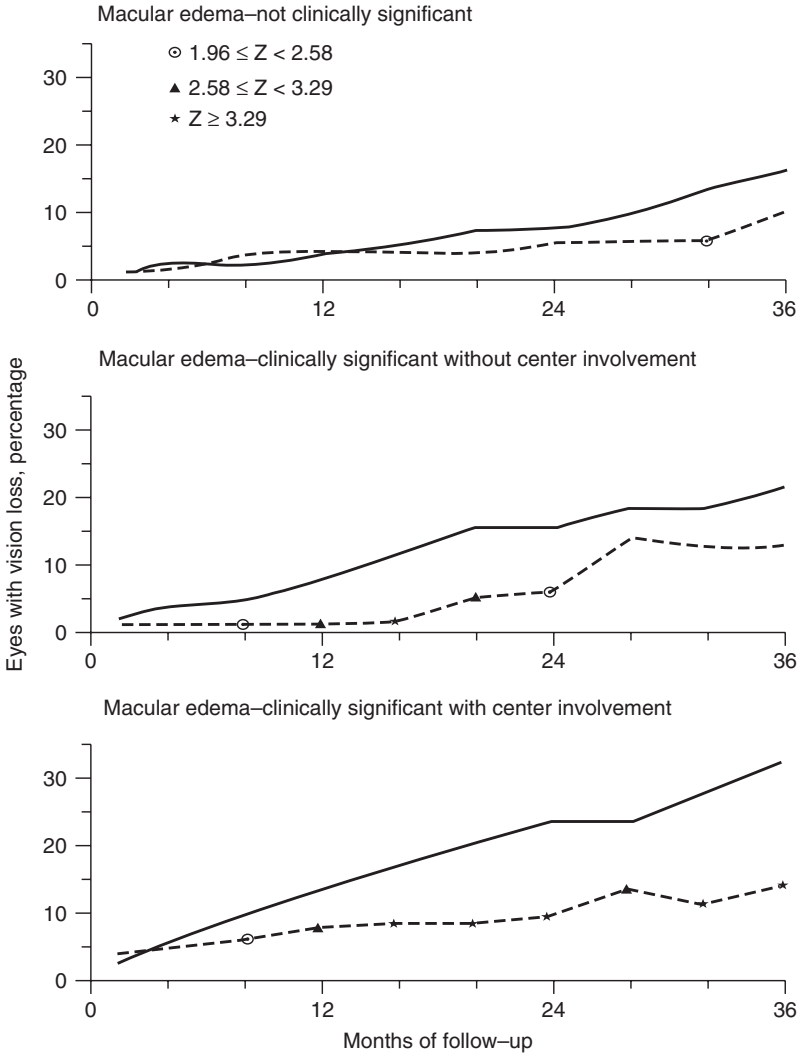

FIGURE 7B.4 Comparison of percentages of eyes with macular edema that experienced moderate visual loss classified by severity of macular edema and assigned to immediate focal treatment (*broken line*) or to deferral of treatment (*solid line*). (From Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report No 4. *Int Ophthalmol Clin*. 1987; 27:265–272.)

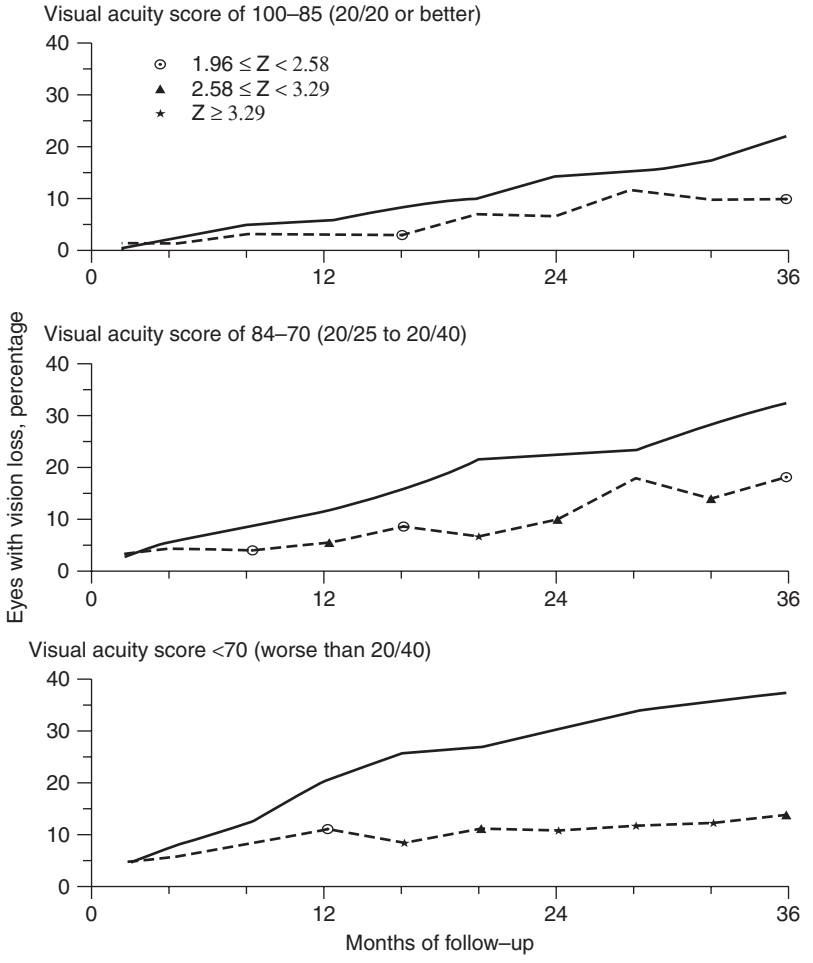

FIGURE 7B.5 Comparison of percentages of eyes with clinically significant diabetic macular edema that experienced moderate visual loss classified by baseline visual acuity and assigned to immediate focal treatment (*broken line*) or to deferral of treatment (*solid line*). (From Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report No 4. *Int Ophthalmol Clin*. 1987; 27:265–272.)

but not statistically significant, difference in visual field scores. Eyes assigned to focal photocoagulation demonstrated slightly more paracentral scotomata on Goldmann visual fields using the I-2 test object.[6]

Implications for Clinical Practice

Prompt focal photocoagulation was recommended for eyes with CSDME as defined by the ETDRS for patients who met the inclusion criteria. Treatment was recommended regardless of baseline VA, since eyes in all categories of VA (20/20 or better, 20/25–20/40, <20/40) were found to benefit from treatment. Treatment was recommended for eyes with or without thickening of the central macula, provided that they met the definition of CSDME. Treatment was most effective for those with worse VA at baseline (<20/40) and for those with central macular thickening.

Focal photocoagulation, when applied using the ETDRS treatment guidelines, resulted in a significant reduction in moderate visual loss. Since visual improvement was rare in this study, the ETDRS recommended that treatment should be considered to prevent visual loss in patients with CSDME.

Macular edema often occurs in association with severe NPDR or PDR. The DRS and the ETDRS demonstrated that scatter PRP may exacerbate macular edema and result in vision loss.[8,9] If PRP can be safely delayed for a patient with CSDME and severe NPDR or early PDR, focal treatment should be applied followed by very close observation for proliferative changes. If panretinal laser cannot be safely delayed, or if a patient has CSDME and PDR with high-risk characteristics, both focal treatment and PRP should be applied, but the scatter treatment should not be given before the focal treatment.

Beginning with the ETDRS, a new VA chart was developed for use in prospective clinical research studies. This chart is still used today in clinical trials to evaluate VA in a standardized manner (see Fig. 7B.6).[10–12]

Unanswered Questions

The ETDRS defined the standard of care (SOC) for the management of DME for over 20 years, and all current clinical trials continue to use ETDRS results for comparison. A direct comparison with new therapies, however, is often difficult due to the multitude of ocular and systemic variables that influence retinopathy.

Despite providing answers to critically important questions, the ETDRS results stimulated additional questions that remain unanswered. For example, the ETDRS did not evaluate eyes with VA less than 20/200. The potential effect of focal treatment in eyes with macular edema and low vision is unknown. In addition, while the ETDRS was designed to determine whether laser was effective, it was not designed to determine the best time to apply laser, and the optimal timing of

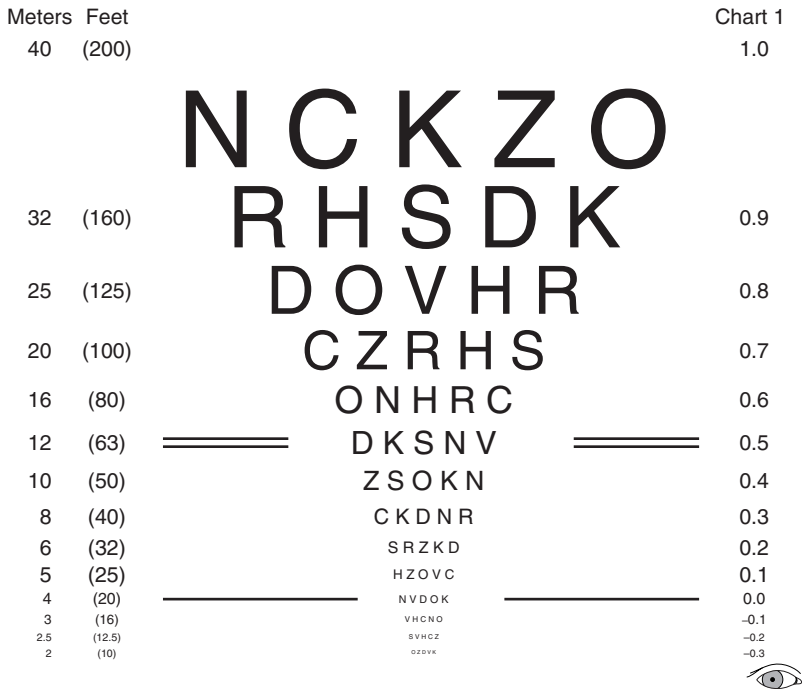

FIGURE 7B.6 One of the three Early Treatment Diabetic Retinopathy Study visual acuity charts. Four-meter testing distance with this chart yields the following Snellen equivalent lines: 20/10, 20/12.5, 20/16, 20/20, 20/25, 20/31.5, 20/40, 20/50, 20/63, 20/80, 20/100, 20/125, 20/160, and 20/200. At 1 m, the following additional Snellen equivalent lines of visual acuity could be measured: 20/250, 20/315, 20/400, 20/500, 20/630, and 20/800. Note that every three lines is a doubling of the visual angle and that there are five letters on each line. (From Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline characteristics. ETDRS Report No 7. *Ophthalmology*. 1991;98:741–756.)

treatment remains unknown. Furthermore, the ETDRS used specific treatment guidelines for macular focal photocoagulation. Alternative laser treatment strategies have since been developed, including modified versions of the ETDRS protocol. The relative benefits of different treatment strategies are difficult to assess since a direct comparison with the ETDRS results is not possible.

Retreatment with focal photocoagulation was allowed in the ETDRS if the edema persisted or recurred. There was no clear recommendation regarding the number of laser treatments that may be beneficial in eyes requiring retreatment, and the management of refractory DME remains one of the most challenging clinical problems today, 20 years after the initial ETDRS results were reported.

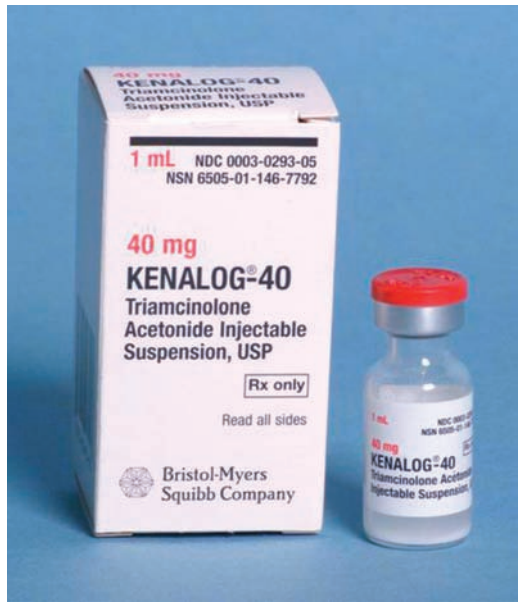

FIGURE 7B.7 Triamcinolone acetonide (Kenalog-40, Bristol-Myers Squibb). (Photograph courtesy of Ronald C. Gentile, MD, New York, NY.)

II. DIABETIC MACULAR EDEMA: PHARMACOLOGIC THERAPIES

Steroids

Introduction

Intraocular corticosteroids are currently being evaluated for the treatment of DME. Triamcinolone, fluocinolone, and dexamethasone are promising pharmacologic agents that are in various phases of clinical trial development.

Triamcinolone acetonide is commonly being used off-label for diabetic and other causes of macular edema, as it is not approved by the U.S. Food and Drug Administration (FDA) for this indication (see Fig. 7B.7). Administered through an intravitreal injection, triamcinolone acetonide has been shown to be effective in improving VA and reducing macular thickness measured by optical coherence tomography (OCT) in patients with DME (see Figs. 7B.8 and 7B.9).[13,14]

In contrast, fluocinolone acetonide and dexamethasone are delivered via intravitreal sustained release devices, and these devices are not approved by the FDA for use in DME. These include the intravitreal fluocinolone acetonide implants (Retisert, [see Fig. 7B.10], Iluvien [see Fig. 7B.11]) and the intravitreal dexamethasone implant (Ozurdex, [see Fig. 7B.12]), which provide prolonged delivery of medication to the target tissue.

Corticosteroids act in a nonspecific manner. Although the exact mechanism of action in the treatment of DME is unknown, corticosteroids decrease the breakdown of the blood–retinal barrier, suppress inflammation, and downregulate the production of vascular endothelial growth factor (VEGF).

Diabetic Retinopathy Clinical Research Network, Protocol B

Background and Study Questions

A number of small studies had demonstrated that intravitreal injections of triamcinolone may be effective in treating DME, but sample size and follow-up were suboptimal at the time. Many practitioners began routinely treating DME with intravitreal triamcinolone, but there were no controlled clinical trials to show evidence of its efficacy. In 2002, a collaborative network of clinical practices in the United States, named the Diabetic Retinopathy Clinical Research Network (DRCR.net), was formed to facilitate multicenter

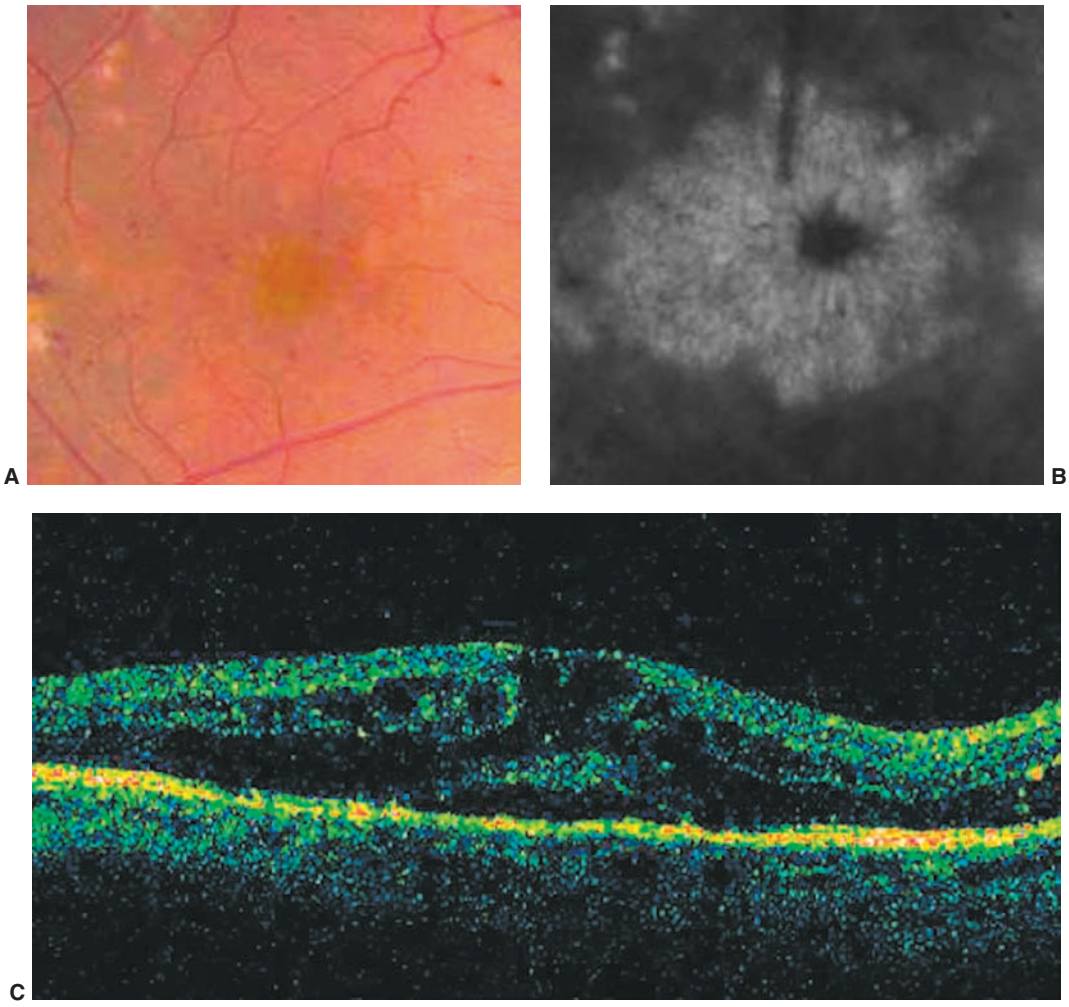

FIGURE 7B.8 The right eye of a 49-year-old man with diabetes of 18 years' duration. Clinically significant diabetic macular edema was present despite a history of prior focal photocoagulation. Visual acuity was 20/200. **(A)** Fundus photograph of the macula shows cystoid retinal thickening, a few small retinal hemorrhages, and prior focal laser spots. **(B)** Late-phase fluorescein angiogram shows leakage in a petalloid pattern. **(C)** Optical coherence tomography shows cystic retinal thickening.

clinical trials dedicated to the investigation of diabetic retinopathy. There are currently over a hundred participating clinical sites.[15] Its establishment represented a unique paradigm where multiple centers, from academic institutions to private practices, could rapidly organize large trials.

In order to better evaluate the use of intravitreal steroid injections for DME, the DRCR.net organized a phase III, multicenter, prospective, randomized trial to compare the efficacy and safety of 1 and 4 mg of preservative-free triamcinolone acetate (Trivaris, Allergan, Inc., Irvine, CA) to focal/grid photocoagulation. The 2-year follow-up data were published in 2008.[16]

Patients Included in the Study

A total of 840 eyes with DME from 693 subjects with type 1 or type 2 diabetes were examined. Inclusion criteria were ETDRS VA scores between 73 (approximately 20/40) and 24 (approximately 20/320), 250 μm or thicker central macular thicknesses on OCT,

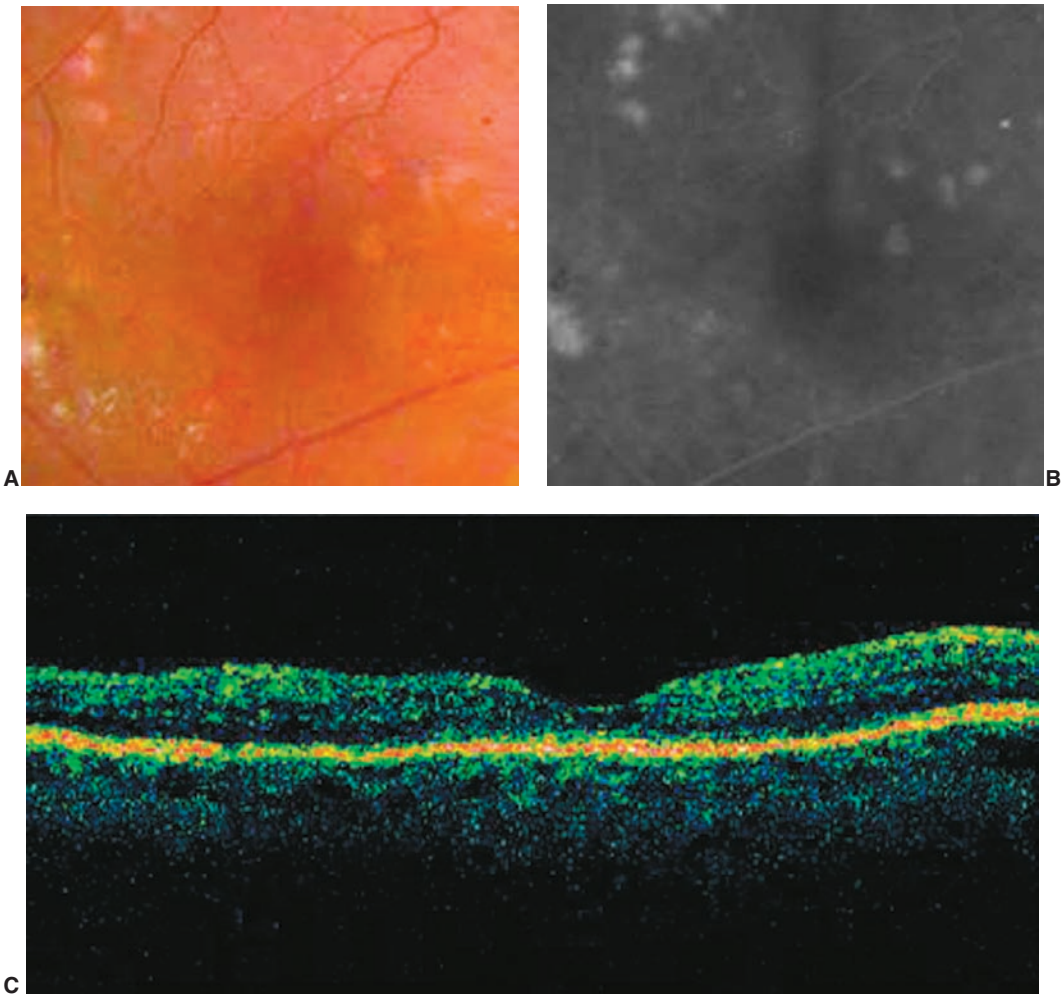

FIGURE 7B.9 Same patient as in Figure 8, 3 months after intravitreous injection of triamcinolone acetonide 4 mg. Visual acuity was 20/80. **(A)** Fundus photograph shows resolution of macular edema. **(B)** Late-phase fluorescein angiogram shows resolution of leakage. **(C)** Optical coherence tomography shows resolution of retinal thickening. (Three months later the patient developed recurrent edema and underwent repeat injection, with subsequent resolution of the edema.)

and no expectations for requiring PRP in the subsequent 4 months. Patients with any history of intravitreal steroid treatment or pars plana vitrectomy, or those with recent periocular steroids or photocoagulation treatment were excluded. Also excluded were those with histories of open-angle glaucoma, steroid-induced ocular hypertension that required intervention, and intraocular pressure (IOP) of 25 mmHg or more. Baseline characteristics showed that the DRCR.net study patients were slightly older with better glycemic control compared to the ETDRS and PKC-DRS2 participants.[17] Other variables were similar.

Intervention and Outcome Measures

Study eyes were randomized to focal/grid photocoagulation, 1 mg triamcinolone, or 4 mg triamcinolone. The laser control group allowed direct comparison to the gold standard. The photocoagulation technique was a modified ETDRS protocol, where burns were smaller and less intense (light gray, 50 μm). Subjects in the triamcinolone groups were allowed to receive laser treatment if they met

FIGURE 7B.10 Fluocinolone acetonide intravitreous sustained release implant (Retisert).

certain failure criteria as a fail-safe system. Patients were followed every 4 months, and retreated based on VA and OCT parameters. The primary endpoint was mean VA, and the secondary outcome measure was central subfield retinal thickness. At the time, this DRCR.net study was the first phase III DRS to use the OCT data.

Major Findings

As we will also see with other intravitreal steroid studies, the treatment response evolved over time. At 4 months, the 4-mg triamcinolone group had the best VA, but by 1 year the difference was not statistically significant, and

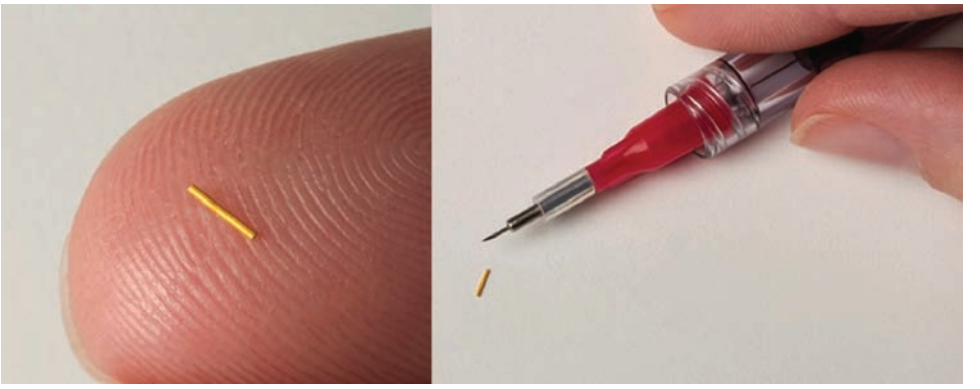

FIGURE 7B.11 Fluocinolone acetonide intravitreous sustained release insert and its injector (Iluvien).

FIGURE 7B.12 Dexamethasone intravitreous sustained release implants (Ozurdex), 350 and 700 μg doses, and the injector.

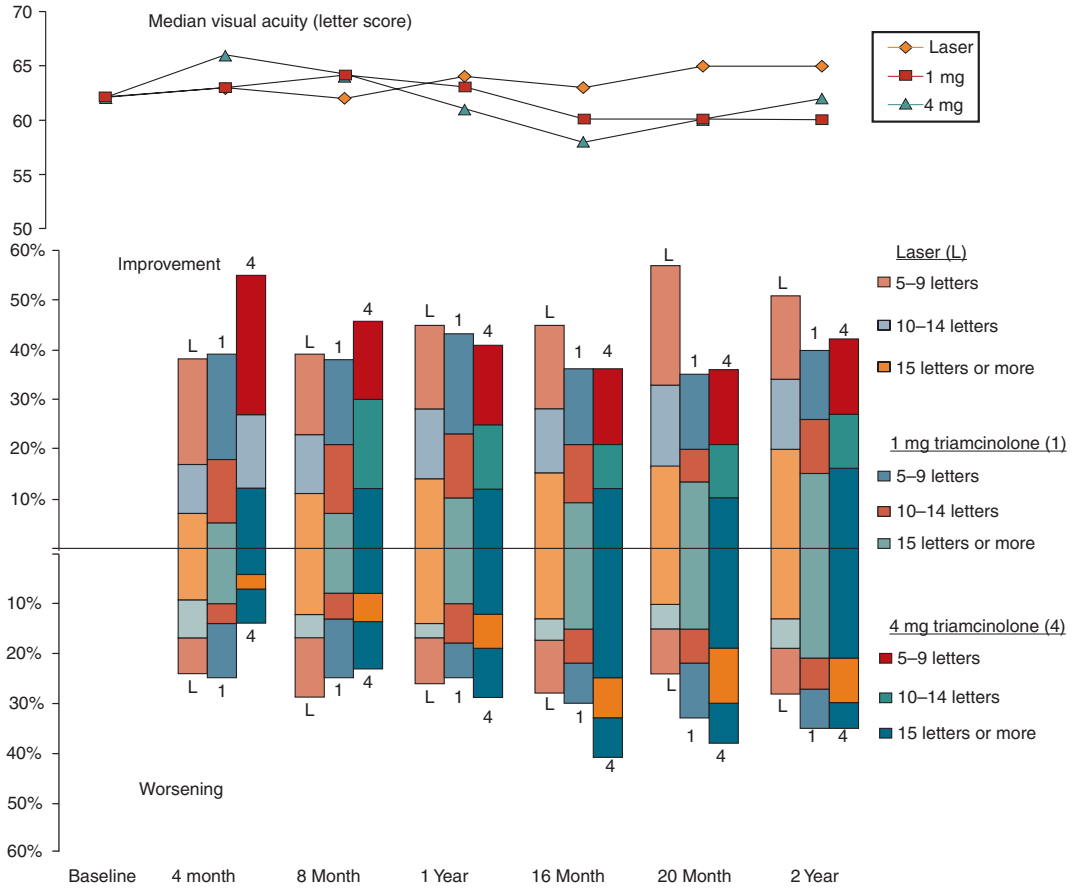

FIGURE 7B.13 Diabetic Retinopathy Clinical Research Network (DRCR.net), Protocol B. The study compared the efficacies of focal/grid photocoagulation, and 1 or 4 mg of intravitreal triamcinolone, in the treatment of diabetic macular edema. The top graph demonstrates the changes in visual acuity over 2 years. The bottom graph shows the percentages of eyes in each treatment group with the corresponding letters gained or lost at each time point. (From Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology*. 2008;115:1447–1449.)

starting at 16 months and persisting to 2 years the laser group developed the best mean VA (see Fig. 7B.13). At 2 years, the mean ± SD change in VA was +1 ± 17 letters in the laser group, −2 ± 18 letters in the 1-mg group ($p = 0.02$), and −3 ± 22 letters in the 4-mg group ($p = 0.002$). The number of treatments in each arm was similar. A subgroup analysis of pseudophakic eyes showed that the respective changes in mean visual acuities were +2 ± 18, +2 ± 17, and −1 ± 19 letters. This analysis was performed because intravitreal steroids are strong risk factors for developing cataract.

The effects of treatment on retinal thickness paralleled VA changes, where the 4-mg group initially performed better, but the laser group ended with the lowest central subfield thickness. At 2 years, the mean decrease in thickness was −139 ± 148 μm in the laser group, –86 ± 167 μm in the 1-mg group, and –77 ± 160 μm in the 4-mg group (all $p < 0.001$).

There were no cases of infectious or sterile endophthalmitis of the 1,649 intravitreal injections. An elevation of IOP more than 10 mmHg from baseline, IOP of 30 mmHg or more, and initiation of IOP-lowering medication/a new diagnosis of glaucoma were

observed at one or more visits in 40% of those in the 4-mg group, 20% in the 1-mg group, and 10% in the laser group (all $p < 0.001$). Cataract surgery was performed in 51% of the 4-mg group, 23% of the 1-mg group, and 13% of the laser group, during the course of the study ($p < 0.001$). A unique adverse event in this study was intravitreal silicone oil droplets that were found in some eyes due to the use of staked silicone syringes. The protocol was amended to use luer cone syringes instead, which eliminated the problem.

The 3-year follow-up study showed continued benefits of the laser group over both triamcinolone arms.[18] The laser group gained 5 letters while the triamcinolone arms improved by 0 letters. The cumulative probabilities of cataract surgery were 31%, 46%, and 83% in the laser, 1-mg, and 4-mg groups, respectively. An IOP rise of 10 mmHg or more was noted in 4%, 18%, and 33%, respectively.

A retrospective exploratory study of the same DRCR.net cohort investigated the progression of diabetic retinopathy.[19] The cumulative progression of retinopathy at 2 years was 31% in the laser group, 29% in the 1-mg group ($p = 0.64$ compared to laser), and 21% in the 4-mg group ($p = 0.005$ compared to laser). Similar results were found at the 3-year study also. However, the authors concluded that the risks of cataract and intraocular elevation did not warrant the use of intravitreal triamcinolone as a primary modality to slow or improve diabetic retinopathy.

Implications for Clinical Practice

This study demonstrated that there is potential for visual and anatomic improvement after intravitreous triamcinolone injection in the DME patients. This is a relatively cost-effective and technically easier procedure compared with the steroid implants discussed below. However, as shown in this study, VA tends to regress over time as the macular edema recurs and repeat injections are required. Furthermore, while the short-term results were superior to laser photocoagulation, the difference soon became insignificant, and the laser group developed the best outcomes after 16 months. This signifies that short-acting boluses of intravitreal steroids alone may not be sufficient to control DME long-term.

In addition, the medication and the intraocular injection procedure have risks. Cataract and glaucoma are well-known complications of steroid therapy. The 4 mg dose was associated with a higher rate of IOP elevation and cataract formation. Infectious endophthalmitis is the most serious complication associated with the intravitreous injection procedure, although it did not occur in this study.

The best approach to using intravitreal triamcinolone in the treatment of DME should be patient-specific with full consideration of the benefits and shortcomings compared to the other treatment modalities discussed below.

Unanswered Questions

This DRCR.net study showed that laser photocoagulation may provide superior long-term visual and anatomic outcomes compared to intravitreal triamcinolone acetate alone. However, the study utilized modified ETDRS laser parameters, so we cannot conclude how intravitreal triamcinolone compares to conventional ETDRS laser with larger and higher intensity ("hotter") spots.

Furthermore, anti-VEGF therapies have recently emerged as a popular treatment for DME. How to most effectively use photocoagulation, intravitreal steroids (short-acting triamcinolone injections and long-acting drug delivery systems), and intravitreal anti-VEGF agents remains an ongoing debate.

Fluocinolone Acetonide Implant (Retisert)

Background and Study Questions

Bausch & Lomb Inc. and pSivida Corp. (Watertown, MA) have developed a sustained release device containing the steroid fluocinolone acetonide (Retisert) (see Fig. 7B.10). The fluocinolone drug pellet is enclosed in a polymer and is similar to but smaller than the ganciclovir intravitreous implant (Vitrasert, Bausch & Lomb Inc./pSivida Corp.) used to treat cytomegalovirus retinitis. The 3 mm × 2 mm × 5 mm implant is inserted into the vitreous cavity

through a pars plana incision and secured to the sclera with a suture. Fluocinolone is released at a constant rate for almost 3 years (initial rate 0.6 μg/day, decreasing over the first month to a steady state 0.3 to 0.4 μg/day for 30 months). The fluocinolone implant has the advantage of maintaining therapeutic levels in the target tissue (the macula) with minimal systemic exposure and an associated reduction in systemic side effects. Retisert was approved by the FDA for the treatment of chronic noninfectious posterior uveitis in 2005.

This 4-year, multicenter, prospective, randomized, masked, controlled clinical trial compared the fluocinolone acetonide implant to SOC in patients with DME.[20]

Patients Included in the Study

A total of 196 patients with persistent or recurrent DME were enrolled. Inclusion criteria were a history of at least one macular laser procedure at least 3 months before enrollment, ETDRS VA ≥ 20/400 and ≤ 20/50, and retinal thickening involving fixation and at least one-disc area in size. Patients with a history of uncontrolled IOP or a history of ocular surgery within 3 months prior to enrollment were excluded.

Intervention and Outcome Measures

Patients were randomized into an implant group (0.59 mg, $n = 127$) and an SOC group (SOC, $n = 69$) that received either macular focal/grid laser or observation. There was initially a 2.1 mg implant arm, but it was discontinued early in the study because it showed no advantage over the lower dose. Focal laser treatment was allowed in implanted eyes within 6 months postimplantation if there was macular edema from microaneurysms. Focal or grid laser photocoagulation was used at the discretion of the investigator after 6 months postimplantation.

The primary endpoint was ≥15-letter increase in VA at 6 months. Secondary outcomes were changes in macular edema, ETDRS Diabetic Retinopathy Severity Scale, and fluorescein angiography leakage.

Major Findings

The primary endpoint of ≥15-letter increase in VA was met. This was significantly higher than in the SOC group at 6 months (16.8% vs. 1.4%; $p = 0.0012$), but at 1 year the difference was not significant (16.4% vs. 8.1%; $p = 0.1191$). VA significantly improved again at 2 years (31.8% vs. 9.3%; $p = 0.0016$), but again lost significance at 3 years (31.1% vs. 20.0%; $p = 0.1566$). The dip in VA at 1 year is presumed to be from cataract progression, and the rebound at 2 years is presumed to be due to cataract extraction. The efficacy of the implant appears to decline by 3 years because its life span is 30 months.

The proportion of eyes with no central retinal thickening based on photographic grading was significantly higher in the Retisert group compared to the SOC arm at 6 months ($p < 0.0001$), 1- and 2-years (72% vs. 22% at 1 y; $p = < 0.0001$), but not at 3- and 4-years (51.2% vs. 37.7% at 4-y). A small subset of patients whose retinal thicknesses were followed with OCT had a similar course.

There was a higher rate of improvement and lower rate of worsening in the diabetic retinopathy severity score in the Retisert group at 6 months ($p = 0.0006$), 1 year ($p = 0.0016$), 2 years ($p = 0.012$), and 3 years ($p = 0.021$). Fluorescein leakage improved more or worsened less in the Retisert group at 12 weeks ($p = 0.001$), 6 months ($p < 0.0001$), and 1 year ($p = 0.006$). There was no significant difference at 2- and 3-years.

Increased IOP was noted in 69% of the Retisert group vs. 12% in the SOC group. An IOP of ≥30 mmHg at any time during the study occurred in 61% of the Retisert group vs. 6% in the SOC group. 34% of eyes in the Retisert group underwent one or more surgical interventions over the 4-year period to lower IOP. Three eyes (2% of those with elevated IOP in the Retisert group) had the implant removed. Cataract progression was noted in 56% of the Retisert group vs. 22% in the SOC group. Cataract surgery was performed in 91% of phakic eyes in the Retisert group vs. 0% of phakic eyes in the SOC group. Vitreous hemorrhage was also noted in 40% of the Retisert group vs. 19% in the SOC group.

Implications for Clinical Practice

This was the first study to demonstrate that sustained (>6 months) drug delivery to the posterior segment is efficacious in the treatment of diabetic retinal disease. On the basis of this study, Retisert has the potential to reduce retinal thickening and improve VA in patients with DME who met the specific inclusion criteria for the first 2 years. The improvements lost statistical significance with longer follow-up, presumably due to the implant approaching the end of its life cycle of 30 months. The improvement in diabetic retinopathy severity had favorable implications; in fact, this was the first study conducted involving an ocular treatment that demonstrated a reversal of NPDR severity. This implant provides sustained levels of targeted fluocinolone and, as expected, is associated with a higher incidence of cataract and IOP elevation. Most patients who were phakic at baseline required cataract surgery during the course of the study, and approximately two-thirds of patients had elevated IOP, and one-third required surgical intervention.

Unanswered Questions

This study showed that the Retisert device has favorable outcomes compared to SOC (additional macular laser photocoagulation or continued observation) in terms of VA, retinal thickness, and progression of diabetic retinopathy in patients with persistent or recurrent DME. However, the device releases fluocinolone acetonide for 30 months, after which the depleted implant loses its efficacy. Algorithms on how to proceed after implant depletion have not been established and remain at the discretion of individual physicians. The potential adverse clinical effects associated with cessation of drug availability are not fully understood either. It is possible to have multiple sequential implants in one eye; however, the necessity, optimal timing, and long-term effects of repeat implantation are unknown. Furthermore, careful patient selection by judicious consideration of the risk-benefit ratio is required due to high rates of cataract progression and elevated IOP.

Fluocinolone Acetonide Vitreous Insert (Iluvien): Fluocinolone Acetonide for Macular Edema

Background and Study Questions

Alimera Sciences (Alpharetta, GA) also developed a sustained release fluocinolone acetonide implant named Iluvien. This insert is a nonbiodegradable cylindrical tube that is loaded with fluocinolone similar to Retisert, but the insert can be placed into the vitreous cavity using a 25-gauge needle in the outpatient setting. The Fluocinolone Acetonide for Macular Edema (FAME) studies A and B were two phase III, 3-year, randomized, double-masked, sham-controlled, parallel, multicenter trials.[21]

Patients Included in the Study

A total of 956 patients with DME were enrolled. Inclusion criteria were a history of at least one macular laser procedure, ETDRS VA between 20/400 and 20/50, and foveal thickening of 250 μm or more. Patients with a history of glaucoma, ocular hypertension, IOP > 21 mmHg, and those taking IOP-lowering drops, were excluded.

Intervention and Outcome Measures

Patients were randomized in a 2:1:1 ratio to 0.2-μg/day fluocinolone insert, 0.5-μg/day fluocinolone insert, or sham injection (using only the needle hub). There was no laser-comparison group, but all patients were allowed rescue laser treatments after 6 weeks. Other treatments such as intravitreal triamcinolone and anti-VEGF agents were also used at the discretion of the investigator. Re-injection of Iluvien was allowed after 1 year. The primary endpoint was the proportion of participants with an increase in VA by ≥15 letters.

Major Findings

Both treatment arms met the primary endpoint. At 24 months, 28% of each treatment group achieved an improvement in best-corrected VA (BCVA) of 15 letters or more, compared to 16% of the sham group (p = 0.002). The treatment arms had better VA at all time points during the study. There

was a dip in VA between 6 and 18 months, and then an improvement between 18 and 24 months, which was attributed to cataract formation and subsequent extraction, similar to what was observed in the Retisert Study. The final foveal thicknesses at 24 months were 293, 308, and 340 μm in the 0.2 μg/day ($p = 0.005$), 0.5 μg/day ($p < 0.001$), and sham groups, respectively. Similar results were obtained by measuring center subfield thickness. Cataract extraction was performed in 41%, 51%, and 7% of the 0.2 μg/day, 0.5 μg/day, and sham groups, respectively. Of the phakic patients, the respective rates were 75%, 85%, and 23%. Incisional glaucoma surgery to control IOP was performed in 3.7%, 8.1%, and 0.5% of the 0.2 μg/day, 0.5 μg/day, and sham groups, respectively.

At the 3-year follow-up assessment, 29% of the 0.2 μg/day group and 28% of the 0.5 μg/day group achieved an improvement of ≥15 letters, compared to 19% of the sham group ($p = 0.018$).[22] Interestingly, when patients were divided into those with DME less than 3 years' duration vs. those with DME greater than 3 years' duration, the VA results are different. At the 3-year follow-up exam for those with DME <3 years, 22.3% of the 0.2 μg/day group achieved an improvement of ≥15 letters, compared to 27.8% of the sham group ($p = 0.275$). In contrast, for those with DME ≥3 years' duration, 34.0% of the 0.2 μg/day group achieved an improvement of ≥15 letters, compared to 13.4% of the sham group ($p < 0.001$).

There was a decline in retinal thickness in all groups, but the decline was most pronounced in the sham group, which resulted in the loss of significant difference in retinal thickness between the treatment and sham groups. There was a ≥2-step improvement in the severity of retinopathy in 14%, 10%, and 9%, respectively. The higher dose provided less protection against progression of retinopathy compared to the lower dose at 36 months, likely because the approximate life span of the higher dose is 24 months, compared to 36 months for the lower dose. Most participants in the treatment arms developed cataract, but their visual acuities improved compared to that of pseudophakic patients after cataract extraction. Glaucoma surgery was performed on 5% of the 0.2 μg/day group and 8% of the 0.5 μg/day group.

Implications for Clinical Practice

This study showed that the nonbiodegradable cylindrical tube drug delivery system can safely and effectively deliver fluocinolone to treat DME. The efficacy and side effects of Iluvien compared to Retisert as such. At 2 years, slightly over 30% of patients implanted with Retisert, and slightly under 30% of patients receiving either concentration of Iluvien inserts, had improved ≥15 letters. In terms of macular thickness, approximately 50% of patients implanted with Retisert had no edema, and approximately 50% of patients receiving Iluvien inserts had foveal thicknesses ≤250 μm, at 2 years. These data show that the efficacy of the two devices appears to be similar. However, incisional glaucoma surgery was required in approximately 34% of Retisert patients at 4 years vs. approximately 8% and 4% of high- and low-dose Iluvien patients, respectively, at 2 years. The FAME study authors theorize that the lower release rates and the more posterior placement away from the trabecular meshwork may have produced fewer glaucomatous events. Iluvien is available in several European countries,[23] but the U.S. FDA did not approve Iluvien. At the time of writing, Alimera is resubmitting the FDA application.[24]

Unanswered Questions

The FAME study did not have a true SOC control arm, making it difficult to compare the results to focal/macular photocoagulation, which is still the gold standard. Retreatment with additional intravitreal injections of Iluvien was allowed once a year, but it is unclear whether that is the best retreatment schedule. Like any other steroid treatment modality, the risk of developing cataract and glaucoma needs to be weighed against the benefit of the device. Clinical experience with Iluvien is limited, especially in the United States, so further studies to better understand its role in the market of increasing treatments for DME are warranted.

Most important, the FAME study found that the role of steroids in DME may differ depending on the duration of DME. Inflammation may play a greater role in the pathogenesis of chronic DME, as those with DME ≥3 years had favorable results with Iluvien compared to those with DME <3 years; however, the exact reason for these findings remains unknown.

Dexamethasone Sustained Release Implant (Ozurdex)

Background and Study Questions

Allergan Inc. has developed a sustained release device containing the steroid dexamethasone (Ozurdex) (see Fig. 7B.12). This is a biodegradable implant, delivering dexamethasone for approximately 6 to 8 weeks. The cylindrical pellet is inserted into the region of the vitreous base through a small sclerotomy. Similar to other sustained release devices, the dexamethasone implant has the advantage of maintaining therapeutic levels in the target tissue (the macula) with minimal systemic exposure and an associated reduction in systemic side effects. It is approved by the U.S. FDA for the treatment of macular edema after retinal vein occlusions and noninfectious uveitis.

This multicenter, prospective, randomized, masked, controlled clinical trial compared the dexamethasone implant to observation in patients with persistent macular edema from a variety of causes.[25] A subsequent publication detailed those patients with DME.[26,27] This section will focus on the DME patients.

Patients Included in the Study

A total of 171 patients with persistent DME were enrolled.[27] Inclusion criteria were macular edema persisting at least 90 days following treatment (laser or medical management), VA worse than 20/40 and attributable to macular edema, retinal thickening in the center of the fovea, and angiographic evidence of leakage involving the perifoveal capillary network. Patients with VA worse than 20/200, retinal neovascularization, or a history of pars plana vitrectomy or glaucoma were excluded.

Intervention and Outcome Measures

Patients were randomized to receive either a single Ozurdex implant containing 350 or 700 μg of dexamethasone or no treatment (observation). The primary efficacy endpoint was a two-line or greater improvement in VA at 90 days. Secondary endpoints were change in retinal thickness measured by OCT, change in contrast sensitivity, and improvement in fluorescein angiographic leakage as determined by masked grading.

Major Findings

Ninety days after receiving the implant, a statistically significant primary efficacy outcome of a two-line improvement in VA was achieved with the 700 μg dose (33% vs. 12%, $p = 0.007$), compared to the observation group, and this effect persisted at the 180-day evaluation but lost statistical significance (30% vs. 23%, $p = 0.4$). At 60 and 90 days, more patients with the 700-μg implant showed an improvement of three or more lines as compared to the observation group ($p = 0.01$ at 60 days, $p = 0.05$ at 90 days). A dose–response trend was noted at all time points, where the effects of 700 μg were superior to those of 350 μg at all time points. Measures of edema correlated with improvement in VA with a statistically significant decrease in retinal thickness and fluorescein leakage in both 700- and 350-μg groups; the effects were more pronounced in the 700-μg group. The aforementioned visual and anatomic outcomes were consistent between the different morphologies of edema: focal, cystoid, and diffuse.[26]

Ocular adverse events were more common in the implant groups and were mostly related to the implantation procedure. These included subconjunctival hemorrhage and vitreous hemorrhage, both of which were self-limited. Patients did not show the development or progression of cataract; however, 15% of the treated patients (both groups) showed a ≥10 mmHg IOP increase over baseline at some point during the study compared with 2% in the observation group. Most readings were transient and recorded only once.

Implications for Clinical Practice

The results of this phase II study indicate that this device has the potential to reduce retinal edema and improve VA in patients with DME who met the specific inclusion criteria. The Ozurdex implant provides sustained levels of dexamethasone and is associated with an increased incidence of IOP elevation. Pressure elevations were successfully treated with topical therapy, and trabeculectomy procedures were not required during the relatively short, 180-day trial. In addition, the development or progression of cataract was not observed during the brief study period. The positive results seen so far must be weighed against the relatively short duration of drug availability and the potential for recurrent disease.

Unanswered Questions

The Ozurdex device releases dexamethasone for 6 to 8 weeks. The 180-day data are encouraging; however, the clinical effects associated with cessation of drug availability are unknown. This device has a relatively short duration of action, and sustained treatment benefit may require multiple implants. Although it is possible to have multiple sequential implants in one eye, the necessity, timing, and sequelae of repeat implantation are unknown. Cataracts and glaucoma are of particular concern, since the risk of these complications increases with prolonged and repeated administration of intraocular steroids.

A single-use 22-gauge applicator preloaded with the implant has been developed for office-based insertion of the implant through the pars plana, and this may reduce the adverse events associated with conjunctival incision and sclerostomy. This applicator is currently being used in the ensuing larger phase III study (MEAD trial).[28] Results are not yet available.

Two other Ozurdex trials are worth mentioning: a prospective, randomized, double-masked study randomized 253 subjects with diffuse DME to Ozurdex followed by grid laser photocoagulation 1 month later, or to laser alone at month 1. At 1 year, the patients who received the combination treatment had better visual and anatomical outcomes compared to laser alone.[29]

Another trial examined whether Ozurdex could still maintain efficacy in vitrectomized eyes, which are known to accelerate the clearing of intraocular medications. The study enrolled 55 patients with long-standing, treatment-resistant DME in eyes with a history of vitrectomy. Visual and anatomic outcomes were favorable at 8 and 26 weeks, showing that the sustained release of Ozurdex may still be effective in vitrectomized eyes.[30]

Protein Kinase C Inhibitors

Introduction

New pharmacologic interventions at the molecular level show great promise in treating visually disabling conditions such as DME and PDR. Two of the molecules being targeted in current clinical trials are VEGF and protein kinase C (PKC). VEGF, a vascular endothelial cell mitogen and potent permeability factor, is produced by glial cells, retinal pigment epithelial cells, and vascular endothelial cells, and is normally present in the retina and vitreous in low levels. Retinal hypoxia upregulates VEGF production, resulting in abnormal angiogenesis and a marked increase in vascular permeability. The PKC family is a group of enzymes involved in signal transduction. The β isoform has been shown to have an important role in regulating vascular permeability and is an important signaling component for VEGF. The chronic hyperglycemia of uncontrolled diabetes leads to increased cellular levels of diacylglycerol, which in turn activates PKC, especially the β isoform. PKC β increases the synthesis of VEGF and also contributes to the microvascular abnormalities in diabetic retinopathy. Inhibition of either VEGF or PKC β moderates the microvascular complications seen in experimental animal models. In addition, PKC β inhibitors given orally have the potential to influence other diabetic complications such as renal insufficiency and peripheral neuropathy.[31]

Ruboxistaurin Mesylate (Arxxant)

Background and Study Questions

One of the clinical trials that has evaluated the role of ruboxistaurin mesylate (Arxxant; Eli Lilly, Indianapolis, IN) is the Protein Kinase C β Inhibitor Diabetic Macular Edema Study (PKC-DMES).[32] The other clinical trial, the Protein Kinase C β Diabetic Retinopathy Study (PKC-DRS), is discussed in Chapter 6C. The PKC-DMES is a multicenter, double-masked, placebo-controlled study that evaluated the progression of DME in patients who were treated with ruboxistaurin or placebo.

Patients Included in the Study

A total of 686 patients with DME that was not imminently sight threatening were enrolled. Eligibility criteria included VA of 20/32 or better and no prior photocoagulation.

Intervention and Outcome Measures

Patients were randomized to placebo or to ruboxistaurin 4, 16, or 32 mg orally per day for ≥30 months. The primary outcome was progression of DME to involve or imminently threaten the center of the macula or application of focal/grid photocoagulation. Eligibility and outcomes were assessed using stereoscopic fundus photographs taken at 3 to 6 month intervals. Analysis was based on time to occurrence of the primary outcome using the intent-to-treat population.

Major Findings

At 36 months, there was no statistically significant difference between the placebo and the ruboxistaurin groups with regard to DME progression. When subgroup analysis of these patients was conducted based on baseline HbA1c (HbA1c at baseline ≤10%, ≤75th percentile), placebo and ruboxistaurin (32 mg) event rates were 45% and 31%, respectively, indicating a risk reduction in the progression of DME of 31% ($p = 0.019$). Ruboxistaurin was well tolerated with no significant adverse events noted.[32]

Implications for Clinical Practice

Treatment with ruboxistaurin did not prevent the primary endpoint of progression of DME to involve or imminently threaten the center of the macula or application of focal/grid photocoagulation in patients with non-imminently sight-threatening DME who met the inclusion criteria. However, when patients with very poor glycemic control at enrollment (HbA1c > 10%) were excluded from the analysis, ruboxistaurin 32 mg was associated with a reduction in DME progression.

When considering systemic therapy, the safety profile of the medication is critical. A prior study using a nonspecific inhibitor of multiple kinases and PKC isoforms was limited by hepatotoxicity and gastrointestinal side effects. In contrast, ruboxistaurin is selective for the β isoform of PKC, and it was well tolerated and not associated with significant adverse events.

Unanswered Questions

The apparent lack of efficacy of ruboxistaurin in preventing the progression of DME to involve or imminently threaten the center of the macula or the application of focal/grid photocoagulation could have occurred for a variety of reasons. PKC β activation occurs very early in diabetes, and it is possible that in patients with very poor glycemic control (HbA1c > 10%), the pathologic retinal changes are no longer amenable to PKC β inhibition. Alternatively, the drug may not be potent enough to overcome these changes. When patients with very poor glycemic control were excluded, ruboxistaurin 32 mg was associated with a reduction in DME progression. Although a statistically significant benefit was achieved in these patients who were treated with ruboxistaurin according to the study protocol, the optimal time to initiate therapy and the optimal duration of therapy remain unknown.

The PKC-DME clinical trial has demonstrated the potential for ruboxistaurin use in the treatment of diabetic microvascular retinal complications, especially with regard to clinically important outcomes such as the reduction of DME in patients with better glycemic control. The results support further evaluation of this approach.

III. ANTI-VEGF AGENTS

Pegaptanib Sodium (Macugen)

Background and Study Questions

Pegaptanib sodium is an aptamer (a synthetic oligonucleotide that binds to a target molecule) that selectively binds to the pathologic isoform of VEGF, $VEGF_{165}$. The aptamer is pegylated (bound to polyethylene glycol) to delay its metabolism in vivo. This increases the half-life of the drug and allows administration every 6 weeks. The medication is delivered through intravitreous injection. Macugen is currently approved by the FDA for neovascular age-related macular degeneration.[33]

Results of a phase II/III prospective, 2-year, randomized, sham-controlled, double-masked, multicenter trial using pegaptanib in eyes with DME are now available.[34]

Patients Included in the Study

A total of 288 patients with DME were enrolled. Eligibility criteria included VA between 20/50 and 20/200 and retinal thickening involving the center of the macula for whom the investigators judged photocoagulation could be safely withheld for 18 weeks.

Intervention and Outcome Measures

Patients received 0.3 mg of pegaptanib through an intravitreous injection or sham injection every 6 weeks for 1 year, and then as needed for another year. Additional focal laser was provided at the discretion of the investigators throughout the trial. Detailed re-assessments were conducted at 54 and 102 weeks.

The primary endpoint was the proportion of subjects with a ≥10-letter improvement at 54 weeks. Secondary endpoints included other measures of VA, degree of retinopathy, retinal thickness as measured by OCT, proportion requiring rescue laser treatment, and change in visual functioning and health-related quality of life using the National Eye Institute-Visual Functioning Questionnaire-25 (NEI-VFQ-25) and the EuroQol 5-Dimension (EQ-5D) self-report questionnaire.

Major Findings

The data were statistically significant for the pegaptanib arm compared to sham with respect to the following outcomes: A ≥10-letter improvement was seen in 37% of the pegaptanib group vs. 20% of the sham group at 54 weeks ($p = 0.0047$). Change in mean VA was superior to sham at all time points, including up to 102 weeks. At 102 weeks, the pegaptanib group had gained 6.1 letters compared to 1.3 letters for the sham group ($p < 0.01$). Rescue laser treatment was required in 23% and 42% of pegaptanib and sham groups, respectively, at 54 weeks ($p = 0.002$), and 25% and 45% at 102 weeks ($p = 0.003$). The proportion of subjects with improving retinopathy was three times higher in the pegaptanib group at 54 weeks (10% vs. 3%, $p = 0.1123$), and four times higher at 102 weeks (16% vs. 4%, $p = 0.0296$). A numerical decrease in ≤25% or ≤50% of retinal thickness was seen more in the pegaptanib group at 54 and 102 weeks, which were not statistically significant. The pegaptanib group also scored better on several components of the NEI-VFQ-25, but not the EQ-5D. There were no cases of endophthalmitis or retinal detachment in either group.

Implications for Clinical Practice

In this phase II/III study, patients who received pegaptanib experienced better visual outcomes, deemed less likely to need additional laser treatment, experienced slower progression of retinopathy, and although not statistically significant, had a trend toward decreased retinal thickness. The specific inhibition of $VEGF_{165}$ in this study was accomplished with an aptamer, a new therapeutic class of nonbiologic agents that possess an exceedingly high degree of target selectivity and binding affinity. Aptamers show promise as therapeutic agents, and the data suggest that inhibiting $VEGF_{165}$ with an aptamer was beneficial for patients with DME who met the specific inclusion criteria. $VEGF_{165}$ is the isoform most associated with pathologic ocular neovascularization and retinal vascular permeability, and its inhibition may result in a clinically meaningful benefit. This form of therapy requires repeated injections, and

while the drug appears to be well tolerated, there are potential serious risks associated with the injection procedure.

In a prior study comprising approximately 1,200 patients with age-related macular degeneration, there was a favorable safety profile for pegaptanib at all three doses.[33] Most adverse events in the study were mild, transient, and attributed by investigators to the injection procedure rather than the study drug. Risks of the injection procedure include endophthalmitis, retinal detachment, and vitreous hemorrhage. Endophthalmitis is a rare complication when simple precautions are implemented, such as the use of topical 5% betadine and a sterile lid speculum. Nevertheless, the decision to undertake long-term administration by repeated injections should be made carefully.

Unanswered Questions

The control group in this trial consisted of sham injection, with deferral of photocoagulation for at least 18 weeks. The SOC at the time for most cases of CSDME was prompt initiation of focal/grid laser after the diagnosis is established. A more appropriate comparison would have involved pegaptanib injections as compared to prompt initiation of laser therapy, thereby avoiding deferral of laser for 18 weeks. In a minority of patients with DME, retinal thickening is confined to the foveal avascular zone, and laser is contraindicated in these patients. Intravitreous triamcinolone or anti-VEGF injections are performed in these patients, and a comparison between pegaptanib and steroid injections or other anti-VEGF agents would be appropriate. In this manner, pegaptanib therapy could be compared with control groups that represent the current standards of care, as opposed to the natural history of DME, and a more accurate assessment of its safety and efficacy could be attained.

Ranibizumab (Lucentis): RISE and RIDE

Background and Study Questions

Ranibizumab (Lucentis; Genentech, South San Francisco, CA) is an affinity-matured anti-VEGF antibody Fab fragment that binds all active VEGF-A isoforms. Its introduction revolutionized the treatment of neovascular age-related macular degeneration (AMD) and has become the new gold standard for the treatment of wet AMD.[35,36] It was also recently approved by the U.S. FDA for the treatment of macular edema after central and branch retinal vein occlusions.[37] In 2012, monthly injections of ranibizumab 0.3 mg (as opposed to 0.5 mg for AMD) was approved by the U.S. FDA for the treatment of DME and it became the first, and at the time of writing the only, FDA-approved treatment for DME (Fig. 7B.14).[38] The RISE and RIDE trials were two parallel 2-year, phase III, multicenter, double-masked, sham injection-controlled, randomized studies.[39]

Patients Included in the Study

A total of 759 patients were enrolled in the studies (377 in RISE and 382 in RIDE). Eligibility criteria included BCVA 20/40 to 20/320 and DME with central subfield thickness $\geq$275 μm. Patients with prior vitreoretinal surgery, laser or intravitreal treatments within 3 months, and uncontrolled systemic disease were excluded.

Intervention and Outcome Measures

Participants were randomized to monthly sham injections, 0.3 mg monthly ranibizumab, or 0.5 mg monthly ranibizumab. After 3 months, monthly visits determined the need for rescue photocoagulation based on prespecified retreatment criteria. The primary endpoint was the proportion of subjects gaining $\geq$15 letters at 24 months. Secondary endpoints included other measures of VA, OCT findings, progression of retinopathy, leakage on fluorescein angiography, and the number of rescue laser treatments.

Major Findings

Significantly more patients treated with ranibizumab gained $\geq$15 letters at 24 months in both studies (RISE: 18% of the sham group vs. 45% of the 0.3-mg group [$p < 0.0001$] vs. 39% of the 0.5-mg group [$p < 0.001$]; RIDE: 12% of the sham group vs. 34% of the 0.3-mg group [$p < 0.0001$] vs. 46% of the 0.5-mg group [$p < 0.0001$]). Statistically significant

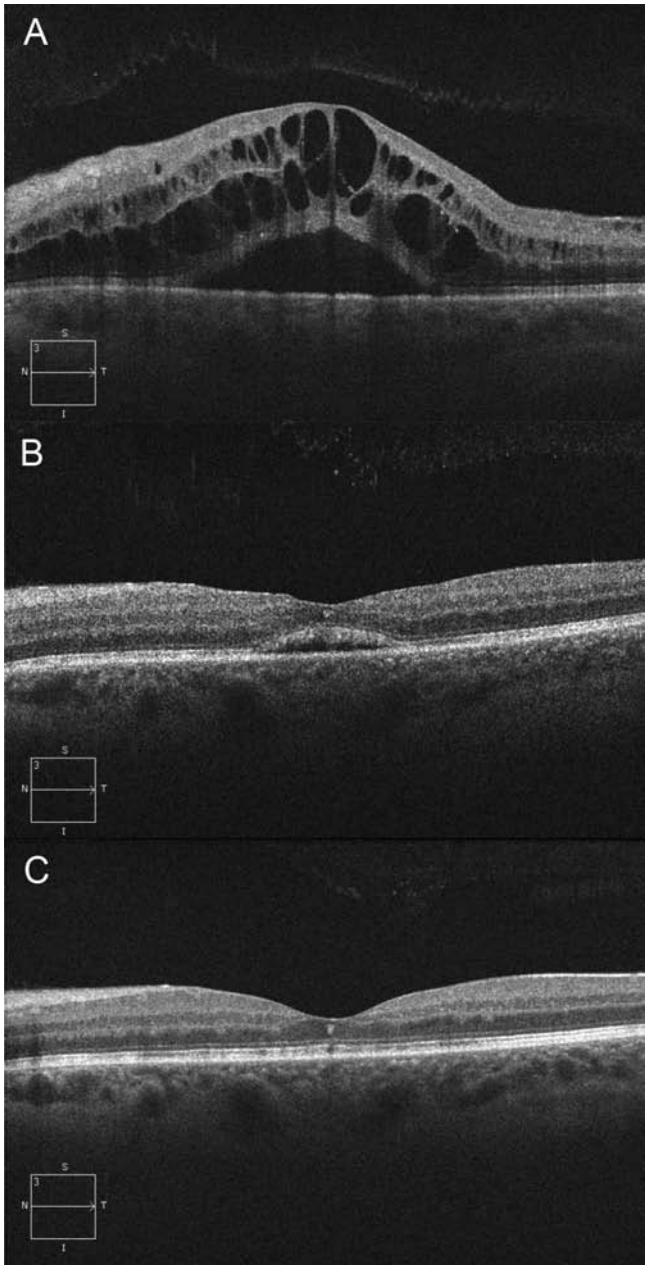

FIGURE 7B.14 Ranibizumab for the treatment of diabetic macular edema: a 41-year-old woman with a 10-year history of type 2 diabetes mellitus was referred for the management of bilateral diabetic macular edema. Visual acuity was 20/50 in the right eye and 20/80 in the left eye. **(A)** Spectral domain optical coherence tomography of the left macula showing intraretinal and subretinal fluid involving the fovea. **(B)** The intraretinal fluid has resolved and the subretinal fluid has significantly decreased 1 month after the first intravitreal ranibizumab injection. **(C)** The fluid has completely resorbed 1 month after the second intravitreal ranibizumab injection. There are subtle outer retinal irregularities, but the visual acuity has improved to 20/40. The right eye followed a similar course (not pictured). Images courtesy of Peter Kertes, MD, CM, FRCSC.

differences in BCVA were seen as early as 7 days after the first injection. Mean VA in the ranibizumab groups continued to improve steadily over the 2 years' duration. At month 24, the average benefit over sham was 8.5 to 9.9 letters. This marked the greatest mean improvement of VA of all previous DME studies (see Fig. 7B.15).

The gains in VA were paralleled by OCT and FA findings. The proportions of subjects with central subfield thicknesses ≤250 μm at 24 months were 43%, 74% ($p < 0.0001$), and 76% ($p < 0.0001$), in the sham, 0.3-mg, and 0.5-mg groups in RISE, and 46%, 76% ($p < 0.0001$), and 81% ($p < 0.0001$), respectively, in the RIDE trial.

Lack of leakage on fluorescein angiography was noted in 1.6%, 30% ($p < 0.0001$), and 26% ($p < 0.0001$) in RISE, and 2.3%, 17% ($p < 0.0001$), and 31% ($p < 0.0001$) in RIDE, respectively. Progression to PDR was noted in 15%, 2% ($p = 0.0001$), and 6% ($p = 0.0114$) in RISE, and 12%, 3% ($p = 0.0069$), and 4% ($p < 0.0206$) in RIDE, respectively. An exploratory study examined the progression of diabetic retinopathy severity and found that the cumulative probability of retinopathy progression was 34% in the sham group and 11 to 12% in the ranibizumab group.[40] The ≥3 or ≥2 steps of worsening or improving of the severity level were all statistically significant. Endophthalmitis was reported in four patients; cardiovascular/cerebrovascular events were not more common in the ranibizumab arms.

Implications for Clinical Practice

The RISE and RIDE studies provided definitive long-term evidence that monthly ranibizumab injections are beneficial in the treatment of DME, which subsequently led to

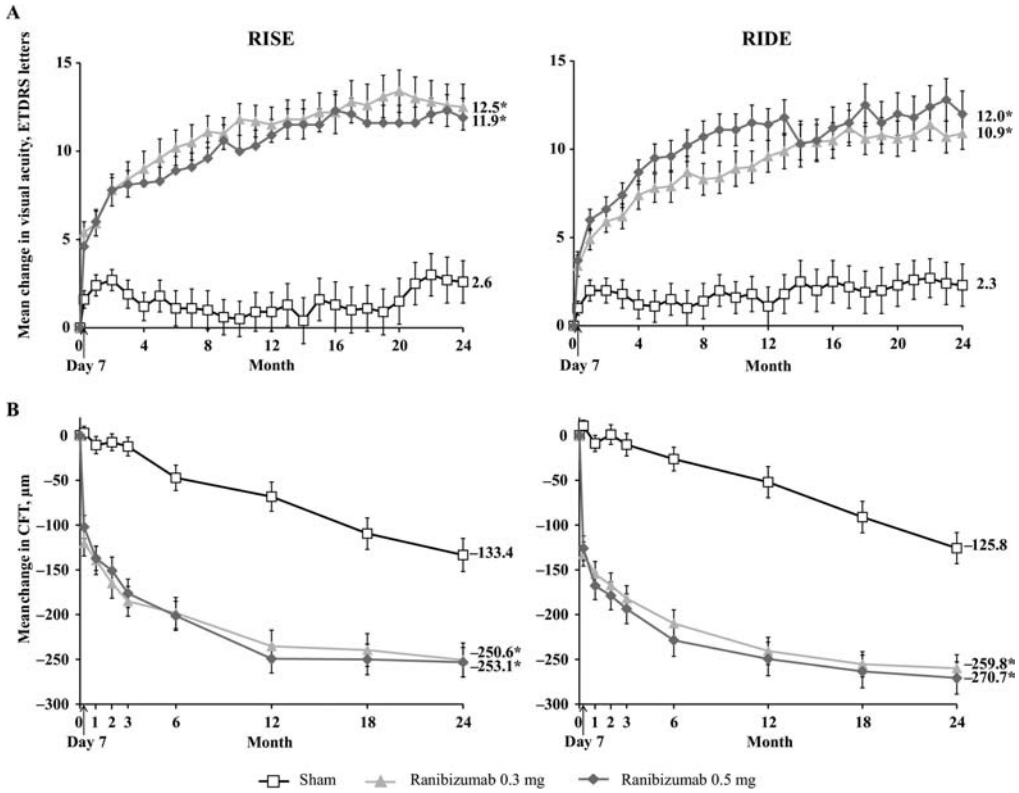

FIGURE 7B.15 RISE and RIDE studies: changes in **(A)** visual acuity and **(B)** central foveal thickness (CFT) from baseline through 24 months. *p<0.0001 versus sham. (From Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from two phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012;119:789–801.)

the FDA approval of ranibizumab for DME. Evidence based on this study and others have made anti-VEGF agents the first-line modality for many practitioners.

Unanswered Questions

This study only shows that monthly ranibizumab is beneficial over sham injections with rescue laser treatment. A true focal/grid photocoagulation control arm would have provided more pertinent data. This study also does not provide comparative analysis with corticosteroids and other anti-VEGF agents. Furthermore, many practitioners prefer an "as needed" use of intravitreal injections as continuous monthly injections for DME is often not practical. Lastly, 2-year follow-up classifies RISE and RIDE as long-term studies, but we do not have data yet beyond 2 years. Diabetes mellitus and DME are chronic conditions that require life-long surveillance and appropriate treatment. The subsequent sections in this chapter describe studies that address several of the shortcomings mentioned above.

Ranibizumab (Lucentis): Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema

Background and Study Questions

The RESTORE (Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema) study was half the size of RISE/RIDE combined, but it directly addressed the important question of how ranibizumab monotherapy compares to laser photocoagulation monotherapy and combination therapy. There are several theories behind the benefits of combination therapy. Intravitreal anti-VEGF therapy is thought to rapidly reduce macular edema, while the effects of laser become more apparent over time. The two modalities could thus complement each other. Laser treatment also may be able to decrease the number of intravitreal injections. RESTORE was a 12-month, double-masked, multicenter phase III study.[41]

Patients Included in the Study

A total of 345 patients with DME were included in the study. Eligibility criteria included stability of diabetes, focal or diffuse DME that was eligible for laser treatment, and visual acuities between 20/32 and 20/160. Excluded were subjects with ophthalmic comorbidities, recent laser or intravitreal treatment, and those with significant cardiovascular risk factors.

Intervention and Outcome Measures

Participants were equally randomized to ranibizumab + sham laser, ranibizumab + laser, or sham injections + laser. All patients were monitored monthly. Monthly injections were given for 3 months and then *pro re neta* (PRN); laser treatments were performed at baseline and then PRN based on ETDRS guidelines. The primary endpoint was the mean change in BCVA at 1 year. Secondary endpoints included other measures of VA, central retinal thickness, diabetic retinopathy severity, patient-reported outcomes, and safety measures.

Major Findings

All treatment groups received approximately seven injections and two laser sessions. Ranibizumab monotherapy and ranibizumab + laser combination therapy resulted in superior improvements in mean VA at 1 year compared to laser monotherapy: +6.1 ($p < 0.0001$) and +5.9 letters ($p < 0.0001$) vs. +0.8 letters, respectively. Gains of BCVA ≥15 letters were seen in 23% ($p = 0.0005$), 23% ($p = 0.0037$), and 8%, respectively. Final BCVA of > 20/40 was achieved in 53% ($p < 0.0001$), 45% ($p < 0.0002$), and 24%, respectively. The mean central retinal thickness decreased by –119 μm ($p < 0.0002$), –128 μm ($p < 0.0001$), and –61 μm, respectively. Central retinal thickness of <250 μm was achieved in 49% ($p < 0.0408$), 55% ($p = 0.0075$), and 39%, respectively. Quality of life measures were also superior in the ranibizumab treatment arms. There were no cases of endophthalmitis, and cardiovascular/cerebrovascular events did not occur in this study.

Implications for Clinical Practice

The RESTORE study showed that ranibizumab monotherapy or combined with laser treatment has superior visual and anatomic outcomes at 1 year compared to laser monotherapy. The injections were performed on an as-needed basis, which is the treatment schedule that many practitioners use in clinical practice. No difference was detected between the ranibizumab monotherapy and combination therapy arms.

Unanswered Questions

While this study demonstrates that laser monotherapy is inferior to ranibizumab monotherapy or combination therapy, it is unclear whether the lack of difference between the ranibizumab monotherapy and combination arms would manifest after longer follow-up. If monotherapy can produce the same outcomes as combination therapy without increasing the number of injections, laser treatment may be able to be deferred until necessary. The DRCR.net study described below addresses this issue.

Ranibizumab (Lucentis): Diabetic Retinopathy Clinical Research Network, Protocol I

Background and Study Questions

The DRCR.net sought to provide insight into several unanswered questions: how laser monotherapy compares with combination therapy using ranibizumab, the timing (prompt vs. deferred) of laser when used in combination with ranibizumab, and whether a laser + triamcinolone combination plays a role in the treatment of DME. Some speculated that laser treatment would be more effective if it were deferred for several weeks after ranibizumab injection, because the laser would be more effective on retina that has been "dried" with ranibizumab. Protocol I was a comparative effectiveness, randomized, partially masked, multicenter, phase III trial.[42]

Patients Included in the Study

A total of 854 eyes of 691 subjects were included in the study. Eligibility criteria included BCVA of 20/32 to 20/320, DME as the main cause of visual decline, and central retinal thickness ≥250 μm. Exclusion criteria included recent DME treatment or ophthalmic surgery, IOP abnormalities, and recent cardio/cerebrovascular events.

Intervention and Outcome Measures

Subjects were randomized to one of the four arms: (1) sham injection with prompt laser, (2) ranibizumab with prompt laser, (3) ranibizumab with deferred laser, or (4) triamcinolone with prompt laser. Prompt laser was defined as laser treatment within 3 to 10 days after the injection, while deferred laser was defined as ≥24 weeks. A modified ETDRS focal/grid photocoagulation protocol was used.

Retreatment was performed based on a predetermined algorithm. Patients were injected every 4 weeks for the first 12 weeks (3 monthly induction injections). From the 16-week visit and onward, retreatment was performed unless there was treatment "success," which was defined as VA 20/20 or OCT central subfield thickness <250 μm, at which point retreatment was at the discretion of the investigator. From the 24-week visit and onward, retreatment was at the discretion of the investigator if there was "no improvement," which was defined as improvement or worsening by <5 letters and OCT thickness decreased or increased by <10%. "Failure" was defined as VA 10 or more letters worse than baseline or OCT 250 μm or thicker at least 13 weeks after complete focal/grid laser treatment, and "futility" was defined as OCT 250 μm or thicker after the 52-week visit and at least 29 weeks since complete focal/grid laser. There was no retreatment under circumstances of "failure" and "futility," but an alternative medication could be provided. Retreatment was allowed every 4 weeks for ranibizumab, every 16 weeks for triamcinolone (with sham injections every 4 weeks in between), and every 13 weeks for focal/grid photocoagulation (unless all microaneurysms within the edema had been previously treated with grid laser applied to all areas of edema). In essence, retreatment continued until stabilization was achieved, or lack of further improvement was noted.

Patients were seen every 4 weeks for the first year. Those in the three prompt laser groups were masked until 1 year, but the ranibizumab with deferred laser group was unmasked. After 1 year, patients were seen every 4 to 16 weeks. The primary outcome was the mean change in VA at 1 year.

Major Findings

The mean improvement in VA score was better in the ranibizumab + prompt laser group (+9 letters, $p < 0.001$) and in the ranibizumab + deferred laser group (+9 letters, $p < 0.001$), but not in the triamcinolone + prompt laser group (+4 letters, $p = 0.31$ compared to the laser group (+3 letters) at 1 year. A ≥15-letter improvement was seen in 30% ($p < 0.001$), 28% ($p < 0.001$), 21% ($p = 0.07$), and 15%, respectively. The respective median numbers of injections during the year were 8, 9, 3, and 11 (sham). In addition to the three triamcinolone injections, a median of five sham injections were also administered in the triamcinolone group. If only pseudophakic eyes were examined, the triamcinolone + laser group had similar gains in vision (+8 letters) as the ranibizumab groups.

A comparable decrease in central retinal thickness was seen in all the ranibizumab and triamcinolone groups, but not the sham + laser group (–131 μm, –137 μm, –127 μm, –102 μm, respectively, $p < 0.001$ for all). The ranibizumab treatment groups had more improvement and less worsening of retinopathy severity compared to the laser/sham group in eyes with baseline moderately severe NPDR or better ($p = 0.08$) and in eyes with baseline severe NPDR or worse ($p = 0.03$). Similar trends that were not statistically significant were observed in the triamcinolone arm.

There were three cases (0.08%) of infectious endophthalmitis out of 3,973 ranibizumab injections. One case of sterile endophthalmitis occurred in the triamcinolone group. IOP elevation ($p < 0.001$) and cataract surgery ($p < 0.001$) were more common in the triamcinolone arm. An IOP increase of ≥10 mmHg from baseline was noted in 5%, 3%, 38%, and 5%, in the ranibizumab + prompt laser, ranibizumab + deferred laser, triamcinolone + prompt laser, and the sham + prompt laser groups, respectively. No glaucoma surgeries were necessary. Of phakic eyes at baseline, cataract surgery took place in 5%, 6%, 15% ($p < 0.001$), and 6%, respectively. There were no differences in systemic adverse events.

In the 2-year follow-up examination, the mean improvements in VA scores were +7 ($p = 0.03$), +9 ($p < 0.001$), +2 ($p = 0.35$), and +3, respectively.[43] A ≥15-letter improvement was seen in 29% ($p = 0.03$), 28% ($p = 0.01$), 22% ($p = 0.18$), and 18%, respectively. If only pseudophakic eyes were examined, the triamcinolone + laser group had similar gains in vision as the ranibizumab groups. A comparable decrease in central retinal thickness was seen in all the ranibizumab and triamcinolone groups, but not the laser monotherapy group (–141 μm [$p < 0.003$], –150 μm [$p = 0.01$], –107 μm [$p = 0.37$], and –138 μm, respectively) (see Table 7B.3). The ocular and systemic adverse events were comparable to the 1-year data.

The 3-year assessment examined those in the ranibizumab arms only. Participants in the triamcinolone/laser and sham/laser arms were provided the option of receiving ranibizumab. The prompt laser group had a mean gain of +7 letters, while the deferred group had gained +10 letters ($p = 0.02$). There were no substantial differences in OCT findings, however.

Implications for Clinical Practice

This pivotal DRCR.net study showed that ranibizumab + prompt or deferred laser can achieve superior visual and anatomic outcomes compared to laser monotherapy. The 3-year results appear to suggest that deferred laser treatment may be more effective than prompt laser. Intravitreal triamcinolone + laser had beneficial outcomes in pseudophakic eyes, but at the cost of IOP elevation that could be managed medically. In addition to these data, this study's retreatment algorithm has been adopted by many practices as a treatment guideline. Close follow-up of patients is still required, because although injections were decreased over the course of 3 years, they were still necessary.

TABLE 7B.3 Diabetic Retinopathy Clinical Research Network Protocol I

	Ranibizumab + Prompt laser (n^a = 136)	Ranibizumab + Deferred laser (n = 139)	Triamcinolone + Prompt laser (n = 142)	Sham + Prompt laser (n = 211)
Mean change from baseline at 1 y (letters)	+9	+9	+4	+3
Mean change from baseline at 2 y (letters)	+7	+9	+2	+3
Change in OCT CST at 1 y (μm)	−131	−137	−127	−102
Change in OCT CST at 2 y (μm)	−141	−150	−107	−138
Median number of drug injections prior to 2 y	11 (of 25 possible)	13 (of 25 possible)	4 (of 8 possible)	not applicable

[a]n at the 2-year visit.
CST, central subfoveal thickening; OCT, optical coherence tomography.

Unanswered Questions

This study provided many answers to important questions. However, this trial did not have a ranibizumab monotherapy arm (although this is addressed in other studies). The RESTORE trials showed no significant difference between the ranibizumab monotherapy and ranibizumab-laser combination arms, but since direct comparison of trials *ad hoc* is limited by many factors, we cannot assume that a ranibizumab monotherapy arm in this trial would have behaved similarly to the combination arms.

Ranibizumab: Other Trials

Many other ranibizumab trials have been published since the last edition of this text. The Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE) and Ranibizumab for Edema of the mAcula in Diabetes (READ-2) studies were earlier studies that primed the field for the subsequent larger RISE and RIDE trials. They are summarized below, along with a recent DRCR.net study.

The RESOLVE study was a 12-month, multicenter, sham-controlled, double-masked clinical trial that randomized 151 patients to ranibizumab 0.3 mg, ranibizumab 0.5 mg, or sham.[44] After three monthly induction doses, retreatment was provided on predetermined criteria. Double doses were also permitted. At 12 months, mean BCVA in the pooled ranibizumab group was +10 letters, while there was a –1-letter decline in the sham group ($p < 0.0001$). Mean reduction in retinal thickness was 194 μm with ranibizumab and 48 μm with sham ($p < 0.0001$). The RESOLVE study demonstrated the efficacy of ranibizumab over the natural history of DME.

The READ-2 study was a prospective, randomized, multicenter, phase II trial that assigned 126 patients with DME to (1) 0.5 mg of ranibizumab at baseline and 1, 3, and 5 months, (2) focal/grid laser at baseline and 3 months if needed, or (3) a combination of ranibizumab and focal/grid laser at baseline and 3 months.[45] At the primary endpoint of 6 months, the changes in mean BCVA in groups 1, 2, and 3 were +7 letters, –0.4 letters ($p = 0.0001$ compared to group 1), and +4 letters ($p = 0.08$), respectively. Improvement of three lines or more was achieved in 22%, 0% ($p = 0.002$), and 8%, respectively. Retinal thickness reduction of 90% or more was attained in 24%, 8%, and 8%, while reduction of 50% or more was seen in 54%, 48%, and 32%, respectively.

After the 6-month endpoint, participants were retreated with ranibizumab if certain criteria were met.[46] The mean numbers of injections were approximately five, four, and three during the subsequent 18 months. At 2 years, the gains in BCVA were +8, +5, and +7 letters (each group statistically significantly improved from baseline, but not between each other), respectively, and the proportions of those that improved three lines or more were 24%, 18%, and 26%, respectively (significance testing not provided). Central subfield thickness of ≤250 μm was achieved in 36%, 47%, and 68%, respectively (significance testing not provided).

The READ-2 study suggested that (1) ranibizumab was superior to focal/grid laser photocoagulation in the short-term, (2) it is beneficial for at least 2 years, and (3) treatment combined with laser may decrease the number of injections. However, this study was limited by its small sample size, which was further diminished during the follow-up period due to participant dropout.

The DRCR.net recently published the results of a large trial where 345 eyes receiving both macular laser for DME and PRP for advanced diabetic retinopathy were randomized to (1) sham, (2) ranibizumab 0.5 mg at baseline and 4 weeks, or (3) triamcinolone 4 mg at baseline and sham at 4 weeks.[47] The rationale for performing this trial was based on observations that DME could be exacerbated after PRP. This phenomenon was also seen in the ETDRS study (see above).

At 14 weeks, the mean changes in VA were significantly better in the treatment arms (+1 letter for ranibizumab [$p < 0.001$], +2 letters for triamcinolone [$p < 0.001$], and –4 letters for sham). These data suggested that intravitreal ranibizumab or triamcinolone might be beneficial, at least in the short-term, for eyes with DME that will undergo PRP for severe retinopathy.

Bevacizumab (Avastin): Prospective Trial of Intravitreal Bevacizumab or Laser Therapy in the Management of DME

Background and Study Questions

Bevacizumab is the full-length parent antibody of ranibizumab. It is approved by the U.S. FDA as chemotherapy for several malignancies, but has been popularized as an off-label cost-effective alternative to ranibizumab in treating VEGF-driven ophthalmic pathology. Many series and short-term studies suggested its efficacy in treating DME,[48–54] but the Prospective Trial of Intravitreal Bevacizumab or Laser Therapy in the Management of DME (BOLT) was the first study with 2-year follow-up that directly compared intravitreal bevacizumab to macular laser photocoagulation. The BOLT study was a prospective, randomized, masked, single-center, 2-year study.[55,56]

Patients Included in the Study

A total of 80 eyes from 80 patients with DME were included in the study. Eligibility criteria included BCVA 20/40 to 20/200, central macular thickness ≥270 μm, and at least one prior macular laser treatment. Excluded were patients with macular ischemia, vision-limiting ophthalmic comorbidities, recent treatment for DME, recent PRP, and uncontrolled systemic disease.

Intervention and Outcome Measures

Participants were randomized to either bevacizumab (1.25 μg/50 μl) every 6 weeks as needed or modified ETDRS macular photocoagulation every 4 months as needed. Those in the bevacizumab arm were injected at baseline, 6 weeks, and 12 weeks, and then examined every 6 weeks for possible retreatment using an OCT-based protocol. Those in the laser arm received modified focal/grid laser at baseline, and then reviewed every 4 months for retreatment based on the ETDRS guidelines. The primary endpoint was the difference in mean BCVA at 1 year.

Major Findings

The median change in BCVA at 1 year was +8 letters in the bevacizumab group, compared to –0.5 letters in the laser group ($p = 0.0002$). Improvement in BCVA by 15 letters or more was achieved in 12% and 5%, respectively ($p = 0.43$). The mean change in central macular thickness was –130 μm and –68 μm, respectively ($p = 0.06$). There was a trend toward reduction in retinopathy severity

in the bevacizumab arm, but not in the laser arm. There were no cases of endophthalmitis.

In the 2-year follow-up assessment, the median change in BCVA at 2 years was +9 letters in the bevacizumab group, compared to +2.5 letters in the laser group ($p = 0.005$); ≥15 letters gain was achieved in 32% and 4%, respectively ($p = 0.004$).[56] The mean change in central macular thickness was –146 μm and –118 μm, respectively ($p = 0.62$). There were still no cases of endophthalmitis reported.

Implications for Clinical Practice

The BOLT study showed that 1.25 mg/50 μl bevacizumab injections might be superior to macular laser treatment for at least 2 years in the treatment of DME. Monitoring patients every 6 weeks appeared to be sufficient.

Unanswered Questions

The BOLT study was limited by its small sample size. It should be placed in the context of the other relatively small bevacizumab treatment trials. Two of those studies are summarized below.

The DRCR.net organized a short-term trial by randomizing 121 participants to one of the five groups: (1) macular laser, (2) bevacizumab 1.25 mg at baseline and 6 weeks, (3) bevacizumab 2.5 mg at baseline and 6 weeks, (4) bevacizumab 1.25 mg at baseline and sham at 6 weeks, or (5) bevacizumab 1.25 mg at baseline and 6 weeks, with macular laser at 3 weeks.[49] At 12 weeks, the changes in VA were –1, +5, +7, +4, and 0 letters, respectively. Improvement of 15 letters or more was seen in 5%, 14%, 13%, 9%, and 15%, respectively. Retinal thickening of <250 μm or ≥50% reduction in thickness was found in 21%, 33%, 33%, 14%, and 25%, respectively. Meaningful significance testing was not possible due to the small sample size, but the data demonstrated the potential of bevacizumab in managing DME. This study led to the subsequent larger DRCR.net bevacizumab trials.

Another study randomized 150 treatment-naïve eyes of 129 patients to (1) 1.25 mg bevacizumab, (2) 1.25 mg bevacizumab and 2 mg intravitreal triamcinolone, or (3) macular laser.[51] Retreatments were performed at 12-week intervals as needed. At 24 weeks, the primary endpoint, visual acuities in the bevacizumab monotherapy ($p = 0.003$) and bevacizumab + triamcinolone groups ($p = 0.033$) were superior to the macular laser group. Central macular thickness decreased in all groups at 6 weeks, but significance was lost thereafter. At the 2-year follow-up assessment, the differences that were achieved earlier lost statistical significance.[54] The improvement in VA and reduction of retinal thickness were the largest in the bevacizumab monotherapy arm, but the differences were not significant. These data suggested that bevacizumab may be beneficial initially for the treatment of DME, but its effect may wane over time.

Aflibercept (Eylea): DA VINCI

Background and Study Questions

Aflibercept (Eylea, Regeneron, Tarrytown, NY) is a soluble decoy receptor that binds all isoforms of VEGF-A, VEGF-B, and placental growth factor (PlGF). It was engineered by fusing VEGF receptor (VEGFR) 1 and VEGFR 2 to the Fc portion of human IgG-1. It was introduced as a new mechanism of VEGF blockade for the treatment of neovascular AMD. Its high affinity and potency have allowed bimonthly dosing, to decrease the injection burden on patients.[57] It was approved by the U.S. FDA for the treatment of neovascular AMD and more recently, for macular edema after central retinal vein occlusion. The DA VINCI study was a 52-week, multicenter, double-masked, randomized, phase II clinical trial to examine the safety and efficacy of aflibercept in the treatment of DME.[58]

Patients Included in the Study

A total of 221 subjects were included in the study. Eligibility criteria included BCVA 20/40 to 20/320, DME as the main cause of visual decline, and central retinal thickness ≥250 μm. The exclusion criteria included recent DME treatment, recent ophthalmic surgery, and recent cardio/cerebrovascular events.

Intervention and Outcome Measures

Subjects were randomized to one of the five arms: (1) 0.5 mg aflibercept every 4 weeks (0.5q4), (2) 2 mg aflibercept every 4 weeks

(2q4), (3) 2 mg aflibercept every 8 weeks after 3 monthly initiation injections with sham injections on months without aflibercept (2q8), (4) 2 mg aflibercept as needed after 3 monthly initiation injections (2PRN), or (5) modified ETDRS macular laser photocoagulation with monthly sham injections. The primary endpoint was the mean change in BCVA at 24 weeks.

Major Findings

At 24 weeks, the respective gains in VA in the aflibercept groups were +9 ($p = 0.0054$), +11 ($p < 0.0001$), +9 ($p < 0.0085$), and +10 letters ($p = 0.0004$), compared to +3 letters for the laser group. There was no significant difference between the four aflibercept arms; ≥15 letters were gained in 34%, 32%, 17%, and 27%, compared to 21% of the laser group (significance testing not provided). Central retinal thicknesses mirrored the VA results: mean reductions were –145 μm ($p = 0.0002$), –195 μm ($p < 0.0001$), –127 μm ($p = 0.0066$), and –153 μm ($p < 0.0001$), compared to –68 μm, respectively. Two cases of endophthalmitis were reported.

At the 2-year follow-up assessment, mean improvements in BCVA were +11, +13, +10, and +12 letters, compared to –1 letter for the laser group ($p < 0.001$).[59] There was no significant difference between the four aflibercept arms; ≥15 letters were gained in 41%, 46%, 24%, and 42%, compared to 11% of the laser group ($p \leq 0.001$). Central retinal thicknesses mirrored the VA results: mean reduction was –165 μm, –227 μm, –188 μm, and –180 μm, compared to –58 μm, respectively ($p < 0.0001$). Improvements in the diabetic retinopathy severity scale were seen in 40%, 31%, 64%, and 32%, compared to the laser group with only 12%. No further cases of endophthalmitis were reported, and no systemic complications were directly attributed to the aflibercept injections.

Implications for Clinical Practice

This study demonstrated that all aflibercept regimens were superior to macular laser treatment at every time point throughout the 52 weeks. Of the different dosing/retreatment protocols, the 2q4 group had the best VA improvements. The 2q8 group had the least impressive visual outcomes, but it appears that it was due to differences in the baseline characteristics of the participants.

Unanswered Questions

Numerous studies, including this one, have established that intravitreal anti-VEGF agents are superior to macular photocoagulation in treating central foveal-involving DME. The main unanswered question is which anti-VEGF agent to use: pegaptanib, ranibizumab, bevacizumab, or aflibercept. Ranibizumab has undergone the most scrutiny with the largest number of clinical trials, and its efficacy is undeniable. Based on the DA VINCI trial and experience from the AMD trials,[57] it appears that aflibercept may have a similar level of efficacy. The bevacizumab trials are too small to draw similar conclusions, and pegaptanib has not been widely adopted as the anti-VEGF agent of choice, and its effectiveness appears to be lower than the other agents. However, bevacizumab will remain a popular choice for its cost-effectiveness. A DRCR.net study is currently under way to compare the efficacy between ranibizumab, bevacizumab, and aflibercept.[60]

CONCLUSION

Tremendous advances have been made in the treatment of DME. The ETDRS conclusively demonstrated that focal photocoagulation was effective in the treatment of DME, and it proved that for eyes with CSDME, the risk of moderate visual loss was substantially reduced. The ETDRS defined the SOC for over 20 years, and all DME clinical trials continue to use ETDRS results for comparison.

Emerging pharmacologic therapies in various phases of clinical trial development hold great promise in the treatment of DME. Steroids such as triamcinolone, fluocinolone, and dexamethasone, and the anti-VEGF agents ruboxistaurin (Arxxant), pegaptanib (Macugen), ranibizumab (Lucentis), bevacizumab (Avastin), and aflibercept (Eylea) represent new approaches to the management of DME, and the clinical trial results are encouraging. In fact, numerous trials now show that anti-VEGF agents are more

effective than macular photocoagulation for patients with center-involving DME. We may be approaching the point where some may start considering anti-VEGF agents as the new gold standard. However, they alone will not be the end-all for DME treatment. All of the anti-VEGF trials enrolled patients with center-involving DME with decreased vision. For patients with CSDME that spares the fovea and thus central acuity, focal/grid laser is still the only proven treatment of choice. DME is a heterogeneous disease that will require patient-specific approaches using a carefully selected combination of laser, steroids, and anti-VEGF agents.

Sustained release drug delivery devices such as Retisert, Iluvien, and Ozurdex represent early devices in a field that is rapidly expanding. The future may involve oral and intravitreal (probably via sustained release devices) administration of new pharmacologic agents, and emphasis will likely be on prevention and early treatment. The visual morbidity associated with DME will hopefully, one day, be eliminated.

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7C Proliferative Diabetic Retinopathy: Clinical Trials

Dean Eliott MD

I. DIABETIC RETINOPATHY STUDY

Introduction

Eyes that develop proliferative diabetic retinopathy (PDR) have at least a 50% probability of becoming blind within 5 years without treatment.[1–3] Retinal photocoagulation, introduced by Meyer-Schwickerath in 1960 with the xenon arc, appeared to have a beneficial effect on neovascularization; however, there was uncertainty as to its exact role.[4] The xenon arc was used to treat patches of surface neovascularization directly, while the ruby laser and, subsequently, the argon laser, were used in the same manner as well as in an indirect scatter pattern. Results of several small clinical trials in the late 1960s suggested that photocoagulation might be a promising new treatment for retinal neovascularization.[5] The Diabetic Retinopathy Study (DRS) was organized in the 1970s to determine the effect of photocoagulation on diabetic retinopathy. This was the first prospective, multicenter, randomized controlled trial (RCT) sponsored by the newly formed National Eye Institute of the National Institutes of Health. In addition to its historical importance, the DRS has contributed tremendously to our understanding of the role of photocoagulation in the management of PDR.[6,7]

Background and Study Questions

When the DRS was organized, visual loss from diabetic retinopathy was a growing public health problem. There was no consensus regarding the treatment of PDR and diabetic macular edema (DME), the two major causes of blindness in patients with diabetes. The DRS, which attempted to seek answers to an important public health issue, was unprecedented in its scope and size.

To describe fundus findings in a consistent manner, the DRS used a modified version of the Airlie House Classification of diabetic retinopathy.[8] The original Airlie House Classification was developed in 1968 at a symposium where the most up-to-date knowledge of diabetic retinopathy was discussed. Despite a symposium among more than 50 international experts in retinal disease, the best approach for the management of diabetic retinopathy was unknown.[9,10]

It was in this historical context that the DRS was established. The DRS sought to determine whether photocoagulation (xenon or argon) was effective in the treatment of diabetic retinopathy. Specifically, it attempted to determine whether photocoagulation could prevent severe visual loss in eyes with PDR, whether there was a difference in safety and efficacy between xenon arc and argon laser, and whether certain stages of retinopathy demonstrated different responses to treatment.[6,7]

Patients Included in the Study

Approximately 1,750 patients with PDR in at least one eye or severe nonproliferative diabetic retinopathy (NPDR) in both eyes, and visual acuity of at least 20/100 in both eyes were enrolled.[11]

Severe NPDR was defined by the DRS as cotton-wool spots (see Fig. 7C.1), venous beading (see Fig. 7C.2), and intraretinal microvascular abnormalities (see Fig. 7C.3) in at least two of four contiguous photographic fields or two of these findings and moderately severe hemorrhages and/or microaneurysms

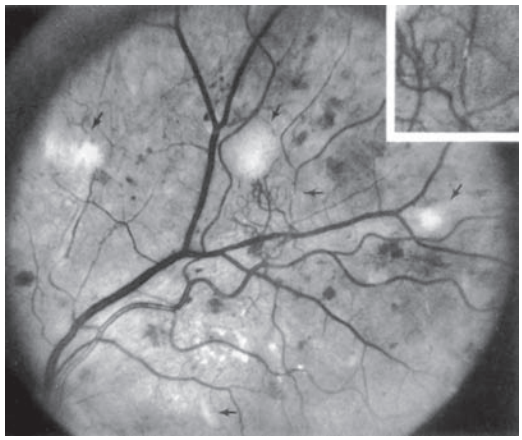

FIGURE 7C.1 Diabetic Retinopathy Study standard photograph 5, the more severe of two standards for soft exudates. There are four soft exudates (cotton-wool spots) in the upper half of this photograph: two (almost confluent) at the 9:30 position, one just above the center, and one at the 3 o'clock position. This photograph also shows hard exudates (lipid) below the center of the picture and a small segment of arteriolar sheathing (*inset*). Some of the abnormal vessels at the center of the photograph are intraretinal microvascular abnormalities and some are new vessels. (From Diabetic Retinopathy Study Research Group. A modification of the Airlie House Classification of diabetic retinopathy. DRS Report No. 7. *Invest Ophthalmol Vis Sci.* 1981;21(1): 210–226 and from Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House Classification. ETDRS Report No. 10. *Ophthalmology.* 1991;98:786–806.)[12]

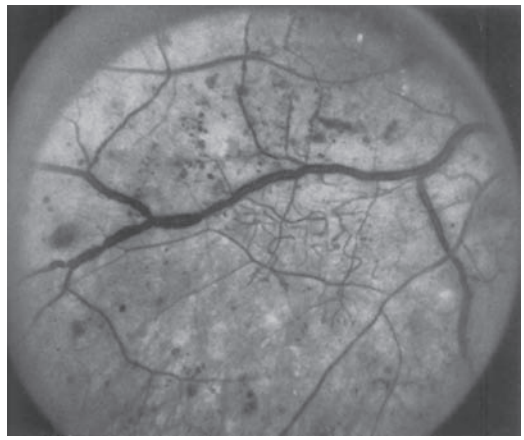

FIGURE 7C.2 Diabetic Retinopathy Study standard photograph 6B, more severe standard for venous beading. Most venous branches, both large and small, are involved by severe beading. (From Diabetic Retinopathy Study Research Group. A modification of the Airlie House Classification of diabetic retinopathy. DRS Report No. 7. *Invest Ophthalmol Vis Sci.* 1981;21(1):210–226 and from Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House Classification. ETDRS Report No. 10. *Ophthalmology.* 1991;98:786–806.)[12]

(see Fig. 7C.4) in at least one photographic field. There are seven standard 30-degree photographic fields (see Fig. 7C.5).[8,11]

Neovascularization of the disc (NVD) was defined by the DRS as the presence of abnormal vessels on or within one-disc diameter of the optic disc (see Fig. 7C.6), and neovascularization elsewhere (NVE) as the presence of abnormal vessels located more than one-disc diameter from the disc (see Fig. 7C.7).

Intervention and Outcome Measures

One eye of each patient was randomized to receive treatment, either with the xenon arc or the argon blue-green laser, and the other eye served as a control and was observed without treatment. All treated eyes received both direct photocoagulation to surface neovascularization (NVE only) and scatter panretinal photocoagulation from the vascular arcades to beyond the equator (laser burns separated by one burn width). In addition, eyes randomized to argon laser treatment also had NVD treated directly only in the initial part of the study (this was not possible with xenon). Argon laser burns were generally smaller and less intense than xenon arc burns (see Fig. 7C.8).

Outcome measures included severe visual loss, defined as visual acuity less than 5/200 at each of two consecutive visits 4 months apart.

Major Findings

The DRS demonstrated a 50% reduction in severe visual loss in eyes that received photocoagulation (see Fig. 7C.9).[13,14] This

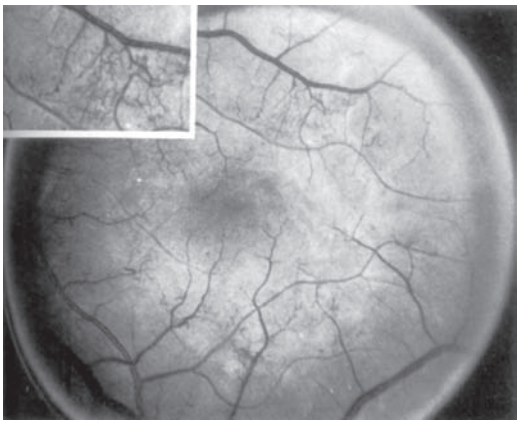

FIGURE 7C.3 Diabetic Retinopathy Study standard photograph 8B, more severe standard for intraretinal microvascular abnormalities (IRMA). This photograph shows IRMA in all quadrants. Inset shows IRMA superotemporal to the center of the macula. (From Diabetic Retinopathy Study Research Group. A modification of the Airlie House Classification of diabetic retinopathy. DRS Report No. 7. *Invest Ophthalmol Vis Sci.* 1981;21(1):210–226 and from Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House Classification. ETDRS Report No. 10. *Ophthalmology.* 1991; 98:786–806.)[12]

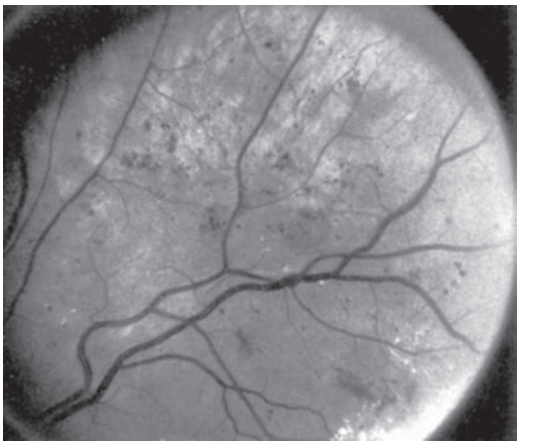

FIGURE 7C.4 Diabetic Retinopathy Study standard photograph 2B, severe standard for hemorrhages and microaneurysms. (From Diabetic Retinopathy Study Research Group. A modification of the Airlie house classification of diabetic retinopathy. DRS Report No. 7. *Invest Ophthalmol Vis Sci.* 1981;21(1):210–226 and from Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House Classification. ETDRS Report No. 10. *Ophthalmology.* 1991;98:786–806.)

finding was so impressive that the protocol was amended to allow the control group to receive photocoagulation.[14]

The study also identified features that were associated with a particularly high risk of severe visual loss.[14–17] These risk factors were based on the presence, location, and severity of neovascularization, as well as the presence of vitreous or preretinal hemorrhage. Specifically, these risk factors were defined as (a) the presence of new vessels; (b) the location of new vessels on or within one-disc diameter of the optic disc (NVD); (c) the severity of new vessels, defined for NVD as equal to or greater than one-fourth to one-third disc area in extent (equal to or greater than standard photograph 10A) (Fig. 7C.6),[8] or for NVE, equal to or greater than one-half disc area; and (d) preretinal or vitreous hemorrhage. Eyes with at least three of these risk factors were considered to be at high risk for severe visual loss, and these eyes demonstrated the most benefit from photocoagulation (see Table 7C.1, Fig. 7C.10).

After 2 years of follow-up in the DRS, severe visual loss occurred in 26% of eyes in the control group as compared with 11% in the treated group for eyes with high-risk characteristics (HRC). After 4 years, 44% of control eyes and 20% of treated eyes developed severe visual loss, and the unequivocal benefit of photocoagulation was substantiated in all additional reports with longer follow-up.[18,19] Prompt photocoagulation was recommended for eyes with HRC.

For eyes with PDR and less than high-risk retinopathy, the risk of developing severe visual loss at 2 years was 7% for the control group and 3% for the treated group. For eyes with severe NPDR, these rates were even lower. The DRS did not recommend prompt treatment for these categories of eyes.

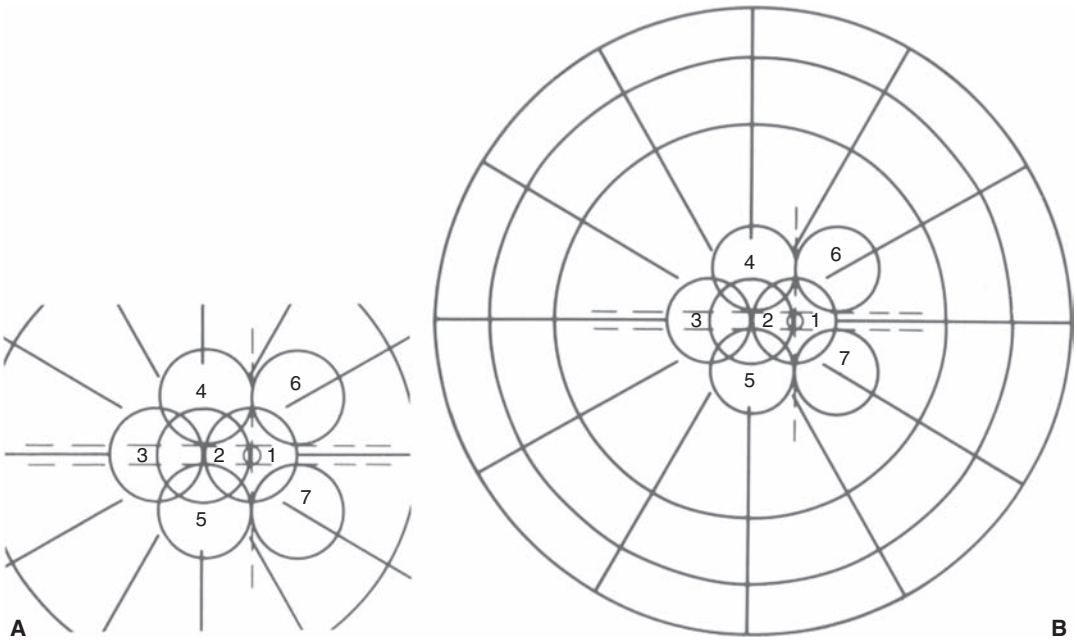

FIGURE 7C.5 Seven standard photographic fields of the modified Airlie House Classification shown for the right eye. Field 1 is centered on the optic disc; field 2 on the macula; field 3 temporal to the macula. Fields 4 through 7 are tangential to horizontal lines passing through the superior and inferior edges of the optic disc and to a vertical line passing through its center. (From Diabetic Retinopathy Study Research Group. A modification of the Airlie House Classification of diabetic retinopathy. DRS Report No. 7. *Invest Ophthalmol Vis Sci.* 1981;21(1):210–226 and from Olk RJ, Lee CM. Review of national collaborative studies. In: *Diabetic Retinopathy: Practical Management.* Philadelphia, PA: JB Lippincott Co; 1993:22.)

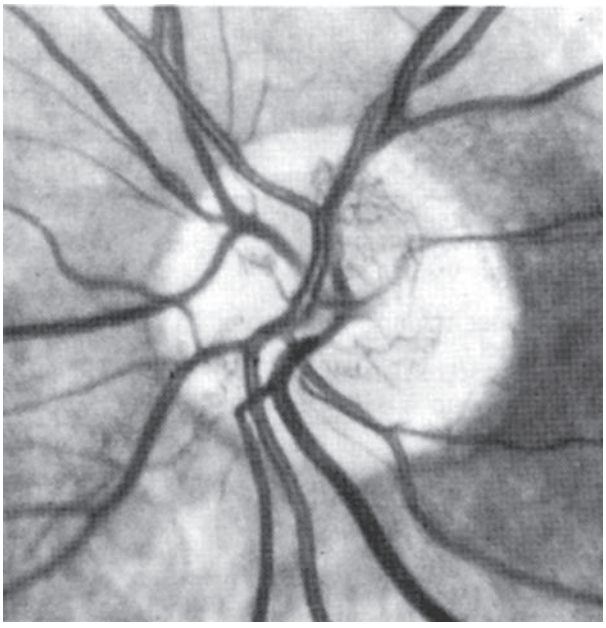

FIGURE 7C.6 Diabetic Retinopathy Study standard photograph 10A demonstrating neovascularization of the disc, one-fourth to one-third disc area in extent. (From Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: the second report of Diabetic Retinopathy Study findings. *Am J Ophthalmol.* 1978;85:82–106 and from Early Treatment Diabetic Retinopathy Study Research Group. ETDRS Report No. 10. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie house classification. *Ophthalmology.* 1991;98:786–806.)

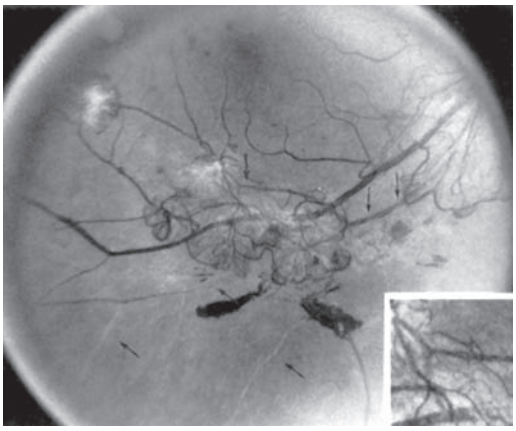

FIGURE 7C.7 Diabetic Retinopathy Study standard photograph 7 demonstrating the lower boundary of severe new vessels elsewhere. This photograph also shows new vessels within 1 disc diameter from the disc (neovascularization of the disc) in the upper right part of the picture, focal arteriolar narrowing, arteriolar sheathing, "white threads" (completely opaque arteriolar branches), and small preretinal hemorrhages. (From Diabetic Retinopathy Study Research Group. A modification of the Airlie House Classification of diabetic retinopathy. DRS Report No. 7. *Invest Ophthalmol Vis Sci.* 1981;21(1):210–226 and from Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie house classification. ETDRS Report No. 10. *Ophthalmology.* 1991;98:786–806.)[12]

Regarding the safety and efficacy of argon versus xenon photocoagulation, the DRS demonstrated that decreased visual acuity and constricted visual fields were more common in the xenon group. Persistent visual acuity loss of one line occurred in 19% of xenon-treated eyes as compared with 11% in the argon group; a loss of two or more lines occurred in 11% for xenon and 3% for argon. A modest loss of visual field (measured on Goldmann perimetry using the largest test object, IVe4) occurred in 25% of xenon-treated eyes as compared with 5% of argon-treated eyes; more severe field loss occurred in an additional 25% in the xenon group.[14,18]

Implications for Clinical Practice

The DRS conclusively demonstrated that photocoagulation was effective in the treatment of PDR, and the overwhelming benefit associated with treatment had important public health implications.

The DRS identified four retinopathy risk factors for severe visual loss in eyes with PDR that met the inclusion criteria. Eyes with at least three of these risk factors were considered to be at high risk. Since these eyes demonstrated a 50% reduction of severe visual loss with photocoagulation, prompt treatment was recommended for eyes with PDR and HRC as defined by the DRS.

Three clinical situations were thus characteristic of eyes with high-risk retinopathy: (a) NVD equal to or greater than one-fourth to one-third disc area (greater than photograph 10A); (b) less extensive NVD with preretinal or vitreous hemorrhage; (c) NVE equal to or greater than one-half disc area with preretinal or vitreous hemorrhage (Table 7C.1).

For high-risk eyes, the risk of severe visual loss was substantially reduced at 2 years and 4 years using either xenon or argon photocoagulation, and the beneficial effects far outweighed the side effects of either modality. Nevertheless, argon was recommended rather than xenon arc because of similar benefits and less harmful effects.

Before a protocol amendment, the initial DRS protocol included direct treatment of NVD in eyes randomized to argon laser. Since this was associated with an increased risk of hemorrhage at the time of treatment without an increase in NVD regression, this treatment technique was discontinued.

Unanswered Questions

Although prompt photocoagulation was recommended for eyes with PDR and HRC as defined by the DRS, the DRS did not provide a clear recommendation for eyes with early PDR or those with severe NPDR. The question remained as to whether photocoagulation performed at an earlier stage of retinopathy would be more beneficial. At the other end of the spectrum, the DRS did

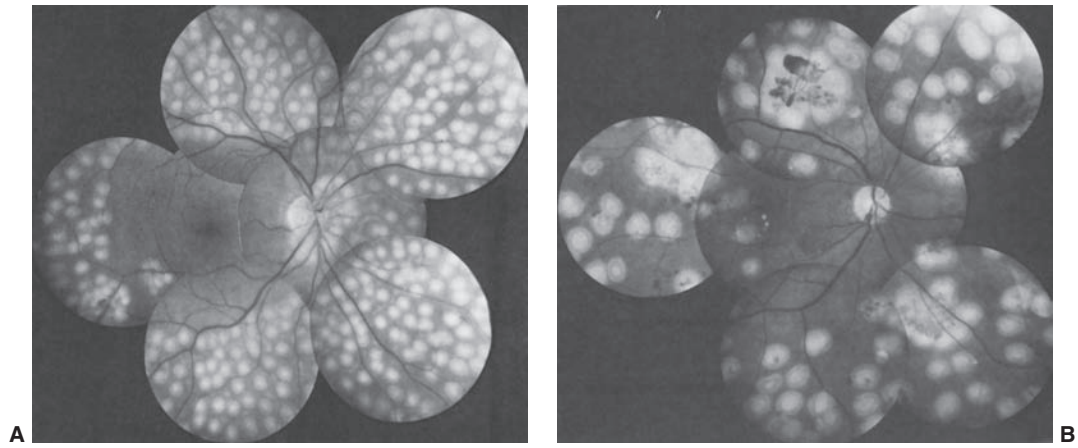

FIGURE 7C.8 (A) Twenty-four-hour posttreatment photographs after Diabetic Retinopathy Study argon technique. Note extensive 500-μ scatter burns, focal treatment of neovascularization of the disc adjacent to the disc, and confluent focal treatment of two small patches of neovascularization elsewhere (NVE) along the inferotemporal artery inferotemporal to the macula. **(B)** Twenty-four-hour posttreatment photographs after DRS xenon technique. Scatter burns are less evenly spaced than the argon burns in Figure 7C.8A. Confluent focal treatment has been applied to four patches of NVE. A small preretinal hemorrhage within the NVE superotemporal to the disc has occurred since treatment. Focal treatment has been applied to microaneurysms (thought to be the cause of mild macular edema) temporal to the macula. (From Diabetic Retinopathy Study Research Group. Photocoagulation of proliferative diabetic retinopathy: clinical applications of DRS findings. DRS Report 8. *Ophthalmology*. 1988;88:583–600.)

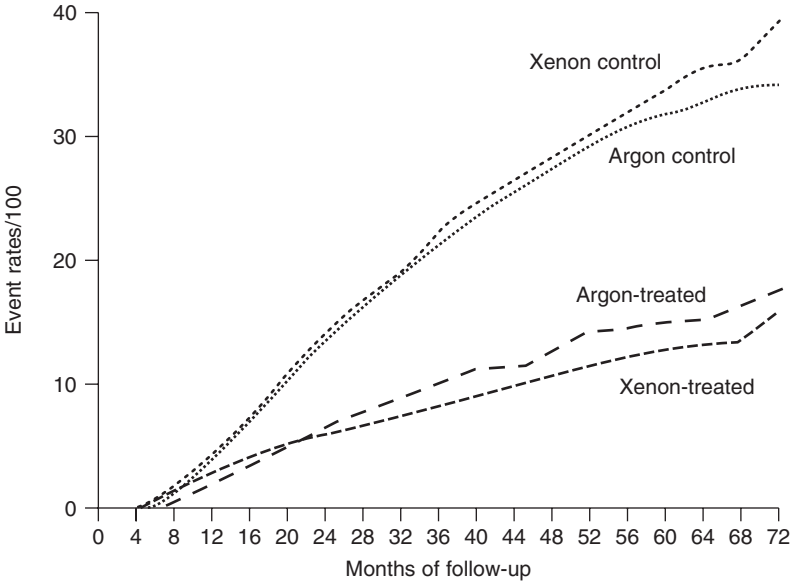

FIGURE 7C.9 Cumulative rates of severe visual loss for argon-treated and xenon-treated groups and controls. (From Diabetic Retinopathy Study Research Group. Photocoagulation of proliferative diabetic retinopathy: clinical applications of DRS findings. DRS Report 8. *Ophthalmology*. 1988;88:583–600.)

not address the surgical management of late complications of diabetic retinopathy, such as severe fibrovascular proliferation and vitreous hemorrhage.

In addition to PDR, DME remained a significant cause of visual loss in diabetic patients. In the DRS, panretinal scatter photocoagulation was associated with

TABLE 7C.1 **Eyes with at Least Three of These Risk Factors (High-Risk Characteristics) Were Considered to Be at High Risk for Severe Visual Loss, and These Eyes Demonstrated the Most Benefit from Photocoagulation**

Features associated with a particularly high risk of severe visual loss
1. The presence of new vessels
2. The location of new vessels on or within one-disc diameter of the optic disc (NVD)
3. The severity of new vessels (one of the following):
a. NVD equal to or greater than one-fourth to one-third disc area in extent (equal to or greater than standard photograph 10A)
b. Equal to or greater than one-half disc area
4. Preretinal or vitreous hemorrhage

High-risk characteristics of severe visual loss.
NVD, neovascularization of the disc.

progression of macular edema in some patients.[20] The DRS did not adequately assess this effect, nor did it evaluate the potential benefit of focal photocoagulation.

II. DIABETIC RETINOPATHY VITRECTOMY STUDY

Introduction

The Diabetic Retinopathy Vitrectomy Study (DRVS) has provided tremendous value to our understanding of the sight-threatening complications related to PDR. While the DRS addressed laser treatment for eyes with PDR and severe NPDR, the DRVS sought to evaluate the surgical management of eyes with more severe complications, and it attempted to define the role and timing of vitrectomy. Specifically, the DRVS was established by the National Eye Institute to evaluate the risks and benefits of performing early pars plana vitrectomy in eyes with advanced PDR.

Conducted in the late 1970s and early 1980s, this multicenter, prospective, RCT comprised three studies.[21–25] One was a natural history study that included eyes with severe PDR but without severe vitreous hemorrhage, and these eyes were followed up with conventional management.[21] The other two studies were RCTs involving vitrectomy. The first of these randomized trials compared

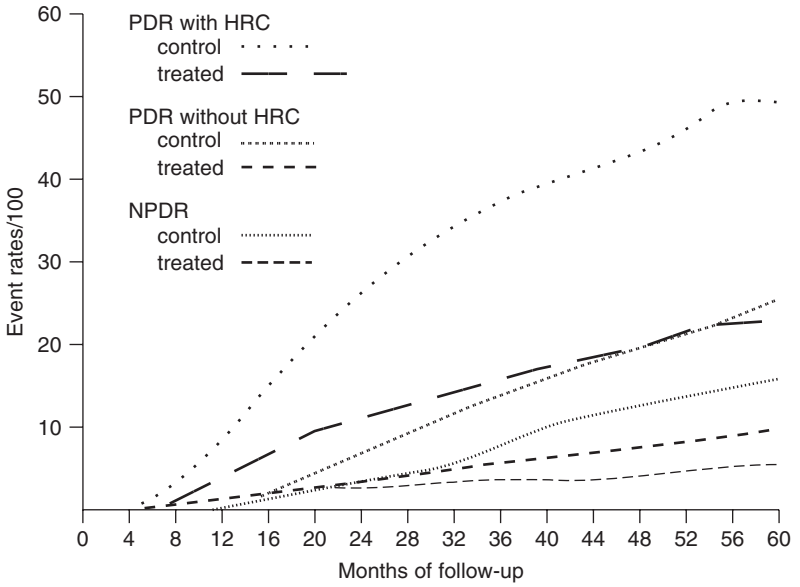

FIGURE 7C.10 Cumulative rates of severe visual loss for eyes classified to have proliferative diabetic retinopathy (PDR), high-risk characteristics (HRC), and nonproliferative diabetic retinopathy (NPDR) at baseline. Argon and xenon groups combined. (From Diabetic Retinopathy Study Research Group. Photocoagulation of proliferative diabetic retinopathy: clinical applications of DRS findings. DRS Report 8. *Ophthalmology*. 1988;88:583–600.)

early vitrectomy (before 6 months) versus deferral of surgery (1 year) in eyes with severe nonclearing vitreous hemorrhage,[22,25] and the second compared early vitrectomy versus conventional management in eyes with advanced, active PDR (severe fibrovascular proliferation) and useful vision.[23,24] Each of these studies is addressed separately.

III. NATURAL HISTORY STUDY

Background and Study Questions

Despite the early success obtained with vitrectomy, the procedure had a high rate of complications and some patients lost all perception of light. As technical advances were made, vitrectomy was offered to an increasing number of patients with the sequelae of PDR. It was difficult for clinicians to determine the proper role of vitrectomy because of a lack of sufficient information regarding the natural course of the disease.

It was in this context that a natural history study was undertaken. Eyes with severe PDR but without severe vitreous hemorrhage were followed up with conventional management for 2 years.

Patients Included in the Study

A total of 744 eyes (622 patients) with very severe PDR were enrolled. There were three subgroups, defined by the dominant retinopathy at baseline: eyes with severe new vessels at least four disc areas in size and visual acuity 10/50 or better, eyes with extramacular traction retinal detachment at least four disc areas in extent and visual acuity 10/50 or better, and eyes with vitreous hemorrhage obscuring at least one-half of at least three standard photographic fields with visual acuity 10/200 or better or between 5/200 and hand motion.

Intervention and Outcome Measures

Patients were followed up with conventional management, including photocoagulation, over a 2-year period. Patients were offered vitrectomy only if they developed retinal detachment involving the center of the macula or if they developed severe vitreous hemorrhage that did not clear after 1 year of follow-up. The primary outcome measure was visual acuity, assessed at 1 and 2 years. Good vision was defined as 10/20 or better, and poor vision was less than 5/200.

Major Findings

Decreases in visual acuity were more frequent during the first year of follow-up than during the second year, and were related to retinopathy severity and baseline visual acuity. In eyes with more than four disc areas of new vessels and visual acuity of 10/30 to 10/50 at baseline, visual acuity decreased to $<$ 5/200 in 45% at 2 years. In contrast, in eyes with traction retinal detachment not involving the center of the macula and without active new vessels or fresh vitreous hemorrhage at baseline, visual acuity decreased to $<$ 5/200 in only 14%. Vitrectomy, which was required only if a macula-involving retinal detachment occurred or if severe vitreous hemorrhage did not clear after 1 year, was performed in 25% of eyes during the 2-year follow-up period.[21]

Implications for Clinical Practice

When the DRVS was planned, most surgeons followed up patients with severe vitreous hemorrhage for at least 1 year before recommending vitrectomy. Because of the high rate of visual loss and the high likelihood of the need for vitrectomy in the natural history study, investigators suggested evaluating the benefit of early vitrectomy (before 6 months) in patients with severe vitreous hemorrhage. The relatively good prognosis of eyes with traction retinal detachment not involving the center of the macula did not justify surgical intervention for this indication.

Unanswered Question

Does early vitrectomy (before 6 months) offer any benefit compared with vitrectomy

performed after 1 year for severe vitreous hemorrhage?

IV. SEVERE NONCLEARING VITREOUS HEMORRHAGE

Background and Study Questions

Of historical interest, the first pars plana vitrectomy ever performed was by Robert Machemer in 1970 for a nonclearing diabetic vitreous hemorrhage of 5 years' duration, resulting in improvement in visual acuity from 2/200 to 20/50.[26] Vitreous hemorrhage from retinal neovascularization is a frequent complication of PDR, and a report from 1977 indicated that this was the most common indication for diabetic vitrectomy.[27]

Since the optimal timing of vitrectomy was unknown, this study compared early vitrectomy (<6 months) to deferral of surgery (1 year) in patients with severe nonclearing vitreous hemorrhage.

Patients Included in the Study

A total of 616 eyes were enrolled. Severe vitreous hemorrhage was defined as central vitreous hemorrhage reducing visual acuity to 5/200 or less for at least 1 month. Patients were classified as having type I diabetes if diabetes was diagnosed at or before age 20 and if they were receiving insulin at the time of entry into the study. Type II diabetes included patients aged 40 or older at diagnosis (regardless of insulin use) and patients with diabetes diagnosed at a younger age if they were not receiving insulin. An intermediate group comprised patients diagnosed between 21 and 39 years of age, inclusive, who were receiving insulin.

Intervention and Outcome Measures

Patients were randomized into one of two groups. The early vitrectomy group underwent vitrectomy within a few days of randomization (from 1 to 6 months after the onset of severe vitreous hemorrhage), and the deferral group was offered surgery 1 year after randomization (if severe vitreous hemorrhage persisted at 1 year, or sooner if macular detachment occurred). The primary outcome measure was visual acuity, with particular regard to recovery of good vision (10/20 or better) and no light perception.

Major Findings

After 2 years of follow-up, the DRVS demonstrated that in eyes with severe vitreous hemorrhage, early vitrectomy resulted in final visual acuity of 20/40 or better in 25% of cases, compared with 15% of cases in the group with deferred surgery. Early vitrectomy helps in the recovery of good vision, as was most apparent in type I diabetics, as 36% of eyes in this group achieved visual acuity of 20/40 or better, whereas only 12% of eyes in the deferral group achieved this level. In the type II and intermediate groups, however, there was little difference between early vitrectomy and deferral of surgery regarding the recovery of good vision (16% vs. 18%).[22] After 4 years of follow-up, the advantage for the early vitrectomy group persisted.[25]

This study also demonstrated that progression to no light perception was similar for the early vitrectomy and deferral groups at 2-year follow-up (25% vs. 19%). For patients with type I diabetes, the risk of losing light perception was the same with either treatment strategy, but for the type II and intermediate groups, there was a (nonsignificant) trend toward less frequent visual acuity of no light perception in the deferral group.

Implications for Clinical Practice

For patients with type I diabetes, the more favorable visual results after early vitrectomy were attributed to their more advanced retinopathy, as these patients had greater severity of new vessels, fibrous proliferations, and vitreoretinal adhesions. Progression of new vessels, contraction of fibrous proliferations, and worsening of traction retinal detachment during the waiting period would be expected to be more severe in the type I group, thereby

reducing their potential for recovery of good vision without vitrectomy.

The prevalence of severe, nonclearing vitreous hemorrhage has been reduced by the more widespread use of panretinal photocoagulation; however, it still remains a major indication for vitrectomy. When adequate fundus visualization is present despite vitreous hemorrhage, panretinal photocoagulation is always performed in an attempt to stabilize or achieve regression of neovascularization. The use of krypton or diode lasers may facilitate treatment through hemorrhage, because red and infrared wavelengths are transmitted through hemoglobin pigments better than the blue and green wavelengths of argon. Alternatively, the laser indirect delivery system may allow treatment when slit lamp delivery is not possible. Restricting patient activity and elevating the head of the patient's bed are additional conservative measures that are usually initially recommended.

When vitreous hemorrhage is of sufficient density to preclude visualization of fundus details, echography is essential to detect the need for earlier intervention. If retinal detachment involving the center of the macula, combined traction/rhegmatogenous retinal detachment, or severe fibro vascular proliferation is identified at any time, vitrectomy is indicated. If spontaneous clearing of a dense vitreous hemorrhage does not occur, vitrectomy is considered, especially for patients with type I diabetes. Surgical goals include removal of vitreous hemorrhage to provide a clear media, excision of the posterior hyaloid and epiretinal fibrovascular membranes to relieve vitreoretinal traction, and application of endolaser photocoagulation to achieve regression of proliferative tissue.[28]

An important point is that the DRVS results were obtained before the development of endolaser photocoagulation. Furthermore, surgery was performed in this study without the benefit of using glucose-fortified infusion solutions to reduce the intraoperative development of cataract. These advances, as well as countless others, have contributed to the more favorable results noted recently. In the DRVS, one-fifth to one-quarter of all patients progressed to no light perception vision; however, using current vitreoretinal instrumentation and techniques, this rate is much lower.

Unanswered Questions

While this study provided information of tremendous clinical value, progressive advances in surgical instrumentation and technique have favorably altered the risk-benefit ratio, and the optimal timing of vitrectomy is constantly evolving. Although a variety of ocular and systemic factors influence the decision to perform vitrectomy, in general, the recommended timing of vitrectomy for severe diabetic vitreous hemorrhage is approximately 3 months. More recently, vitrectomy was advocated by some surgeons even earlier. It is certain that modern advances will continue to alter practice patterns.

V. SEVERE PROLIFERATIVE DIABETIC RETINOPATHY (SEVERE FIBROVASCULAR PROLIFERATION)

Background and Study Questions

When laser treatment was growing in popularity, it was noted that in some patients, active neovascular and fibrovascular proliferations progressed rapidly despite extensive panretinal photocoagulation (see Fig. 7C.11A, B). This typically occurred in young patients with poorly controlled type I diabetes and in patients with an attached hyaloid, as the role of formed vitreous contact with the retina in the development of neovascular proliferation was well known.[29] The fibrovascular tissue usually underwent contraction resulting in vitreous hemorrhage, macular distortion, and/or retinal detachment.

Once a macula-involving traction retinal detachment developed, surgical attempts at retinal reattachment often failed to restore good vision. Surgeons noted that in patients with progressive fibrovascular proliferation, neovascularization rarely occurred after surgical excision of the posterior cortical vitreous (Fig. 7C.11C). Thus, when proliferation was severe and vision was not yet significantly

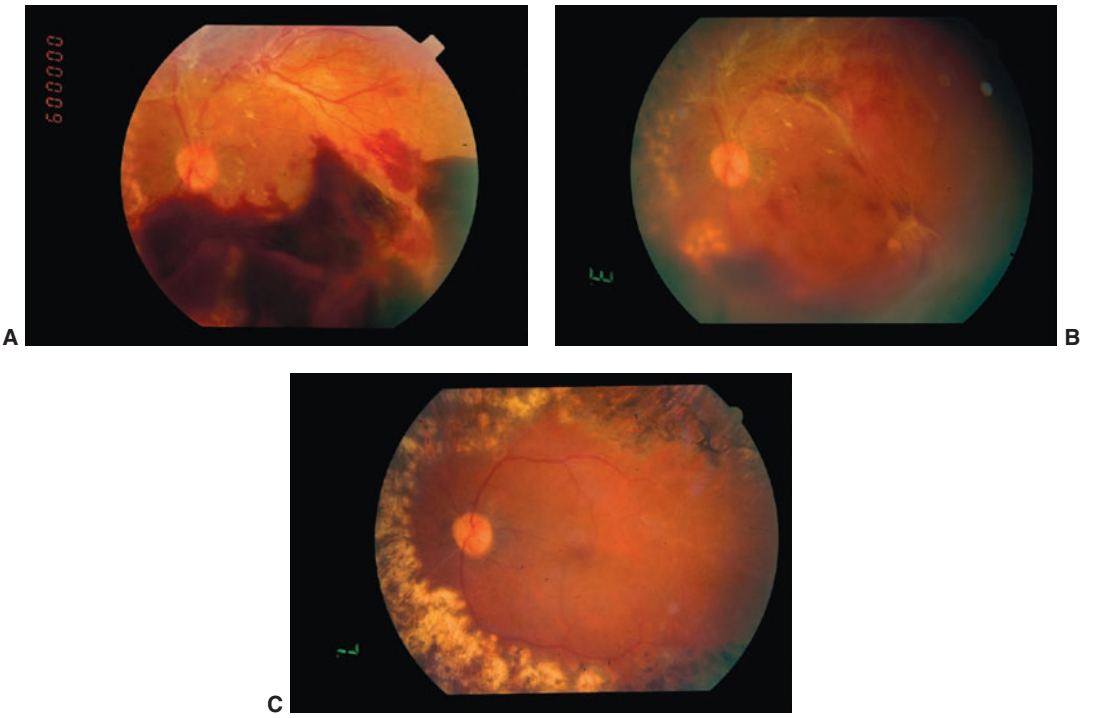

FIGURE 7C.11 **(A)** Proliferative diabetic retinopathy with extensive neovascularization. **(B)** Progression of fibrovascular proliferation and vitreous hemorrhage despite panretinal photocoagulation. **(C)** Postoperative appearance after vitrectomy for severe fibrovascular proliferation. Visual acuity is 20/20. (From Eliott D, Lee MS, Abrams GW. Proliferative Diabetic retinopathy: Principles and techniques of surgical treatment. In: Ryan SJ, ed. *Retina*, 3rd ed. St Louis, MO: Mosby, 2000:2444. Fig. 146–8.)

impaired, early vitrectomy had the potential to stop the proliferative process and preserve vision. These potential benefits were offset by the potential for severe surgical complications, including progression to no light perception vision.

Since the optimal timing of surgical intervention was unknown, this study evaluated the outcome of early vitrectomy versus conventional management in eyes with advanced, active PDR (extensive, active neovascular or fibrovascular proliferations) and useful vision.

Patients Included in the Study

A total of 370 eyes with visual acuity of 10/200 or better and extensive, active, neovascular or fibrovascular proliferations were enrolled. This was defined as severe new vessels (four or more disc areas) and severe fibrous proliferations (two or more disc areas at the disc, or four or more disc areas total); severe new vessels and red vitreous hemorrhage (any preretinal or vitreous hemorrhage); or moderate new vessels (two or more disc areas), severe fibrous proliferations, and red vitreous hemorrhage.

Intervention and Outcome Measures

Patients were randomized to early vitrectomy or conventional management. Conventional management included observation, photocoagulation, and vitrectomy only after traction macular detachment or 6 months of nonclearing vitreous hemorrhage. The primary outcome was visual acuity at each year for a total of 4 years, with particular regard to good vision (10/20 or better), poor vision (less than 5/200), and no light perception.

Major Findings

In eyes with severe fibrovascular proliferation (extensive, active neovascular or fibrovascular proliferations) and useful vision (10/200 or better), early vitrectomy resulted in final visual acuity of 20/40 or better in 44% of cases (at 4-year follow-up), compared with 28% of cases managed conventionally (observation, photocoagulation, or vitrectomy only after traction macular detachment or 6 months of nonclearing vitreous hemorrhage). The advantage of early vitrectomy in the recovery of good vision was most apparent in eyes with the most severe proliferation at baseline. With increasing severity of neovascularization, the outcome with conventional management worsened for each end point. In contrast, the outcome did not worsen by increasing severity for eyes treated with early vitrectomy, accounting for the more favorable results. There was no significant difference between the two treatment groups in the development of poor vision or no light perception vision, although more eyes progressed to no light perception in the early vitrectomy group. Prior photocoagulation increased the chances of good vision.[23,24,28]

Implications for Clinical Practice

The more favorable visual results after early vitrectomy for advanced, active PDR were attributed to the removal of severe fibrovascular proliferations before their contracture led to distortion or detachment of the macula. Eyes most suitable for early vitrectomy are those in which both fibrous proliferations and at least moderately severe new vessels are present, and in which extensive panretinal photocoagulation has already been carried out or is precluded by vitreous hemorrhage.

Unanswered Questions

As noted previously, the DRVS was performed before the development of endolaser photocoagulation. The instrumentation and techniques of vitrectomy surgery have been constantly evolving, and results today are much more favorable than in the past. Although the optimal timing of vitrectomy is constantly changing, the findings from the DRVS serve as the foundation for the decision to perform vitrectomy in the modern era.

VI. EARLY TREATMENT DIABETIC RETINOPATHY STUDY

Background

Because of the overwhelming success of the DRS in finding answers to an important public health problem, the Early Treatment Diabetic Retinopathy Study (ETDRS) was established to address additional questions related to diabetic retinopathy. Conducted in the 1980s, the ETDRS was even larger in scope and size than the recently completed DRS.

The DRS demonstrated that photocoagulation was beneficial for eyes with PDR and HRC, as previously noted. The DRS, however, did not provide a clear recommendation for eyes with early PDR or those with severe NPDR. The question remained as to whether photocoagulation performed at an earlier stage of retinopathy would be even more beneficial. The ETDRS was designed to address this question, as well as questions involving the treatment of DME and the use of aspirin.

The ETDRS sought to determine when panretinal photocoagulation should be initiated to be most effective in the management of diabetic retinopathy, whether focal photocoagulation was effective in the treatment of DME, and whether aspirin was effective in altering the course of diabetic retinopathy. Each of these study questions is addressed separately. The management of DME is addressed in Chapter 7B, and the other two arms of the ETDRS are discussed in the subsequent text.

Study Question

When should scatter panretinal photocoagulation be initiated to be most effective in the management of diabetic retinopathy?

Patients Included in Study

A total of 3,711 patients with mild-to-severe NPDR or early PDR (less than high risk), with or without DME, were enrolled. Visual

acuity criteria were 20/40 or better for eyes without macular edema and 20/200 or better for those with macular edema.

Mild NPDR was defined by the ETDRS as the presence of at least one microaneurysm.[30]

Moderate NPDR was defined as hemorrhages and/or microaneurysms greater than standard photograph 2A (see Fig. 7C.12); and/or the presence of soft exudates, venous beading, or intraretinal microvascular abnormalities (IRMA).[30]

Severe NPDR was defined as soft exudates, venous beading, and IRMA in at least two of fields four through seven; or two of these findings in at least two of these fields and hemorrhages and microaneurysms in all four of these fields (greater than standard photograph 2A in one field); or IRMA in all four of these fields (greater than standard photograph 8A in two fields) (see Fig. 7C.13).[30]

Early PDR was defined as proliferative retinopathy but without DRS HRC.[30] The definition of high-risk proliferative retinopathy is included in Table 7C.1.

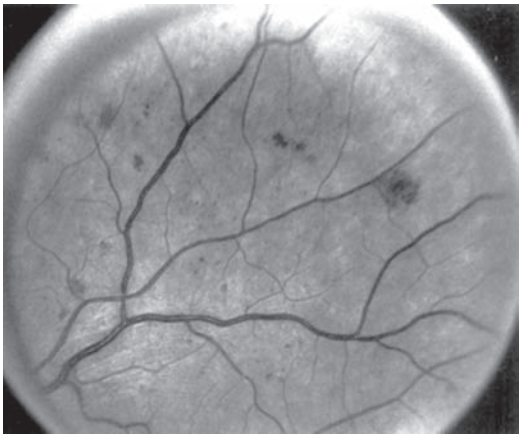

FIGURE 7C.12 Diabetic Retinopathy Study standard photograph 2A, intermediate standard for hemorrhages and microaneurysms. (From Diabetic Retinopathy Study Research Group. A modification of the Airlie House Classification of diabetic retinopathy. DRS Report No. 7. *Invest Ophthalmol Vis Sci.* 1981;21(1):210–226 and from Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House Classification. ETDRS Report No. 10. *Ophthalmology.* 1991;98:786–806.)

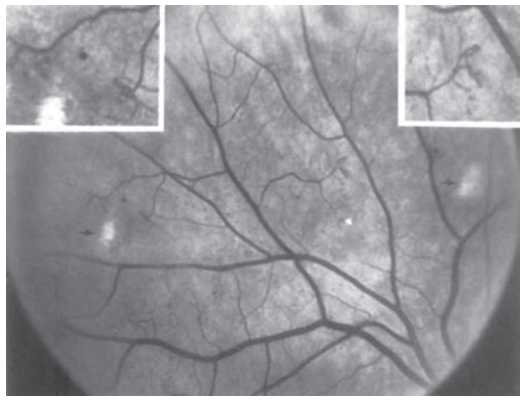

FIGURE 7C.13 Diabetic Retinopathy Study standard photograph 8A, less severe of two standards for intraretinal microvascular abnormalities (IRMA) and soft exudates. This photograph shows four areas of IRMA: two near the soft exudate at the 9 o'clock position (*inset*), one below these at the 7:30 position, and one near the center of the photograph along the 2 o'clock meridian (*inset*). (From Diabetic Retinopathy Study Research Group. A modification of the Airlie House Classification of diabetic retinopathy. DRS Report No. 7. *Invest Ophthalmol Vis Sci.* 1981;21(1):210–226 and from Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie house classification. ETDRS Report No. 10. *Ophthalmology.* 1991;98:786–806.)[12]

Intervention and Outcome Measures

Eyes were randomized to immediate scatter panretinal photocoagulation (either mild or full scatter) or to no treatment. Specifically, eyes were divided among those without macular edema, those with macular edema and less severe retinopathy (mild or moderate NPDR), and those with macular edema and more severe retinopathy (severe NPDR or early PDR). One eye of each patient was randomized to deferral of treatment and the other eye to early photocoagulation using different combinations of scatter panretinal and macular focal photocoagulation. If an eye assigned to treatment deferral developed high-risk proliferative retinopathy, then scatter panretinal laser was initiated as per the DRS recommendations.[6]

In eyes without macular edema, those assigned to early photocoagulation received one of two combinations: immediate mild scatter and delayed focal photocoagulation or immediate full scatter and delayed focal photocoagulation (see Fig. 7C.14A).[30]

In eyes with macular edema and less severe retinopathy, those assigned to early

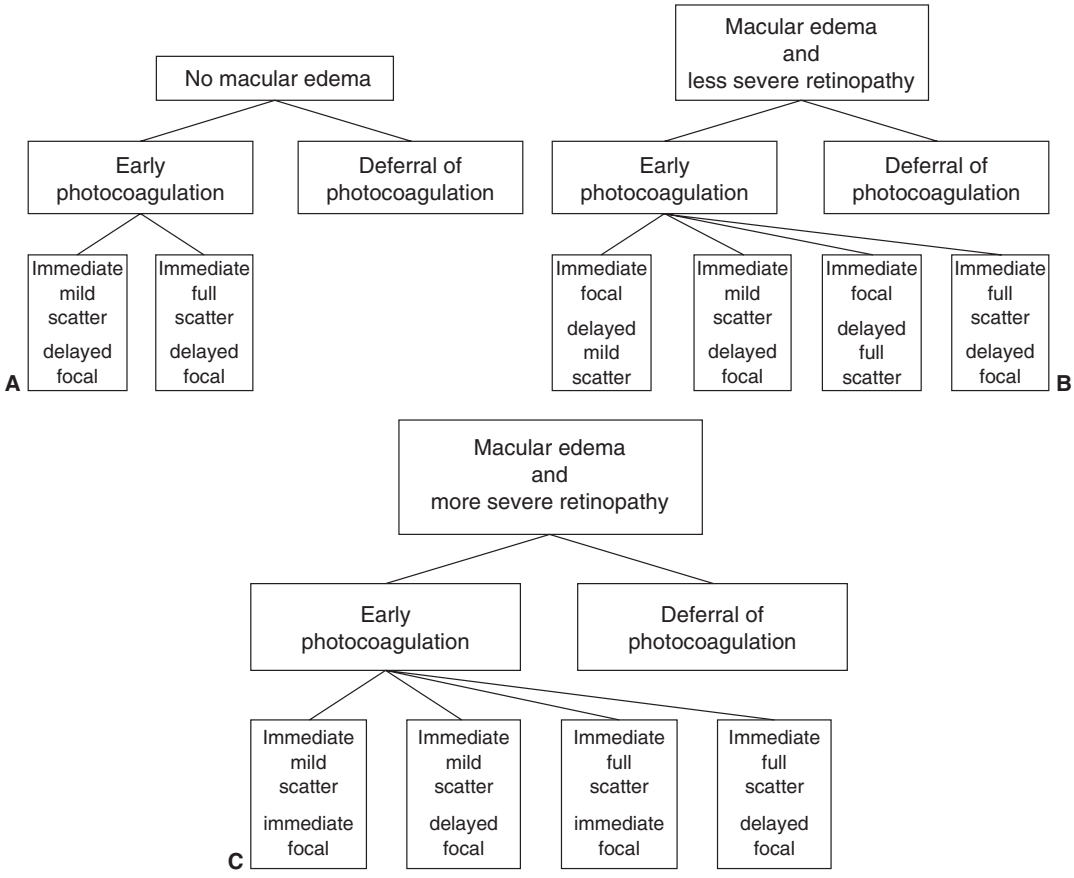

FIGURE 7C.14 **(A)** Early Treatment Diabetic Retinopathy Study photocoagulation treatment scheme for eyes without macular edema and moderate-to-severe nonproliferative or early proliferative retinopathy. Eyes were assigned randomly to early photocoagulation or deferral of photocoagulation. Eyes assigned to early photocoagulation were further assigned randomly to either mild or full scatter (panretinal) photocoagulation. (From Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline characteristics. ETDRS Report No 7. *Ophthalmology.* 1991;98:741–756.) **(B)** Early Treatment Diabetic Retinopathy Study photocoagulation treatment scheme for eyes with macular edema and less severe retinopathy (mild-to-moderate nonproliferative retinopathy). Eyes were assigned randomly to early photocoagulation or to deferral of photocoagulation. Eyes assigned to early photocoagulation were further assigned randomly to either mild- or full-scatter (panretinal) photocoagulation, and to either immediate focal or delayed focal treatment. For eyes assigned to immediate focal treatment, the assigned scatter treatment was not applied initially, but only if severe nonproliferative retinopathy or worse developed during follow-up. (From Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline characteristics. ETDRS Report No 7. *Ophthalmology.* 1991;98:741–756.) **(C)** Early Treatment Diabetic Retinopathy Study photocoagulation treatment scheme for eyes with macular edema and more severe retinopathy. Eyes were assigned randomly to early photocoagulation or to deferral of photocoagulation. Eyes assigned to early photocoagulation were further assigned randomly to either mild- or full-scatter (panretinal) photocoagulation, and to either immediate focal or delayed focal treatment for at least 4 months. (From Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline characteristics. ETDRS Report No 7. *Ophthalmology.* 1991;98:741–756.)

photocoagulation received one of four combinations: immediate focal and delayed mild scatter photocoagulation, immediate focal and delayed full scatter photocoagulation, immediate mild scatter and delayed focal photocoagulation, or immediate full scatter and delayed focal photocoagulation (Fig. 7C.14B).[30]

In eyes with macular edema and more severe retinopathy, those assigned to early photocoagulation received one of four combinations: immediate mild scatter and immediate focal photocoagulation, immediate mild scatter and delayed focal photocoagulation, immediate full scatter and immediate focal photocoagulation, or immediate full scatter and delayed focal photocoagulation (Fig. 7C.14C).[30]

Treatment was performed using the argon blue-green or green laser, although the krypton red laser was allowed if cataract or vitreous hemorrhage was present. Full-scatter panretinal photocoagulation involved 1,200 to 1,600 burns applied in two or more sessions, and mild scatter involved 400 to 650 burns delivered in a single session. A 500-μ spot size was achieved using the Goldmann contact lens (500-μ setting) or the Rodenstock lens (300-μ setting).[31]

Outcome measures included moderate visual loss, defined as a loss of 15 or more letters from baseline, equivalent to a doubling of the visual angle, and severe visual loss, defined as visual acuity $<$ 5/200 at each of two consecutive follow-up visits 4 months apart.

Major Findings

Although the combination of early photocoagulation involving immediate full scatter reduced the rate of progression to high-risk retinopathy by 50%, and those involving immediate mild scatter reduced the rate by 25%, the overall risk for severe visual loss was low for all eyes.[32] Early photocoagulation also reduced the need for vitrectomy.[33]

In eyes without macular edema, there was no significant difference in the rates of moderate or severe visual loss between deferral of treatment or early photocoagulation using either treatment strategy.[32]

In eyes with macular edema and less severe retinopathy, early photocoagulation was associated with a reduced rate of severe visual loss at 5 years compared with deferral of treatment, but the rate was very low in all groups and the difference was not significant. Since the rate of progression to severe visual loss was so low in eyes with mild-to-moderate NPDR, treatment benefits were not considered sufficient to compensate for the side effects associated with photocoagulation, and treatment was not recommended.[32]

In eyes with macular edema and more severe retinopathy, early photocoagulation was associated with a reduced rate of severe visual loss at 5 years (3.8% to 4.7%) compared with deferral of treatment (6.5%), but the rate was low in all groups and the difference was not significant. Nevertheless, treatment benefits were encouraging, and it was suggested that scatter treatment should be considered in eyes with severe NPDR and early PDR.[32] This recommendation was supported by a subsequent report that demonstrated an even greater treatment effect in patients with type II diabetes.[34]

Similar to the DRS, the ETDRS demonstrated treatment-related side effects. Early scatter photocoagulation, especially full-scatter treatment, was associated with visual field constriction and an increased rate of moderate visual loss. Moderate visual loss was increased only during the first year of follow-up (except in eyes with macular edema that received early focal treatment); subsequently, there was a lower rate of moderate visual loss for all combinations of early photocoagulation.

The ETDRS also provided information on the rates of progression from earlier stages of retinopathy to PDR with HRC.[32,35] Eyes with mild NPDR had a 1% risk of developing high-risk retinopathy at 1 year and a 15% risk at 5 years.[36,37] Eyes with moderate NPDR had a 3% risk at 1 year and a 27% risk at 5 years. These rates of progression for mild and moderate NPDR were considered relatively low, and although panretinal photocoagulation was not suggested by the ETDRS, close follow-up was recommended.

In contrast, severe NPDR was associated with a much higher risk of progression to high-risk PDR, and specific characteristics were identified that were especially predictive. The 4-2-1 rule was developed, and an eye with one of the

following features was considered to have severe NPDR: microaneurysms or hemorrhages in 4 quadrants; venous beading in 2 quadrants; and IRMA in 1 quadrant (see Table 7C.2).[6,38] Eyes with severe NPDR as defined here had a 15% risk of developing HRC at 1 year and a 56% risk at 5 years. An additional category was identified, very severe NPDR, and included eyes having two findings of the 4-2-1 rule. These eyes had a 45% risk at 1 year and a 71% risk at 5 years. The ETDRS recommended that the benefits of early photocoagulation should be considered in eyes with severe or very severe NPDR and in those with early PDR.

Implications for Clinical Practice

Since there was a low rate of severe visual loss and a relatively low rate of progression to high-risk retinopathy in eyes with mild-to-moderate NPDR assigned to deferral of treatment, the ETDRS concluded that the adverse effects of panretinal photocoagulation (visual field constriction, early transient moderate visual loss) probably outweighed the small benefits of early treatment, and close follow-up was recommended.

In contrast, in eyes with more severe retinopathy (severe or very severe NPDR and early PDR), the recommendation was that early photocoagulation should be considered since these eyes had a high likelihood of progressing to PDR with HRC. Early treatment or deferral of treatment until progression of retinopathy occurred was considered a reasonable option. This recommendation was based on the assumption of adequate and reliable patient follow-up. If there was any question about a patient's likelihood of returning for follow-up, early photocoagulation was strongly suggested.

Unanswered Questions

The ETDRS recommendation was to consider early treatment in eyes with severe or very severe NPDR and in eyes with early PDR (less than HRC), and reasonable options included early photocoagulation or deferral of treatment until progression of retinopathy occurred. The ETDRS did not provide a clear recommendation, except in circumstances where there was doubt about a patient's ability to return for adequate and timely follow-up. The decision regarding when to treat a patient with these more advanced stages of retinopathy was left to the discretion of the treating physician.

VII. EARLY TREATMENT DIABETIC RETINOPATHY STUDY

Introduction

In the 1970s, a variety of medical therapies for diabetic retinopathy had been proposed, including aspirin, dipyridamole, vitamins, and

TABLE 7C.2 **The Features in the 4-2-1 Rule are Associated with a High Rate of Progression to High-Risk Proliferative Diabetic Retinopathy. Any One of These Features Constitutes Severe Nonproliferative Diabetic Retinopathy, While Any Two Features Constitute Very Severe Nonproliferative Diabetic Retinopathy. See Figures 7C.12, 7C.15, and 7C.13 for Diabetic Retinopathy Study Standard Photographs 2A, 6A, and 8A, Respectively**

4-2-1 Rule
4 quadrants of hemorrhages or microaneurysms equal to or greater than DRS standard photograph 2A
2 quadrants of venous beading equal to or greater than DRS standard photograph 6A
1 quadrant of intraretinal microvascular abnormalities equal to or greater than DRS standard photograph 8A

Features of the 4-2-1 rule.

DRS, diabetic retinopathy study.

calcium dobesilate. The most promising agents seemed to be the ones that reduced platelet aggregation, because patients with diabetes demonstrated alterations in platelet function. The increased platelet adhesiveness was possibly related to the increased arachidonic acid metabolites prostaglandin E_2 and thromboxane E_2, and these alterations were thought to be potentially responsible for the capillary closure observed in diabetic retinopathy.[30]

Background

Aspirin therapy was a potential treatment, since it blocked cyclooxygenase and thus inhibited prostaglandin production and platelet aggregation. In addition, there was some clinical evidence that patients with diabetes who were treated with aspirin, usually for arthritis, had reduced prevalence of retinopathy.[30] Questions related to the potential benefit of aspirin regarding retinopathy progression were offset by those relating to the potential adverse consequences, such as increased hemorrhage. The ETDRS was designed to address these questions, as well as questions involving the treatment of DME and questions involving the use of scatter treatment for earlier stages of retinopathy (mild-to-severe NPDR and early PDR).

The ETDRS sought to determine answers to three questions: whether focal photocoagulation was effective in the treatment of DME, when panretinal photocoagulation should be initiated to be most effective in the management of diabetic retinopathy, and whether aspirin was effective in altering the course of diabetic retinopathy. Each of these study questions is addressed separately. This section reviews the aspirin arm of the ETDRS.

Study Question

Is aspirin effective in altering the course of diabetic retinopathy?

Patients Included in Study

A total of 3,711 patients with mild-to-severe NPDR or early PDR (less than high risk), with or without DME, were enrolled. Visual acuity criteria were 20/40 or better for eyes without macular edema and 20/200 or better for those with macular edema.

Intervention and Outcome Measures

Patients were randomized to receive 650 mg of aspirin per day or placebo (see Fig. 7C.16). The ETDRS used a factorial study design for aspirin use (patients randomized) and photocoagulation (eyes randomized). As indicated above for the other two arms of the ETDRS (DME, early scatter treatment) eyes were grouped into those without macular edema, those with macular edema and less severe retinopathy (mild or moderate NPDR), and those with macular edema and more severe retinopathy (severe NPDR or early PDR). One eye of each patient was randomized to early photocoagulation using different combinations of scatter panretinal and macular focal photocoagulation, and the other eye

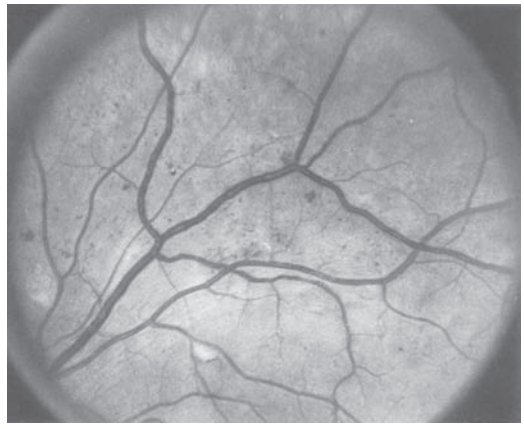

FIGURE 7C.15 Diabetic Retinopathy Study standard photograph 6A, less severe of two standards for venous beading. Two main branches of the superotemporal vein show definite, but not severe, beading. (From Diabetic Retinopathy Study Research Group. A modification of the Airlie House Classification of diabetic retinopathy. DRS Report No. 7. *Invest Ophthalmol Vis Sci*. 1981;21(1):210–226 and from Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House Classification. ETDRS Report No. 10. *Ophthalmology*. 1991;98:786–806.)

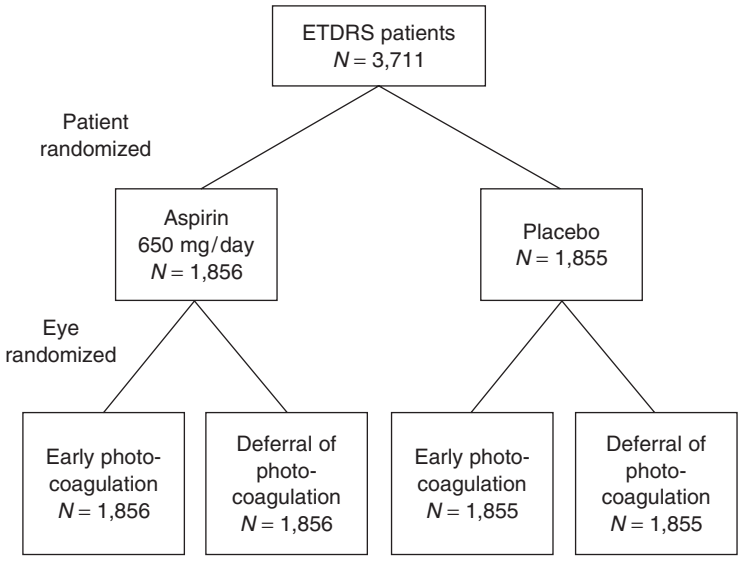

FIGURE 7C.16 Randomization scheme of Early Treatment Diabetic Retinopathy Study patients to aspirin or placebo treatment, and of eyes to photocoagulation strategies. (From Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline characteristics. ETDRS Report No 7. *Ophthalmology*. 1991;98:741–756.)

had deferral of treatment. If an eye assigned to treatment deferral developed high-risk proliferative retinopathy, then scatter panretinal laser was initiated as per the DRS recommendations.

Outcome measures included the progression to high-risk retinopathy (PDR with HRC), the development of vitreous hemorrhage, and visual loss. Moderate visual loss was defined as a loss of 15 or more letters from the baseline, equivalent to a doubling of the visual angle, and severe visual loss was defined as visual acuity < 5/200 at each of two consecutive follow-up visits 4 months apart. Additional end points were the development of cardiovascular disease and mortality.

Major Findings

No difference was found in the progression to high-risk retinopathy, the development of vitreous hemorrhage, and the risk of visual loss between eyes of patients who received aspirin or placebo, despite randomization to immediate photocoagulation or to deferral of treatment.[39,40] Therefore, there was no contraindication to the use of aspirin in patients with mild-to-severe NPDR or early PDR who met the inclusion criteria of the ETDRS.

Interestingly, aspirin use was associated with a 17% decrease in morbidity and mortality from cardiovascular disease, and the benefits of aspirin use in patients with diabetes were evident.[41]

Since aspirin use was not associated with a treatment effect for ocular outcomes, and since its use had no interaction with photocoagulation, the ETDRS results for the other two arms of the study (DME, early scatter treatment) were reported using the combined aspirin and placebo groups.

Implications for Clinical Practice

The ETDRS recommended that aspirin use, when prescribed for nonophthalmic medical conditions, was not contraindicated in patients with mild-to-severe NPDR or those with early PDR who met the inclusion criteria.

Unanswered Question

The ETDRS did not evaluate the use of aspirin in patients with more advanced retinopathy

(PDR with HRC), and there was no clear recommendation regarding the use of aspirin in these patients.

VIII. PROLIFERATIVE DIABETIC RETINOPATHY: EMERGING PHARMACOLOGIC THERAPIES

Ruboxistaurin Mesylate (Arxxant)

Introduction

New pharmacologic interventions at the molecular level show great promise in treating the major causes of visual loss in diabetics: PDR and DME. As previously noted in Chapter 7B, two of the molecules being targeted are vascular endothelial growth factor (VEGF) and protein kinase C (PKC). VEGF is a vascular endothelial cell mitogen and potent permeability factor, and it is produced by glial cells, retinal pigment epithelial cells, and vascular endothelial cells. VEGF is normally present in the retina and vitreous in low levels; however, retinal hypoxia upregulates VEGF production, resulting in abnormal angiogenesis and a marked increase in vascular permeability. The PKC family is a group of enzymes involved in signal transduction. The β-isoform has been shown to have an important role in regulating vascular permeability and is an important signaling component for VEGF. The chronic hyperglycemia of uncontrolled diabetes leads to increased cellular levels of diacylglycerol that, in turn, activates PKC, especially the β-isoform. PKC-β increases the synthesis of VEGF, and also contributes to the microvascular abnormalities in diabetic retinopathy. Inhibition of either VEGF or PKC-β moderates the microvascular complications seen in experimental animal models. In addition, PKC-β inhibitors given orally have the potential to influence other diabetic complications such as renal insufficiency and peripheral neuropathy.[42]

Background and Study Questions

One of the clinical trials that have evaluated the role of ruboxistaurin mesylate is the PKC-β Inhibitor Diabetic Retinopathy Study (PKC-DRS).[43] The other clinical trial, the Protein Kinase C beta Diabetic Macular Edema Study (PKC-DMES), is discussed in Chapter 7B. The PKC-DRS is a multicenter, double-masked, placebo-controlled study that evaluated progression of diabetic retinopathy in patients who were treated with ruboxistaurin or placebo.

Patients Included in the Study

A total of 252 patients with moderately severe to very severe NPDR in at least one eye were enrolled. Eligibility criteria included ETDRS retinopathy severity level between 47B and 53E inclusive (moderately severe to very severe NPDR), visual acuity of 20/125 or better, and no history of scatter (panretinal) photocoagulation.

Intervention and Outcome Measures

Patients were randomized to placebo or ruboxistaurin 8, 16, or 32 mg orally per day for 36 to 46 months. The primary outcome was progression of retinopathy ($\geq$ two-step worsening in the ETDRS retinopathy eye severity scale for patients with one study eye, $>$3-step worsening in the ETDRS retinopathy person severity scale for patients with two study eyes, or application of scatter photocoagulation). Secondary study outcomes were moderate visual loss (visual acuity loss $>$15 letters, doubling or more of the visual angle), and sustained moderate visual loss (loss of $>$15 letters observed at each of two consecutive visits 6 or more months apart).

Eligibility and outcomes were assessed using stereoscopic fundus photographs taken at 6-month intervals. Analysis was based on time to occurrence of the outcome measures using the intent-to-treat population.

Major Findings

Ruboxistaurin did not prevent the progression of diabetic retinopathy, but it reduced the risk of visual loss. Moderate visual loss was lower in the 32-mg group compared with placebo. Sustained moderate visual loss was lower in the 32-mg group only in eyes with definite DME at baseline. Ruboxistaurin was well tolerated with no significant adverse events noted.[43]

Implications for Clinical Practice

Selective systemic inhibition of PKC-β represents a new approach to the treatment of diabetic microvascular retinal complications. Although this study did not demonstrate a treatment effect on the primary end point of progression of diabetic retinopathy in patients who met the inclusion criteria and were treated with ruboxistaurin, it showed that clinically relevant outcomes such as moderate visual loss might be affected by this treatment approach. Ruboxistaurin showed a beneficial effect in reducing moderate visual loss on an oral administration of 32 mg per day, and sustained moderate visual loss was also reduced using this dose, especially in eyes with more severe retinopathy and definite DME at baseline.

When considering systemic therapy, the safety profile of the medication is critical. A prior study using a nonspecific inhibitor of multiple kinases and PKC isoforms was limited by hepatotoxicity and gastrointestinal side effects.[44] In contrast, ruboxistaurin is selective for the β-isoform of PKC, and it was well tolerated and not associated with significant adverse events.

Unanswered Questions

The apparent lack of efficacy of ruboxistaurin in preventing progression of retinopathy could have occurred for several reasons. PKC-β activation occurs very early in diabetes, and it is possible that in this study of moderately severe to very severe NPDR patients, the pathologic retinal changes are no longer amenable to PKC-β inhibition. Alternatively, the drug may not be potent enough to overcome these changes. Although PKC-β is involved in mediating the effects of VEGF, it is not primarily a VEGF inhibitor, and its antiproliferative activity is weaker than its antipermeability effect.[43] It is possible that ruboxistaurin use in patients with less severe retinopathy may have a different effect on retinopathy progression. Similarly, earlier use of ruboxistaurin may have a different effect on moderate visual loss and sustained moderate visual loss. The optimal time to initiate therapy and the optimal duration of therapy remain unknown.

The PKC-DRS clinical trial has demonstrated the potential for ruboxistaurin use in the treatment of diabetic microvascular retinal complications, especially with regard to clinically important outcomes such as the reduction of moderate visual loss. The results supported further evaluation of this approach, and the Protein Kinase C-β Inhibitor Diabetic Retinopathy Study 2 (PKC-DRS2) was initiated.

Preliminary results from the PKC-DRS2 trial have just become available.[45] Inclusion criteria were similar to those of the PKC-DRS, and patients were randomized to receive placebo or 32 mg of ruboxistaurin per day ($n = 684$). There was a reduction in the occurrence of sustained moderate visual loss from 9.1% in the placebo group to 5.5% in the ruboxistaurin group at 36 months ($p < 0.05$). Mean baseline to end point change in visual acuity (ETDRS letters) was –2.6 for placebo and –0.9 for ruboxistaurin ($p < 0.05$).[45]

Ovine Hyaluronidase (Vitrase)

Introduction

Current management options for vitreous hemorrhage include observation and vitrectomy. A pharmacologic approach such as enzymatic vitreolysis has the potential benefit of earlier clearance of vitreous hemorrhage compared with conventional treatment. This would result in earlier visualization of the retina and more timely treatment of the underlying pathology.

Hyaluronidase cleaves glycosidic bonds of hyaluronic acid, a major component of vitreous. Dissolution of the hyaluronic acid and collagen complex increases the diffusion of red blood cells and phagocytes because of vitreous liquefaction, thereby facilitating erythrocyte lysis and phagocytosis. Vitrase (Alliance Medical, Inc, Irvine, CA) is a highly purified preservative-free ovine hyaluronidase, and it has recently been evaluated as an intravitreous pharmacotherapy for the treatment of vitreous hemorrhage.

Background and Study Questions

Ovine hyaluronidase has been approved by the U.S. Food and Drug Administration (FDA) for use as a spreading or diffusing

agent to increase the absorption and dispersion of other injected drugs. Although this medication is not approved for intravitreous use at this time, pooled data is available from two phase-III clinical trials that evaluated ovine hyaluronidase administered through intravitreous injection in patients with vitreous hemorrhage. These randomized, double-masked, placebo-controlled, multinational studies were designed to assess the safety and efficacy of intravitreous ovine hyaluronidase for the treatment of diabetes and other causes of vitreous hemorrhage.[46,47] The trials were conducted in North America (Vit-02 Study) and outside of North America (Vit-03 Study).

Patients Included in the Study

Over 1,300 patients with severe vitreous hemorrhage for at least 1 month and visual acuity worse than 20/200 were enrolled. Severe vitreous hemorrhage was defined as the density sufficient to obscure fundus visualization on indirect ophthalmoscopy such that no retinal details were visible posterior to the equator. Patients whose hemorrhages were possibly due to trauma or sickle cell disease were excluded.

Intervention and Outcome Measures

Patients were randomized to 55 IU or 75 IU of ovine hyaluronidase or saline (50 microliters injection volume for all groups). The primary outcome was a reduction in hemorrhage density sufficient to enable a diagnosis and, when indicated, to perform laser treatment in at least 6 clock hours (for PDR or central retinal vein occlusion) or at least 3 clock hours (for branch retinal vein occlusion) by month 3. Secondary outcomes were visual acuity improvement $>$ 3 lines, hemorrhage density reduction assessment using a grading scale, and therapeutic utility assessment (clearance sufficient to diagnose, but without the requirement to treat the underlying pathology). Outcomes were measured at 1, 2, and 3 months.

Major Findings

Efficacy data was evaluated in 1,125 patients from the above indicated dose groups (in one of the two trials, 181 patients received a 7.5 IU dose, and these patients were excluded from the pooled efficacy data).[46] At enrollment, 90% of patients had counting finger vision or worse and 76% were patients with diabetes (60% type I, 40% type II). Mean hemorrhage duration was 120 days.

For the primary end point, efficacy was achieved for the 55 IU dose group at months 1 and 2, but not at month 3 (month 1: 13.2% vs. 5.5%; month 2: 25.5% vs. 16.2%; month 3: 32.9% vs. 25.6% for 55 IU vs. saline). The secondary end points confirmed the treatment effect at both doses and all time points.[46]

Safety data was evaluated in 1,362 patients.[47] Hyaluronidase was used in 966 patients, saline in 378, and 18 received no treatment (the initial version of one of the two trials contained an observational control group). Pooled safety data was collected until at least month 3, with some patients followed up to 32 months. Iritis was the most common adverse event in both the saline (33% of patients) and hyaluronidase groups (60% of patients), occurring in patients who received hyaluronidase in a dose–response manner. Most cases were mild to moderate and were easily managed; however, some patients (1.6% in the 55 IU group) developed sterile, self-limited hypopyon. No eye developed infectious endophthalmitis. The incidence of rhegmatogenous retinal detachment was not statistically different between groups. No serious safety issues were reported.[47]

Implications for Clinical Practice

While the primary outcome was to be achieved by month 3, it was seen with statistical significance as early as month 1 and through month 2 (but not at month 3) in patients who met the inclusion criteria and were treated with a single intravitreous injection of 55 IU of ovine hyaluronidase. The secondary end points were reached by month 1 and persisted through month 3. The fact that the greatest treatment effect was seen by month 1 may be consistent with the relatively short half-life of ovine hyaluronidase (60 to 112 hours in ocular tissues), and this may allow earlier diagnosis and treatment of the underlying pathology while minimizing risk. These results suggest a potential clinically useful new pharmacologic approach to the management of vitreous hemorrhage due to diabetes and other causes.

Unanswered Questions

These studies included patients with vitreous hemorrhage from a variety of causes. In addition to PDR, etiologies included central retinal vein occlusion, branch retinal vein occlusion, exudative macular degeneration, hemorrhagic posterior vitreous detachment, and macroaneurysm. The published results are inclusive of all causes, and outcomes in the subset of diabetic patients have not been reported.

It is possible that the saline injection control (required by the FDA) may have had a treatment effect, for example, by mechanical induction of a posterior vitreous detachment. Comparison with a sham injection would be of interest. In addition, only a single injection of ovine hyaluronidase was allowed in these studies. The potential benefits and complications of additional injections of ovine hyaluronidase are unknown.

IX. CONCLUSION

Over the past several decades, significant advances have been made in the management of PDR. The DRS conclusively demonstrated that photocoagulation was effective in the treatment of PDR, and it proved that for eyes with HRC, the risk of severe visual loss was substantially reduced. The DRVS showed that early vitrectomy was beneficial for eyes with nonclearing vitreous hemorrhage and for eyes with severe PDR (severe fibrovascular proliferation). The ETDRS established that photocoagulation should be considered for eyes with severe or very severe NPDR and for eyes with early PDR, and that aspirin did not alter the course of diabetic retinopathy. As a result of these overwhelmingly successful multicenter, randomized, controlled clinical trials, laser photocoagulation and vitrectomy surgery have remained the standards of care for years, and countless patients have avoided the blinding sequelae of PDR.

Emerging pharmacologic therapies such as ruboxistaurin mesylate (Arxxant) and ovine hyaluronidase (Vitrase) represent new approaches to the prevention and management of PDR, and the results of clinical trials are encouraging. Additional new medications such as pegaptanib (Macugen), ranibizumab (Lucentis), and bevacizumab (Avastin) have not been subjected to controlled clinical trials for PDR, but they offer tremendous potential in the treatment of retinal disease since they target specific molecules. A greater understanding of the molecular pathways underlying diabetic retinopathy will enable new pharmacologic interventions. The future will likely involve oral and intravitreous (probably via sustained-release devices) administration of new drugs, and emphasis will likely be on prevention.

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8A Clinical Trials in Nonneovascular Age-Related Macular Degeneration

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Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world.[1,2] There are two forms of advanced AMD: central geographic atrophy (CGA) and neovascular (wet) AMD. Although new treatments have improved outcomes in neovascular AMD over the last decade, there remains no proven treatment for geographic atrophy (GA). Therapies that focus on prevention by addressing modifiable risk factors such as diet and nutritional status are important approaches to reducing the burden of AMD. Such preventive strategies are especially important as life expectancy in the United States and Europe continues to increase.

Scientific publications on early AMD and GA have greatly increased over the last decade. Some of this scientific interest has resulted in the development of clinical trials for early AMD and GA. This chapter summarizes the key clinical trials of therapies for early and intermediate AMD and GA that have been published to date. None of these trials, with the exception of the Age-Related Eye Disease Study (AREDS), has resulted in a widely adopted new therapy. These trials do, however, inform the design of ongoing and future studies.

Treatment of Early and Intermediate Age-Related Macular Degeneration

Trials of treatment for early and intermediate AMD have largely been designed to target various aspects of AMD pathogenesis. The specifics of AMD pathogenesis remain unknown, but aging, genetic factors, and environmental factors play important roles. Oxidative damage is implicated as an end effector in the pathogenesis of AMD. The retina is uniquely susceptible to oxidative damage given its high metabolic activity and daily exposure to light.[3,4] Pathologic examination and proteome analysis of retinas of eyes with AMD reveal more protein adducts resulting from oxidative modification of carbohydrate and lipid than control eyes.[5] The increasing incidence of macular degeneration with advancing age may be related to gradual dysfunction and degeneration of retinal tissues as oxidative damage accumulates. A growing body of evidence also implicates inflammatory processes in the pathogenesis and progression of macular degeneration.[3]

The trials of early and intermediate AMD presented below fall broadly into three groups: nutritional supplements and antioxidants, treatments that affect microcirculation and oxygen delivery, and macular laser. The nutritional supplements investigated to date have been targeted toward the oxidative stresses and inflammation implicated in AMD pathogenesis. Studies of supplements gained momentum with the publication of AREDS in 2001, and many studies since then have looked at related supplements and potential improvements upon the AREDS formula. Trials that have targeted oxygen delivery and the intraocular microcirculatory environment have employed rheopheresis and oxygen ozone therapy. Age-related thinning of the choroid[6] and decreased choroidal blood flow in AMD[7] underlie the hypotheses that improving blood viscosity and oxygen delivery might help halt the progression of AMD. Finally, macular

laser was proposed by Donald Gass as a potential therapy for early AMD in part because it induces regression of macular drusen.[8] These three groups of trials are summarized below.

Age-Related Eye Disease Study

Study Design

The AREDS was a multicenter, randomized, placebo-controlled trial designed to study the natural history of AMD and age-related cataract and to assess the impact of antioxidant vitamins and zinc supplementation on these conditions.[9] The intervention incorporated antioxidant vitamins and zinc for two main reasons.[9] First, several epidemiologic studies and clinical trials at that time had suggested a role for antioxidants in reducing the risk of cancer, cardiovascular disease, and eye disease. A small trial had also suggested that pharmacologic doses of zinc reduced the risk of vision loss in AMD.[10] The second reason was the growing use of commercially available antioxidant and zinc supplements among AMD patients, despite a paucity of clinical evidence. A large, randomized trial was needed to evaluate these supplements for AMD.

The AREDS trial randomized 3,640 participants with AMD to antioxidant supplements, zinc, combined antioxidants and zinc, or placebo (Table 8A.1). The combined AREDS supplement contained 15 mg beta-carotene, 500 mg vitamin C, 400 IU vitamin E, 80 mg zinc oxide, and 2 mg of copper as cupric oxide. Participants were stratified into four categories of AMD by clinical appearance:

Category 1: No drusen to few drusen; 0.44% developed advanced AMD by year 5.

Category 2: Extensive small drusen, pigment abnormalities, or at least one intermediate drusen in at least one eye; 1.3% probability of progression to advanced AMD by year 5.

Category 3: Extensive intermediate drusen, large drusen, or non-CGA in at least one eye; 18% probability of progression to advanced AMD by year 5. Patients within category 3 who had bilateral large drusen or noncentral GA in at least one eye at enrollment were four times more likely to progress to advanced AMD than the remaining participants in category 3 (27% vs. 6% at 5 years).

Category 4: Advanced AMD or vision loss due to nonadvanced AMD in one eye; 43% probability of progression to advanced AMD in 5 years.

Primary Outcome

Progression to advanced AMD
15-letter decrease in visual acuity score

Key Secondary Outcomes

Worsening of AMD classification
30-letter decrease in visual acuity score
Loss of acuity to level of 20/100

Major Inclusion Criteria

Age 55 to 80 years
20/32 acuity or better in study eye

Results

The interventional AMD study results were published in 2001.[11] The combination of antioxidant vitamins with zinc was protective against the development of advanced AMD (odds ratio [OR] 0.72, 99% confidence

TABLE 8A.1 AREDS Treatment Groups

Formulations	Beta-carotene	Vitamin C	Vitamin E	Zinc oxide	Cupric oxide
Placebo	-	-	-	-	-
Antioxidants	15 mg	500 mg	400 IU	-	-
Zinc	-	-	-	80 mg	2 mg
Antioxidants + Zinc	15 mg	500 mg	400 IU	80 mg	2 mg

AREDS, Age-Related Eye Disease Study; IU, international units.

interval [CI] 0.52–0.98). The treatment effect was greater when category 3 and 4 participants were analyzed (OR 0.66, 99% CI 0.47-0.91). Those with category 1 or 2 AMD had a very low risk of progression to advanced AMD, and a much larger sample size and longer follow-up would be required to evaluate for a treatment effect for the AREDS formulation for these patients.

The zinc without antioxidants treatment group in AREDS had a suggestive, but not statistically significant, reduction in risk of progression to advanced disease (OR 0.75, 99% CI 0.55-1.03). When analysis was restricted to category 3 and 4 participants, there was a significant reduction in progression to advanced AMD (OR 0.71, 99% CI 0.52-0.99). For zinc alone, there was no significant reduction in rates of moderate vision loss. Secondary analyses of the AREDS cohort revealed that participants who took zinc had a significantly lower mortality (mean follow-up 6.5 years, relative risk 0.73, 95% CI 0.61-0.89).

The antioxidant vitamin–only group had a nonsignificant reduction in risk (OR 0.80, 99% CI 0.59-1.09). The risk reduction remained statistically nonsignificant when analysis was restricted to category 3 and 4 participants (OR 0.76, 99% CI 0.55-1.05).

The AREDS formulation was shown to be protective against the development of advanced AMD, but subgroup analysis indicates that the supplements reduce the rate of neovascular disease but not CGA. The number of participants who developed CGA in AREDS was not sufficient to rule out a treatment effect, but analysis of all AREDS patients who developed at least moderate GA also did not indicate a benefit.

Safety

In AREDS, patients taking zinc were hospitalized more often for genitourinary complaints than controls (7.5% vs. 4.9%; $p = 0.001$).[11] Those in the zinc arm had a higher self-reported rate of anemia (13.2% vs. 10.2%; $p = 0.004$), although measured hematocrit did not differ between the two groups. Antioxidant vitamins were associated with skin yellowing. Circulatory adverse experiences (0.3% vs. 0.8%; $p = 0.04$) and skin conditions (2.2% vs. 1.0%; $p = 0.003$) were more frequent in the antioxidant vitamin group.

Two large, randomized, controlled clinical trials have reported an increased lung cancer risk with beta-carotene supplementation.[12,13] Beta-carotene supplements are therefore generally avoided in smokers.

Future Directions

The National Eye Institute has conducted AREDS2, a multicenter, randomized, placebo-controlled trial, to assess the effects of daily oral supplementation of lutein, zeaxanthin, and/or omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid and eicosapentaenoic acid) on the progression to advanced AMD (Table 8A.2). More than 4,000 participants aged 50 to 85 years were enrolled and have been followed for 5 years. At baseline, participants had bilateral large drusen or large drusen in one eye with advanced AMD in the fellow eye. The primary outcome is the development of advanced AMD.

AREDS2 provides an opportunity to further refine the original AREDS formulation by testing the macular carotenoids and a lower dose of zinc. The macular carotenoids may provide additional benefit over beta-carotene, which is not found in the eye but was available for study at the time of the original AREDS study. The full 80 mg of zinc may not be necessary, as recent data suggest that maximal systemic absorption of zinc is about 25 mg/day (Table 8A.3).[4]

TABLE 8A.2 Treatment Groups in the Primary Randomization in AREDS2[4]

Supplement	Daily dose
Placebo	-
Lutein/zeaxanthin	10 mg/2 mg
DHA/EPA	350 mg/650 mg
Lutein/zeaxanthin + DHA/EPA	10 mg/2 mg + 350 mg/650 mg

mg, milligrams; AREDS, Age-Related Eye Disease Study; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

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TABLE 8A.3 Treatment Groups in the Secondary Randomization in AREDS2[4]

Formulations	Vitamin C	Vitamin E	Beta-carotene	Zinc oxide	Cupric oxide
1	500 mg	400 IU	15 mg	80 mg	2 mg
2	500 mg	400 IU	**0 mg**	80 mg	2 mg
3	500 mg	400 IU	15 mg	**25 mg**	2 mg
4	500 mg	400 IU	**0 mg**	**25 mg**	2 mg

AREDS, Age-Related Eye Disease Study; mg, milligrams; IU, international units. Bold values show doses in secondary randomization.

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Oral Zinc in Macular Degeneration

Study Design

The first clinical evidence of a beneficial effect of zinc supplementation in AMD came in 1988 from a small (n = 151), randomized, placebo-controlled trial of 100 mg of oral zinc sulfate for a wide range of AMD patients.[10]

Primary Outcome

Change in visual acuity at 12 to 24 months

Major Inclusion Criteria

Drusen and pigmentary change on clinical examination
Vision of 20/80 or better in one eye

Results

There was a 2.5× risk reduction for loss of 20 letters of acuity. At the final study visit, 86% of treated patients had lost less than 9 letters of acuity versus 66% in the placebo group.

Safety

Two patients in the treatment group experienced mild gastrointestinal irritation.

Oral Zinc and the Second Eye in Age-Related Macular Degeneration

Study Design

In 1996, Stur and colleagues published a randomized, placebo-controlled trial of 200 mg of oral zinc sulfate over 2 years in patients with unilateral exudative AMD (n=112).[14] Patients were followed for 24 months. The original study design called for 500 participants, but the drug maker stopped recruitment based on interim analyses that did not suggest a treatment effect.

Primary Outcome

Development of choroidal neovascularization (CNV) in the study eye

Major Inclusion Criteria

Unilateral exudative AMD
20/40 or better acuity in study eye (nonexudative disease at baseline)
Macular drusen in the study eye

Results

Just 14 participants developed new neovascularization during the 2-year study, and there was no apparent treatment benefit. Nine eyes in the treatment group developed CNV versus five in the placebo group.

Safety

Six participants withdrew from the study due to gastrointestinal symptoms related to the study medication. Fourteen further participants withdrew from the study for unspecified reasons.

Zinc Monocysteine

Study Design

In 2008, Newsome published a trial (n=80) of zinc monocysteine for dry AMD.[15] This compound in theory delivers both a zinc supplement and a cysteine supplement.

Cysteine is a precursor molecule in the glutathione pathway, and the objective of cysteine supplementation in this trial was to boost levels of the antioxidant glutathione. Subjects with early or intermediate AMD were randomized 1:1 to zinc monocysteine 25 mg daily or placebo, and the study drug was administered for 6 months.

Primary Outcome

Tolerability of study supplement
Change in best-corrected visual acuity at 6 months
Change in contrast sensitivity at 6 months
Change in photorecovery time at 6 months

Major Inclusion Criteria

Macular drusen with or without pigment changes
Best-corrected visual acuity between 20/25 and 20/70

Results

The study supplement was well tolerated, and there was a statistically significant improvement in visual acuity (3–4 letter mean improvement, $p < 0.0001$), contrast sensitivity, and photorecovery time at 6 months.

Safety

One patient in the supplement group developed significant gastrointestinal irritation due to the study intervention. There were no other supplement-related adverse events.

Vitamin E, Cataract, and Age-Related Maculopathy Study

Study Design

The results of the AMD trial within the Vitamin E, Cataract, and Age-Related Maculopathy Study (VECAT) were published in 2002.[16] VECAT was a randomized, placebo-controlled trial of 500 IU vitamin E. The study group enrolled 1,204 participants and followed them over 4 years. At baseline, 18% had early or intermediate AMD and 0.5% had advanced AMD.

Primary Outcome

Development of early or intermediate AMD
Development of cataract

Key Secondary Outcomes

Progression of early AMD
Development of advanced AMD
Change in visual acuity
Change in visual function

Major Inclusion Criteria

Age 55 to 80 years
Phakic in at least one eye

Results

VECAT showed no effect of vitamin E supplementation on the incidence of early or late AMD.[16] In the vitamin E group, 8.6% of participants developed early or intermediate AMD versus 8.1% in the placebo group. For late AMD, the treatment group had a 0.8% rate versus 0.6% for the placebo group. Vitamin E supplementation did not affect the incidence or progression of cataract,[17] and there were no significant differences among the secondary outcome measures.

Safety

There were no serious adverse events, and no vitamin E–related adverse effects were identified.

CARMA (Carotenoids with Coantioxidants in Age-Related Maculopathy)

Study Design

The AREDS supplement incorporates the carotenoid beta-carotene, but lutein and zeaxanthin have long been carotenoids of interest for AMD and other macular diseases because, unlike beta-carotene, they occur naturally in the macula. They are thought to protect the outer retina and retinal pigment epithelium (RPE) from damage.[18] CARMA was a randomized, controlled trial of a supplement (12 mg lutein, 0.6 mg zeaxanthin, 15 mg vitamin E, 150 mg ascorbic acid, 20 mg zinc oxide, and 0.4 mg copper gluconate [marketed by Bausch and Lomb under the Ocuvite® brand]) versus placebo.[19] The 433 participants took the supplement once daily for at least 1 year.

Primary Outcome

Best-corrected visual acuity at 1 year

Key Secondary Outcomes

Change in best-corrected acuity at 24 and 36 months
Contrast sensitivity
Progression of AMD

Major Inclusion Criteria

Group 1: unilateral late AMD and early or intermediate AMD in the study eye
Group 2: intermediate AMD in one eye and early or intermediate AMD in the fellow eye
Age 55 years or older
Study eye acuity of 20/40 or better

Results

There was no difference in visual acuity at 1 year. In those with 36 months of follow-up (n=34), there was a significant difference in visual acuity (4.8 letters better in the treatment group, p = 0.04). Increased serum lutein was associated with better acuity and less progression of AMD. The event rate for conversion to advanced AMD was not sufficient to detect a difference between the two groups.

Safety

A total of 88 participants withdrew before the primary endpoint. Five of these withdrawals were attributed to gastrointestinal irritation, but the relationship to study medication is not specified. No other study drug–related adverse events occurred.

Lisa (Lutein Intervention Study Austria)

Study Design

LISA was a relatively short-term (6-month) study of lutein supplementation in participants with AREDS category 2, 3, or 4 AMD.[20] The 126 subjects were randomized 2:1 to supplement or placebo. The study supplement decreased from 20 mg in the first 3 months to 10 mg in the final 3 months.

Primary Outcome

Macular pigment optical density, which is a surrogate measurement of macular uptake of orally supplemented carotenoids. There is no single, standardized method for measurement of macular pigment optical density, but this study employed a technique in which the reflectance patterns of numerous wavelengths of light reflected from the fundus were assessed with a mathematical model to estimate the concentration of molecules (pigments) that absorb at different wavelengths.

Key Secondary Outcomes

Change in best-corrected acuity
Mean differential light threshold (microperimetry)

Major Inclusion Criteria

AREDS category 2 to 4 AMD
Age 50 to 90 years
Acuity of 20/50 or better

Results

Supplementation was associated with a significant increase in macular pigment optical density. Increased pigment optical density after 6 months was associated with better visual acuity and microperimetry parameters.

Safety

No supplement-related adverse events occurred.

Effect of Lutein and Zeaxanthin on Macular Pigment and Visual Function

Study Design

This randomized, controlled trial of 108 Chinese subjects involved 1:1:1:1 randomization to placebo, lutein 10 mg/day, lutein 20 mg/day, or lutein 10 mg/day with zeaxanthin 10 mg/day.[21] Participants received study medication for 48 weeks.

Primary Outcome

Macular pigment optical density at 48 weeks

Key Secondary Outcomes

Best-corrected visual acuity
Contrast sensitivity
Photorecovery time
Amsler grid testing results

Major Inclusion Criteria

Age 50 to 79 years
Early AMD (any soft drusen or pigment changes)
No prior cataract surgery

Results

Macular pigment optical density increased significantly in the treatment groups, and there was a significant dose–response relationship. There was no statistically significant change in visual acuity at 48 weeks, but there was a significant improvement in contrast sensitivity upon subgroup analysis when comparing the 20 mg lutein group with the placebo group. Improvements in acuity and contrast sensitivity correlated with increasing macular pigment optical density.

Safety

There were no study drug–related adverse events.

Saffron and Retinal Function in Early Age-Related Macular Degeneration

Study Design

Saffron, derived from the plant *Crocus sativus*, is thought to have neuroprotective properties that can protect the retina from oxidative damage.[22] Two of its major component molecules, crocin and crocetin, are antioxidants and carotenoid derivatives. Saffron has been shown to be protective in a rat model of light-induced photoreceptor degeneration.[22] For these reasons, saffron has been investigated in a randomized, cross-over trial of saffron 20 mg daily or placebo.[23] The 25 subjects received the first intervention for 3 months and crossed over for an additional 3 months.

Primary Outcome

Focal electroretinogram (ERG) amplitudes, phase, and modulation thresholds

Major Inclusion Criteria

Bilateral nonneovascular AMD
Any soft drusen, with or without pigment abnormalities
Baseline acuity of 20/40 or better

Results

Focal ERG amplitudes increased significantly with saffron administration. Focal ERG thresholds decreased after taking saffron. These findings suggest that retinal flicker sensitivity, a measurement of macular cone function, may increase with saffron supplementation in early or intermediate AMD.

Safety

There were no saffron-related adverse effects.

Acetyl-L-Carnitine, *N*-3 Fatty Acids, and Coenzyme Q10

Study Design

Damage to mitochondrial DNA in photoreceptors has been shown to increase with age,[24] and rod photoreceptor and RPE mitochondrial DNA is particularly susceptible to oxidative stress.[25] For these reasons, this trial studied the effect of a commercially available supplement thought to target mitochondrial health.[26] This supplement combination would in theory improve the metabolic function, membrane composition, and oxidative environment for retinal and RPE mitochondria. The 106 subjects received the supplement (Phototrop®, 100 mg acetyl-L-carnitine, 530 mg n-3 fatty acids, and 10 mg CoQ10 taken twice daily) for 1 year.

Primary Outcome

Change in the visual field mean defect (VFMD), which is the reciprocal of visual field mean sensitivity, was determined in this study with a Humphrey Field Analyzer 10-2 pattern from baseline to 12 months.

Major Inclusion Criteria

Bilateral early AMD (criteria not provided)
Age 55 to 70 years
Caucasian race
Baseline acuity of 20/25 to 20/50

Results

There was no significant difference between the treatment and placebo groups in change in VFMD at 12 months.

Safety

There were no supplement-related adverse events.

Randomized Clinical Trial France DMLA2

Study Design

Trimetazidine is an oral antianginal agent that inhibits fatty acid metabolism (β-oxidation). It is thought to increase intracellular adenosine triphosphate and phosphocreatine levels, reduce free radical–mediated cellular damage, inhibit apoptosis, and improve endothelial cell function.[27] This large, randomized, placebo-controlled trial investigated 35 mg of trimetazidine twice daily versus placebo in subjects with unilateral neovascular AMD.[28] The 1,086 subjects received study medication for 3 years.

Primary Outcome

Development of CNV in the study eye
Time to development of CNV

Key Secondary Outcomes

Development of CGA in the study eye

Major Inclusion Criteria

Unilateral exudative AMD
Early or intermediate AMD in the study eye
Age 55 to 83 years
White race

Results

There was no significant reduction in the rate of CNV in the trimetazidine group. There was a trend toward a protective effect for the development of GA (hazard ratio = 0.76; 95% CI, 0.56–1.02; $P = 0.069$). On subgroup analysis, trimetazidine was statistically protective against GA in participants younger than 75 years of age, in subjects with pigment changes only at baseline, and in men.

Safety

The drug was well tolerated, and there was no difference in the rate of adverse events between the trimetazidine and placebo groups. No drug-related adverse effects were identified.

Art (Dry Age-Related Macular Degeneration Treatment with Rheopheresis Trial)

Study Design

Rheopheresis is a specific method of plasma filtration that removes large proteins from plasma. Rheopheresis is thought to improve microcirculatory parameters. The technique has been investigated in a variety of microcirculatory diseases.[29–31] The ART trial investigated rheopheresis in 43 participants with unilateral neovascular AMD.[32] Participants were randomized to 10 sessions of rheopheresis over 17 weeks or no treatment.

Primary Outcome

Change in best-corrected visual acuity at 7.5 months

Major Inclusion Criteria

Unilateral exudative AMD
Early or intermediate AMD in the study eye
Age 45 to 85 years
Baseline acuity of ~20/25-20/125 in the study eye

Results

At 7.5 months, there was a mean improvement of 0.63 lines of acuity in the treatment group and a mean loss of 0.31 lines in the control group ($p = 0.014$). None of the treatment eyes had deterioration in best-corrected acuity of ≥1 line versus a 24% rate in the control group; 19% of controls had a ≥2 line loss, and 9.5% had a ≥3 line loss. Just 19 participants returned for assessment for CNV at 2 years, and among these subjects 2/10 treatment eyes and 4/9 control eyes had developed CNV.

Safety

Transient treatment-related hypotension was the most frequent adverse event (3/236 treatments). None of the adverse events were considered serious adverse events. Vascular access problems were encountered in 5.1% of treatments.

MIRA-1 (Multicenter Investigation of Rheopheresis for Age-Related Macular Degeneration)

Study Design

MIRA-1 was a multicenter, randomized, controlled trial of rheopheresis in 216 participants with nonexudative AMD.[33] Participants were randomized 2:1 to treatment with eight sessions of rheopheresis over 10 weeks or sham treatment. Participants who met criteria for improvement at 3 months were eligible for further treatment at 9 months.

Primary Outcome

Mean best-corrected visual acuity at 12 months

Major Inclusion Criteria

High-risk, nonexudative AMD in the study eye
Age 50 to 85 years
Baseline acuity of 20/32-20/125 in the study eye
Elevated baseline concentrations of two of the following three factors: total serum cholesterol, fibrinogen, or serum immunoglobulin A

Results

A total of 37% of the participants were found at the time of data analysis to have not met all prespecified inclusion criteria. Upon intent-to-treat analysis, there was no significant difference in mean visual acuity at 12 months. The treatment group had a logarithm of the minimum angle of resolution (logMAR) acuity improvement of 0.02 ± 0.213, and the placebo group had a logMAR acuity improvement of 0.02 ± 0.20 ($P = 0.977$). When enrolled participants who did not meet the inclusion criteria were excluded, there was an apparent treatment effect (0.08 ± 0.166 improvement compared with –0.01 ± 0.164, $p = 0.001$).

Safety

On treatment days, 24.0% of subjects in the treatment group had "an incident that required an intervention" versus 5.8% in the control group. Serious adverse events included bigeminy ($n=1$), angina ($n=1$), and pneumonia ($n=1$) in the treatment group. The likelihood that these events were related to the study treatment was felt to be low.

Oxygen Ozone Therapy in Macular Degeneration

Study Design

This study investigated a technique called major ozonated autohemotherapy, in which a subject's blood is exposed to medical oxygen ozone and then reinfused, for dry AMD.[34] This treatment is thought to improve oxygen delivery to the ischemic tissue through several mechanisms including enhanced formation of 2,3-diphosphoglycerate and by upregulation of antioxidant enzymes.[35] The 140 participants were randomized to either major ozonated autohemotherapy or AREDS supplements. Treatments were administered twice weekly for the first 7 weeks, twice monthly for the next 3 months, and then monthly through the end of the 1-year study.

Primary Outcome

Mean change in visual acuity at six and 12 months

Major Inclusion Criteria

Macular large drusen in the study eye
Absence of CNV in the study eye
Age 59 to 82 years
Baseline acuity of 20/32-20/125 in the study eye

Results

Visual acuity was not statistically different between the treatment and vitamin groups at six or 12 months. Upon secondary analysis, there were significantly fewer eyes that lost 3 or more lines of acuity at 12 months in the treatment group (0% versus 38%, $p < 0.05$).

Safety

In the treatment group, 3% experienced a transient reddening of the face after reinfusion. There were no other treatment-related adverse effects.

Choroidal Neovascularization Prevention Trial

Study Design

The Choroidal Neovascularization Prevention Trial consisted of two parts, both of which investigated macular laser for the prevention of CNV.[36–38] The Bilateral Drusen Study (BDS) involved macular laser in one eye of participants with bilateral intermediate or large drusen. In the Fellow Eye Study (FES), subjects with unilateral neovascular AMD and drusen in the fellow eye were randomized to macular laser or observation. The laser treatment consisted in most participants of twenty 100 μm laser burns in a pattern of three rows along the temporal margin of the fovea. In the absence of drusen regression, a second laser treatment of 20 burns was required to be placed on the nasal side of the fovea in a mirror-image pattern. These studies were stopped because of a higher rate of CNV at 12 months in the treated eyes.

Primary Outcome

Change in visual acuity

Major Inclusion Criteria

Ten or more intermediate or large macular drusen in the study eye
Bilateral drusen (BDS) or unilateral CNV (FES)
Age 50 years or older
Baseline acuity of 20/40 or better

Results

Study enrollment was stopped at 18 months because of a significantly higher rate of CNV in the FES treatment group (in the FES, 10/59 treated eyes versus 2/61 controls, $p = 0.02$). Through four years of follow-up, there was no significant difference in visual acuity between the treatment and observation groups in either study. Laser treatment was associated with regression of drusen.

Safety

Laser treatment increased the risk of CNV in high-risk eyes, and these studies were stopped by their data safety monitoring committee before enrollment was completed.

Prophylactic Treatment of Age-Related Macular Degeneration

Study Design

The Prophylactic Treatment of Age-Related Macular Degeneration trial examined the effect of macular subthreshold diode laser treatment in eyes at risk for neovascular AMD.[39] This study was conducted after the Choroidal Neovascularization Prevention Trial, and the hypothesis was that the lighter laser burns in a subthreshold treatment protocol would obviate the safety problems encountered in the Choroidal Neovascularization Prevention Trial. The laser treatment consisted of 48 subthreshold (invisible) diode laser spots in a circular pattern sparing the fovea. The 883 participants were followed for 3 years.

Primary Outcome

Development of CNV
Change in visual acuity

Major Inclusion Criteria

Unilateral advanced AMD or bilateral intermediate/large drusen
Age 50 years or older
Baseline acuity of 20/63 or better

Results

In subjects with unilateral advanced disease, the rate of CNV in the study eye was consistently higher in the treatment group (15.8% versus 1.4% at 1year, $p = 0.05$). Treated eyes were more likely to have a 3 line vision loss at 3 and 6 months. There was no significant difference in CNV development in the bilateral intermediate AMD group. Although a statistical acuity benefit was seen at 2 years for the bilateral intermediate AMD treatment group, there was no significant benefit at 3 years.

Safety

Macular subthreshold laser was associated with a high rate of CNV at 1 year in high-risk eyes and is therefore not considered a safe treatment for the prevention of advanced AMD.

Complications of Age-Related Macular Degeneration Prevention Trial

Study Design

The Complications of Age-Related Macular Degeneration Prevention Trial **(CAPT)** was also a trial of macular laser for the prevention of vision loss due to advanced AMD.[40] Although the earlier Choroidal Neovascularization Prevention Trial showed that macular laser increased the risk of CNV in the fellow eye of patients with unilateral neovascular AMD, this trial used a lower intensity laser treatment in subjects with bilateral large drusen. One eye was selected for laser treatment and the contralateral eye served as a control. The treatment involved placement of 60 barely visible burns in a circular pattern that spared the fovea and retreatment at 12 months if drusen failed to regress. The 1,052 participants were followed for 5 years.

Primary Outcome

Proportion of participants with loss of 3 or more lines of vision at 5 years

Key Secondary Outcomes

Incidence of CNV and GA

Major Inclusion Criteria

Ten or more large drusen in both eyes
Age 50 years or older
Baseline acuity of 20/40 or better

Results

At 5 years, 188 eyes in both the treatment and control groups had lost 3 or more lines of acuity. There was no difference in the rate of either CNV or GA through 6 years of reported data. Drusen regression was greater in the treated eyes, particularly at 2 years (34.3% vs. 8.6%, with 50% reduction of macular drusen area).

Safety

There were no adverse effects attributed to macular laser treatment in this study.

Treatment of Central Geographic Atrophy

CGA is the advanced atrophic form of AMD and is responsible for progressive moderate and severe vision loss. The prevalence of CGA is expected to increase to affect approximately 3.8 million people in the United States by 2050.[41] CGA is characterized by central areas of atrophy of the retina, RPE, and choroid that enlarge and coalesce with time. No effective treatment exists to prevent either onset or progression of GA. The landscape of investigational therapies for CGA is rapidly expanding and evolving, with an exponential increase in the number of compounds in preclinical or early-stage clinical trials for the treatment of GA in recent years.[42] Outcome measures for assessment of GA progression are also evolving. Visual acuity often underestimates the extent of disease and is a poor measure of disease progression.[43,44] Secondary measures of progression are therefore critical for the development of new therapies. The majority of recent trials use change in area of GA as a primary outcome measure (Fig. 8A.1). The area of CGA is often measured using fundus autofluorescence images.

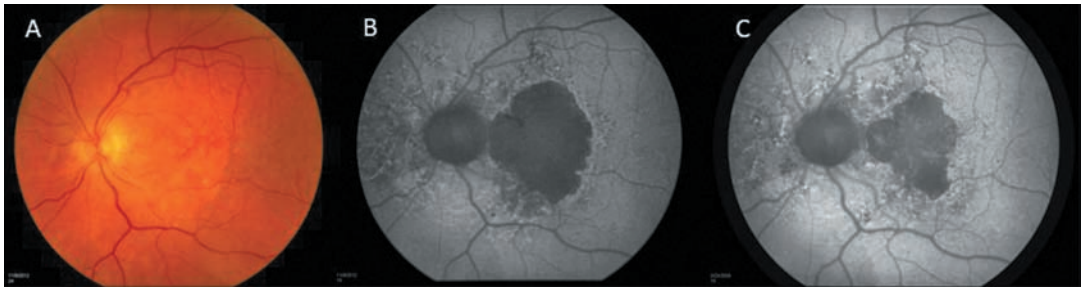

FIGURE 8A-1 **(A)** A color fundus photograph of an eye with central geographic atrophy (CGA). **(B)** A fundus autofluorescence image that corresponds with the color photo in **(A)**. Note that the central area of atrophy is dark or hypoautofluorescent. **(C)** The same eye 2.5 years earlier with a smaller area of central atrophy. The growth of this area of atrophy is used as an outcome measure in some studies of CGA.

The few completed, published trials for the treatment of GA are summarized below. Much of the data from recent trials for GA remain to be published, and such data will be important for the medical literature going forward.

Fenretinide

Study Design

Products and byproducts of the visual cycle including all-trans retinal and *N*-retinyl-*N*-retinylidene ethanolamine (A2E) have been shown to be toxic to photoreceptors and the RPE.[45–47] For this reason, investigators have pursued treatments for CGA that slow the visual cycle. Fenretinide (*N*-4-hydroxy(phenyl)retinamide) (Sirion Therapeutics, Tampa, FL) is a compound that reduces the delivery of vitamin A to the retina by causing a dose-dependent reduction in circulating retinol by displacing all-trans retinol from the retinol-binding protein (RBP).[48,49] It has previously been used in clinical trials for cancer, and it therefore has a known safety profile. Fenretinide has been previously shown to impair dark adaptation.[50] This was a multicenter, randomized, placebo-controlled trial of oral fenretinide 100 mg or 300 mg daily.[51] The 246 participants received study medication for 2 years.

Primary Outcome

Annualized change in aggregate lesion size growth

Key Secondary Outcomes

Reduction in serum RBP-retinol levels
Incidence of CNV
Change in visual acuity

Major Inclusion Criteria

50 to 89 years of age
1 to 8 disc areas of confluent GA within 500 μm of the fovea
Acuity of 20/20 to 20/100
No exclusion for past CNV

Results

There was no statistically significant reduction in lesion growth, although there was dose-dependent trend toward less growth in the treatment groups. Participants in the 300 mg group that achieved the lowest serum retinol levels (≤1 μM) had a mean reduction of 0.33 mm^2 in the yearly lesion growth rate compared with subjects in the placebo group (1.70 mm^2/year vs. 2.03 mm^2/year, respectively, $p = 0.1848$). There was also a trend toward a lower incidence of CNV in the fenretinide groups (approximately 45% reduction in incidence rate in the combined fenretinide groups vs. placebo, $p = 0.0606$).

Safety

A total of 68/246 participants withdrew before the study conclusion. This was due to adverse events in 6.1%, 17.5%, and 20.2% in the placebo, 100 mg, and 300 mg groups, respectively. The most common reason for withdrawal was study drug–induced rash and pruritus. Four patients withdrew due to symptoms of night blindness, four withdrew due to drug-related visual disturbances, and another four withdrew due to reduced visual acuity.

ACU-4429

Study Design

ACU-4429 is an inhibitor of the visual cycle protein RPE65, which is a *trans*- to *cis*-retinal isomerase.[52] The rationale for the use of ACU-4429 for CGA is similar to the rationale for fenretinide in that both compounds have the potential to reduce the production of toxic visual cycle byproducts. This study was a single-center dose-escalating, randomized, placebo-controlled trial to assess the safety ACU-229 and its effect on human rod function in 46 healthy subjects. Subjects were given a single dose and assessed with ERG and safety examinations.

Primary Outcome

Safety of ACU-4429, as assessed by ERG and incidence of adverse events

Major Inclusion Criteria

Healthy subjects aged 55 to 80

Results

ACU-4429 was well tolerated up to a dose of 75 mg. Rod amplitudes decreased in a

dose-dependent fashion, and they were most depressed on day 2 after administration. About 50% of subjects in the treatment groups experienced mild, reversible visual side effects versus no subjects in the placebo group.

Future Directions

An industry-sponsored phase 2, randomized, controlled trial of ACU-4429 for CGA has been completed. The study targeted an enrollment of 72 subjects, and the primary outcomes were safety and pharmacokinetic parameters.

Othera

Study Design

OT-551 (Othera Pharmaceuticals, Conshohocken, PA), which has been formulated as an eye drop, is converted to Tempol-H in the eye.[53] Tempol-H reacts directly with free radicals and exerts an antioxidant effect. The OTHERA trial was a 10 patient, open-label, phase 2 clinical trial of OT-551 in patients with bilateral CGA. Each patient received one drop of the investigational agent three times per day in the study eye for 2 years. The fellow eye served as a control.

Primary Outcome

Change in best-corrected visual acuity at 24 months

Key Secondary Outcomes

Change in the area of GA
Change in total drusen area
Change in contrast sensitivity
Change in microperimetry measurements

Major Inclusion Criteria

Minimum 60 years of age
AMD with bilateral GA
Some GA that was not contiguous with peripapillary atrophy
No history of exudative AMD

Results

A statistically significant difference was found between the study and fellow eyes in final visual acuity. The mean change in acuity at 2 years was –0.2±13.3 letters in the study eyes and –11.3±7.6 letters in the fellow eyes ($p = 0.0259$). Secondary analyses of disease progression did not reveal a difference between study and control eyes.

Safety

There were no significant adverse effects.

Future Directions

The OMEGA (NCT00485394) trial is an ongoing multicenter, dose-ranging, placebo-controlled study using 0.3% and 0.45% of the OT-551 compound in patients with GA.[54] The recruitment target is 198 participants.

Ciliary Neurotrophic Factor

Study Design

Ciliary neurotrophic factor (CNTF) has been shown to reduce degeneration of photoreceptors in animal models.[55] A CNTF intravitreal implant (NT-501) has been well tolerated in patients with retinitis pigmentosa.[56] The implant uses encapsulated cell technology whereby human cells within a semipermeable polymer capsule release CNTF into the vitreous cavity at a sustained, controlled rate. This study was a multicenter, randomized, sham-controlled clinical trial of the NT-501 CNTF implant in patients with GA.[57] The 51 participants underwent surgical implantation of a 5 ng/day implant or a 20 ng/day implant or a sham surgical procedure.

Primary Outcome

Change in best-corrected visual acuity at 12 months

Key Secondary Outcomes

Change in optical coherence tomography (OCT) central retinal thickness
Change in OCT macular volume
Visual acuity stabilization (loss of less than 15 letters)
Change in lesion size

Major Inclusion Criteria

Minimum 50 years of age
GA in study eye meeting AREDS category 3 or 4 criteria
Acuity of 20/50-20/200

Results

There was a statistically significant difference in final visual acuity when the high-dose group was compared with the low-dose and placebo groups combined. The high-dose group gained a mean 0.8 letters versus a mean 9.7 letter loss in the combined low-dose/sham group ($p = 0.0315$). The high-dose group also had a statistically significant increase in retinal thickness. In subgroup analysis, participants with a baseline acuity of 20/63 or better had a 100% rate of acuity stabilization in the high-dose group versus 55% in the combined low-dose/sham group ($p = 0.033$).

Safety

There were no drug- or procedure-related serious adverse events during the 12-month study period. CNTF was not detectable on serum testing.

Conclusions

Although the scientific community continues to progress in its understanding of early AMD and GA, these areas remain vast frontiers for future clinical trials. The AREDS supplement has been shown to reduce the 5-year risk of advanced AMD in those with category 3 or 4 disease. Studies of other supplements including a variety of carotenoids are promising for early disease, and the AREDS2 results are likely to answer several pressing questions about supplement use for patients at risk for advanced AMD.

No proven treatment for GA has yet been identified, but the CNTF implant and other ongoing trials offer hope for the future. Numerous trials of new interventions for GA are in progress or are yet to be published. Such studies have employed antioxidants such as AL-8309A, other visual cycle pathway modifiers, anti-inflammatory drugs including sirolimus and Iluvien, complement inhibitors including eculizumab and ARC 1905, neuroprotective agents, and stem cell therapy. Outcome measures will require continuous refinement, and continued development of surrogate outcome measures is critical for efficient evaluation of novel therapies.

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8B Clinical Trials in Wet Age-Related Macular Degeneration

Stephen A. McNutt MD and Peter K. Kaiser MD

Age-related macular degeneration (AMD) remains the leading cause of blindness in the developed world and is a major cause of blindness worldwide.[1] Wet macular degeneration accounts for 10% to 20% of cases of AMD, but makes up 80% to 90% of severe vision loss associated with the disease.[2] The management of AMD has drastically changed in the past 10 years. Previously, the available treatments for AMD decreased the incidence of moderate to severe vision loss, but in many cases visual loss still occurred. The Macular Photocoagulation Study (MPS) involved the evaluation of delivery of laser to choroidal neovascularization (CNV) in an effort to halt severe vision loss.[3–5] Similarly, verteporfin photodynamic therapy (PDT) trials including the **T**reatment of **A**ge-related macular degeneration with **P**hotodynamic therapy (TAP) study demonstrated a reduced risk for moderate to severe vision loss in certain patients with CNV from AMD, however showed only a minimal proportion of patients gaining vision.[6–9] The pathogenesis of wet AMD includes angiogenesis, the formation of new blood vessels, from existing vasculature. Vascular endothelial growth factor (VEGF) has been shown to play a role in this process of neovascularization in AMD.[10] With a better understanding of the relationship of angiogenesis and VEGF in the pathogenesis of wet AMD came more therapies targeted toward VEGF, namely the anti-VEGF antibodies ranibizumab and bevacizumab. These medications have changed the care of patients with AMD and have given them the possibility of regaining lost vision.

This chapter describes the main studies currently relevant for the treatment of wet AMD.

I. ANTI-VEGF ANTIBODY FOR THE TREATMENT OF PREDOMINANTLY CLASSIC CHOROIDAL NEOVASCULARIZATION IN AGE-RELATED MACULAR DEGENERATION (ANCHOR) STUDY

The ANCHOR study was designed to compare the efficacy and safety of intravitreal ranibizumab, a 48-kDa humanized, affinity-matured antibody to VEGF-A isoforms, and PDT with verteporfin in patients with predominantly classic CNV due to AMD. Together, the ANCHOR and MARINA studies lead to a paradigm shift in the management of neovascular AMD.

Study Design

In the ANCHOR study, 423 patients were randomized 1:1:1 to receive 24 monthly intravitreal injections of 0.3 mg or 0.5 mg ranibizumab (Lucentis, Genentech, South San Francisco, CA) with sham PDT or monthly sham injections with standard verteporfin (Visudyne, QLT, Vancouver, BC) PDT. Patients were eligible to receive additional sham or standard PDT treatment every 3 months if they showed leakage from CNV on fluorescein angiography (FA).[11]

Primary Outcome

- Proportion of patients who lost <15 letters at month 12 compared with the baseline in the best-corrected visual acuity (BCVA) score.

Key Secondary Outcomes

- Proportion of patients who lost <15 letters at 24 months versus baseline
- Mean change in BCVA at 12 and 24 months
- Percentage gaining ≥ 15 letters
- Change in FA lesion characteristics
- Ocular and systemic side effects

Major Inclusion Criteria

- Age ≥50
- Predominantly classic subfoveal CNV due to AMD
- ETDRS BCVA (Snellen equivalent) between 20/40 to 20/320 in the study eye
- Lesion eligible for PDT (<9 MPS disc areas [DA])
- No prior laser treatment involving the center of the fovea
- No prior PDT or experimental treatments for AMD

Results

Efficacy analysis was performed using an intent-to-treat analysis. At month 12, the proportion of patients losing <15 letters was found to be 94.3% in the 0.3 mg ranibizumab group, 96.4% in the 0.5 mg group, and 64.3 % in the PDT group ($P < 0.001$).[11] Figure 8B.1 shows the mean change in visual acuity (VA) (letters) (± standard error) over time in the study through month 12, and clearly shows a significant trend toward gain of vision in the ranibizumab groups versus the PDT group. At 24 months statistical significance remained in this comparison with 90.0% and 89.9% of patients losing <15 letters in the 0.3 mg and 0.5 mg ranibizumab groups, respectively, versus 65.7% in the PDT group.[12] A gain of ≥15 letters was seen in 35.7%, 40.3%, and 5.6% of patients in the 0.3 mg ranibizumab, 0.5 mg ranibizumab, and PDT groups at 12 months, respectively ($P < 0.001$ for ranibizumab

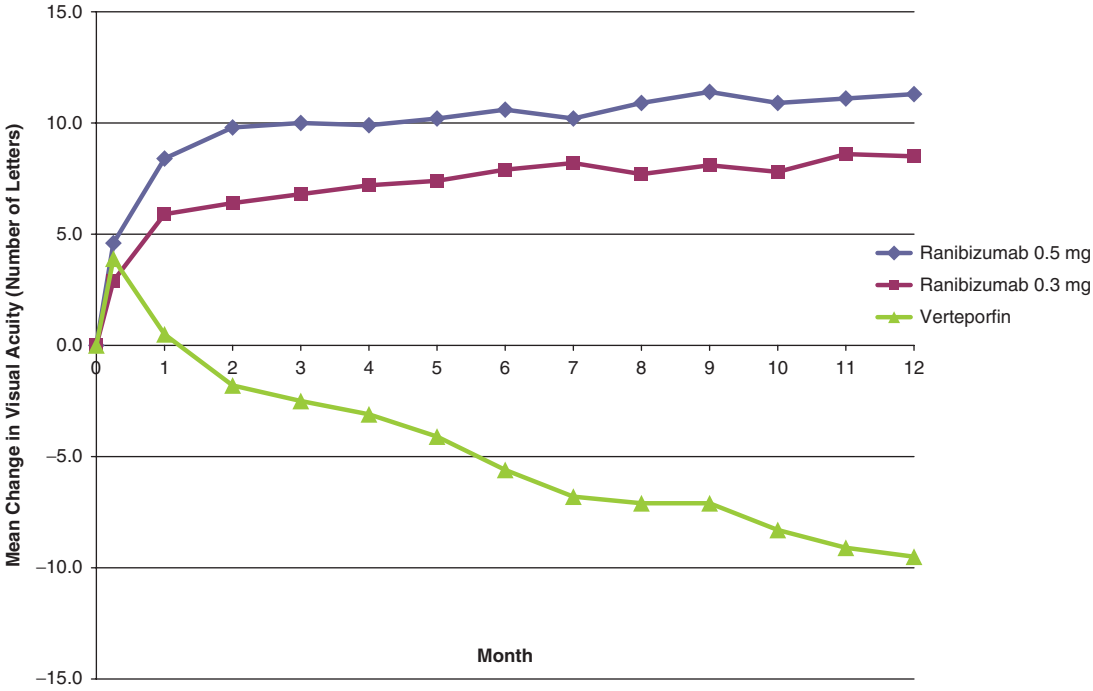


FIGURE 8B.1 Mean change in number of letters read versus month in ranibizumab 0.5 mg, ranibizumab 0.3 mg, and verteporfin treatment groups of the ANCHOR trial. (Reproduced from Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *New Engl J Med.* 2006;355:1432–1444, with permission.)

groups vs. sham).[11] Similar gains in VA remained at 24 months. The mean change in VA at 12 months was +8.5 and +11.3 letters for the 0.3 mg and 0.5 mg groups, respectively, with a mean loss of –9.5 letters in the PDT group ($P < 0.001$).[11] At 24 months, the mean change in BCVA was +8.1 letters for 0.3 mg ranibizumab, +10.7 letters for 0.5 mg ranibizumab, and –9.8 letters in the PDT group, which remained statistically significant.[12] Ranibizumab showed significantly more favorable changes at both 12 and 24 months with respect to total area of CNV lesion, CNV area, and total area of CNV leakage[11,12] compared to PDT.

Safety

There were no imbalances in serious or nonserious ocular adverse events (AEs) between the three groups at 24 months.[12] Also, no imbalance was seen in serious nonocular AEs between groups. There was no significant difference at 24 months between ranibizumab groups versus PDT when comparing rates of arterial thrombotic events as defined by the Antiplatelet Trialists' Collaboration.[12,13]

II. MINIMALLY CLASSIC/OCCULT TRIAL OF THE ANTI-VEGF ANTIBODY RANIBIZUMAB IN THE TREATMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (MARINA)

The MARINA study set out to evaluate ranibizumab versus sham injection in patients with minimally classic and occult with no classic CNV due to wet AMD. Taken with the results of the ANCHOR study, the treatment of wet AMD changed direction toward the use of anti-VEGF agents.

Study Design

The MARINA study was a prospective, 2-year, randomized, double-masked, sham-controlled study of the efficacy and safety of the use of ranibizumab in patients with minimally classic and occult with no classic CNV due AMD[14]; 716 patients were randomized (1:1:1) to receive 24 monthly intravitreal injections with 0.3 mg ranibizumab, 0.5 mg ranibizumab, or sham intravitreal injections in minimally classic or occult with no classic, subfoveal CNV.

Primary Outcome

- Proportion of subjects who lost <15 letters at month 12 compared with baseline in their BCVA

Key Secondary Outcomes

- Patients who gained 15 or more letters in BCVA from baseline
- Mean increase in BCVA from baseline at 12 months
- Ocular and systemic side effects

Major Inclusion Criteria

- Age ≥50 years
- ETDRS BCVA (Snellen equivalent) between 20/40 and 20/320 in the study eye
- Subfoveal CNV secondary to AMD
- Lesion composition by FA:
  - Area of CNV must be ≥50% of the total lesion
  - Minimally classic or occult with no classic CNV
  - Evidence of presumed recent disease progression as evidenced by new subretinal hemorrhage, recent growth on FA or recent VA loss
  - Lesion size ≤ 12 DA

Results

Efficacy analysis was performed using an intent-to-treat analysis; 94.5% patients receiving 0.3 mg ranibizumab and 94.6% of those receiving 0.5 mg ranibizumab lost less than 15 ETDRS letters versus 62.6% in the sham group at 12 months ($P < 0.001$ for both groups vs. sham).[14] The significant difference in patients losing <15 letters remained

at 24 months. At 12 months, 24.8% of the patients in the 0.3 mg ranibizumab group and 33.8% in the 0.5 mg group gained ≥15 letters versus 5.0% in the sham group ($P < 0.001$) with the percentages remaining similar at 24 months.[14] The mean change in BCVA from baseline to 12 months was +6.5 letters and +7.2 letters in the 0.3 mg and 0.5 mg ranibizumab groups, respectively versus a loss of 10.4 letters in the sham injection group ($P < 0.001$).[14] Again, the difference between the groups remained at 24 months (Fig. 8B.2).

Safety

There was no significant difference in AEs at 24 months. Seventeen deaths were reported over the 24-month period with similar rates in all groups— approximately 2.5%. Arterial thrombotic events were reported at a rate of 3.8%, 4.6%, and 4.6% in the sham, 0.3 mg ranibizumab, and 0.5 mg ranibizumab groups, respectively.[14]

III. A PHASE IIIB, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, SHAM INJECTION-CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF RANIBIZUMAB IN SUBJECTS WITH SUBFOVEAL CHOROIDAL NEOVASCULARIZATION WITH OR WITHOUT CLASSIC CNV SECONDARY TO AGE-RELATED MACULAR DEGENERATION STUDY (PIER) STUDY

The PIER study set out to study an alternate dosing regimen of ranibizumab to the monthly treatment protocol studied in the MARINA and ANCHOR studies.

Study Design

This was a 2-year, Phase IIIb, multicenter, double-masked, sham injection-controlled evaluation of the efficacy and safety of ranibizumab in patients with subfoveal CNV due to AMD.[15]

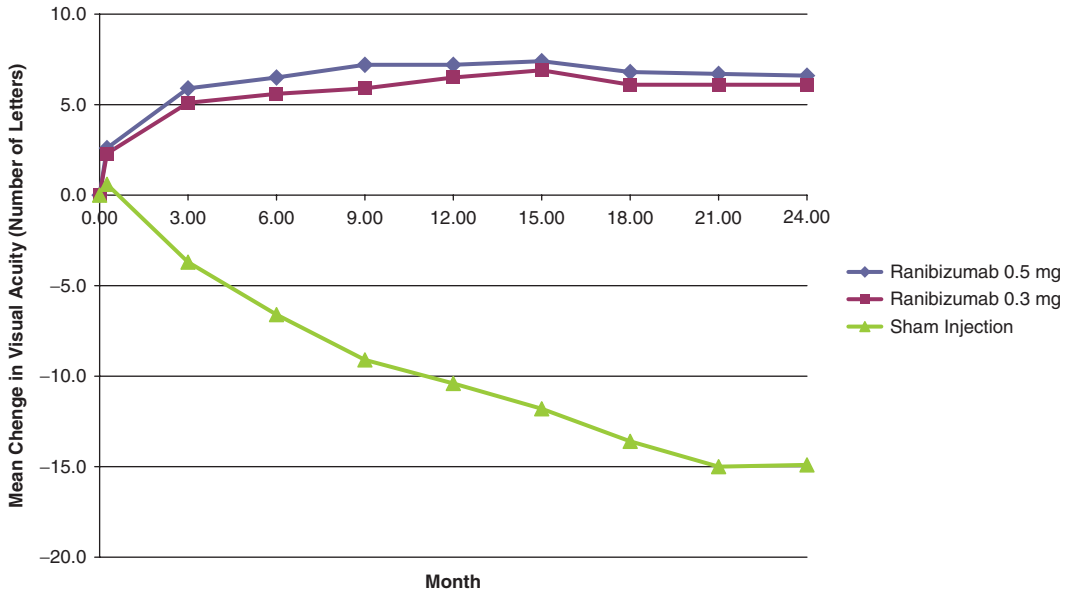


FIGURE 8B.2 Mean change in number of letters read versus month in ranibizumab 0.5 mg, ranibizumab 0.3 mg, and sham injection treatment groups of the MARINA trial. (Reproduced from Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *New Engl J Med.* 2006;355:1419–1431, with permission.)

Patients included those with and without classic CNV. The study evaluated quarterly dosing, an alternative and less frequent regimen than the monthly ranibizumab dosing tested in MARINA and ANCHOR; 184 patients were randomized to one of three treatment groups in a 1:1:1 fashion. Treatment groups included those receiving 0.3 mg ranibizumab, 0.5 mg ranibizumab, and sham injections. Patients in the ranibizumab groups received injections at day zero, month 1, and month 2 with subsequent doses every 3 months thereafter irrespective of clinical exam or findings. After 12 months of evaluation, patients in the sham injection group were allowed to "crossover" to receive 0.5 mg ranibizumab every 3 months. It was later deemed necessary to offer monthly injections with 0.5 mg ranibizumab for the duration of the 2-year study "roll over" patients.[16]

Major Inclusion Criteria

- Age ≥50 years
- Primary or recurrent subfoveal CNV due to AMD with ≥50% of the lesion composed of active CNV
- Total AMD lesion size ≤ 12 DA
- BCVA of 20/40 to 20/320 Snellen equivalent as per ETDRS charts
- Minimally classic and occult lesions were eligible if they met any of the following:
  - ≥10% increase in lesion size on FA measured ≤ 1 month versus ≤ 6 months prior to day zero
  - >1 Snellen VA line loss, or equivalent within 6 months prior to day zero
  - CNV-associated hemorrhages ≤ 1 month prior to day zero

Exclusion Criteria

- Any prior treatment with verteporfin PDT, external-beam radiation, transpupillary thermotherapy, or subfoveal laser photocoagulation
- Juxtafoveal or extrafoveal laser photocoagulation ≤ one month prior to day zero
- Permanent structural damage to the central fovea
- Subretinal hemorrhage involving the fovea if ≥1 DA or ≥50% total lesion area
- Treatment of either eye in a previous anti-angiogenic treatment trial
- PDT in the nonstudy eye ≤ 7 days prior to day zero

Primary Outcome

- Mean change in VA from baseline to 12 months

Secondary Outcomes

- Mean change in VA from baseline to 24 months
- Proportion of patients who lost <15 VA letters from baseline
- Proportion of patients who gained ≥15 VA letters from baseline
- Proportion of patients with Snellen equivalent VA of 20/200 or less
- Mean change from baseline in total area of CNV and total area of leakage from CNV

Results

All randomized patients were evaluated with an intent-to-treat analysis with last observation carried forward; 85% or more patients in the ranibizumab groups received all scheduled injections and 27% of patients in the sham group discontinued treatment prior to 12 months. The mean change in VA from baseline was –16.3 letters in the sham group versus –1.6 letters and –0.2 letters in the 0.3 mg ranibizumab and 0.5 mg ranibizumab groups, respectively ($P = 0.0001$ and $P < 0.0001$, respectively) at 12 months. VA was compared at 3 and 12 months to evaluate quarterly "maintenance" dosing. Both ranibizumab groups lost an average of –4.5 letters between month 3 and 12 with both declines considered significant as none of the 95% confidence intervals included zero.

The proportion of patients losing <15 Snellen letters was significantly lower in the ranibizumab groups versus the sham groups with 83.3% and 90.2% in the 0.3 mg and 0.5 mg groups losing < 15 letters, respectively, and 49.2% in the sham group ($P < 0.0001$ for both groups vs. sham). There was no significant difference in the proportion of patients gaining at least 15 letters versus sham. There

were significantly fewer patients in the ranibizumab groups with ≤ 20/200 Snellen VA versus sham. Both ranibizumab groups showed a significant reduction in growth of CNV and in total area of leakage from CNV.

At 24 months, mean loss from baseline VA was –21.4, –2.2, and –2.3 letters in the sham, 0.3 mg, and 0.5 mg ranibizumab groups, respectively ($P < 0.0001$ for both ranibizumab vs. sham).[16] The total area of CNV remained significantly different at 24 months with an increase in 1.9 disc areas (DA) in the sham group and 0.29 DA in the 0.3 mg group ($P = 0.0015$) and 0.64 DA in the 0.5 mg group ($P = 0.0021$).

Safety

There were no cases of endophthalmitis during the 2 years. Rates of arteriothrombotic events (ATE) were zero in all groups at 1 year. Rates of ATEs at 2 years were reported at 1.6% in the postcrossover from sham group, 1.7% in the postcrossover 0.3 mg group, and 0% in the postcrossover 0.5 mg group.

IV. A PHASE IIIB, OPEN-LABEL, MULTICENTER 12-MONTH STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF RANIBIZUMAB (0.3 MG AND/OR 0.5 MG) IN PATIENTS WITH SUBFOVEAL CHOROIDAL NEOVASCULARIZATION SECONDARY TO AGE-RELATED MACULAR DEGENERATION: THE SUSTAIN STUDY

SUSTAIN looked to evaluate PRN dosing of ranibizumab based on defined retreatment criteria including change in vision and OCT central retinal thickness (CRT).

Study Design

This was a 12-month, phase III, multicenter, open-label, single-arm study evaluating the safety and efficacy of intravitreal ranibizumab in patients with CNV secondary to AMD.[17] Patients received three monthly doses of 0.3 mg ranibizumab intravitreally followed by monthly evaluations and intravitreal injections on an as-needed basis (PRN) as defined by prespecified criteria. As-needed injections were given in the setting of VA loss of >5 letters or an increase in CRT of >100 μm. After January 2007, patients received 0.5 mg ranibizumab as opposed to 0.3 mg.

Inclusion Criteria

- Age ≥ 50 years
- Diagnosis of active primary or recurrent subfoveal CNV secondary to AMD
- Total area of CNV ≥ 50% of total lesion area
- Total lesion area ≤ 12 DA
- BCVA between 73 and 24 ETDRS letters (~20/40 to 20/320 Snellen equivalent)

Primary Outcome

- Incidence and severity of ocular AEs over 12 months

Key Secondary Outcomes

- Mean change from baseline to 3 and 12 months in BCVA and CRT
- Total treatments

Results

455 of the initial 513 enrolled patients completed 12 months of treatment; 48.5% of patients experienced at least one ocular AE, including reduced VA, retinal hemorrhage, increased intraocular pressure, and conjunctival hemorrhage[17]; 3.7% of patients experienced arterial thrombotic events, with 1% experiencing a transient ischemic attack, cerebral infarction, or cerebrovascular accident.[17] There were seven deaths during the 12 months of treatment with one death caused by an event thought to be associated with ranibizumab.[17]

Mean change in BCVA from baseline was +5.8 and +3.6 letters at months 3 and 12, respectively.[17] A steady increase in BCVA change was observed over the first 3 months with a decrease from month 3 to 6 and a stable period from month 6 to 12[17]; 96.7% and 92.5%

of patients lost <15 letters at months 3 and 12, respectively. Change in CRT was –101.1 μm at month 3 from baseline with a change of –91.5 seen at month 12 versus baseline.[17] The mean number of injections over 12 months was 5.6 when including the three initial injections.[17]

Although SUSTAIN is a single-arm, unmasked study, the authors contend that the trial is comparable to MARINA and ANCHOR in that patient CNV characteristics and study designs were similar. The authors note ~80% efficacy of PRN injections versus monthly injections when comparing treatments to controls.

V. EFFICACY AND SAFETY OF MONTHLY VERSUS QUARTERLY RANIBIZUMAB TREATMENT IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: THE EXCITE STUDY

The EXCITE study was designed to evaluate the monthly dosing regimen of ranibizumab as in the MARINA and ANCHOR trials versus quarterly dosing as performed in the PIER study.

Study Design

This was a 1-year, randomized, multicenter, active-controlled, Phase IIIb study evaluating efficacy and safety of monthly versus quarterly dosing of ranibizumab in patients with subfoveal CNV secondary to AMD.[18] Patients were randomly assigned in a 1:1:1 fashion to one of three treatment groups. Patients received either three consecutive monthly intravitreal loading doses of 0.3 mg ranibizumab (arm A) or 0.5 mg ranibizumab (arm B) followed by quarterly dosing (every three months) or 0.3 mg ranibizumab monthly for the duration of the study (arm C). Patients in arm A and B received sham injections monthly when not receiving ranibizumab to maintain masking.

Inclusion Criteria

- Age ≥ 50 years
- Total area of CNV ≥ 50% of total lesion area
- Total lesion area ≤12 DA for minimally classic or occult with no classic, or ≤ 9 DA for predominantly classic lesions
- BCVA between 73 and 24 letters (approximately 20/40 to 20/320 Snellen equivalent)

Primary Outcome

- Mean change in BCVA from baseline to month 12

Results

353 of 482 screened patients were randomized to one of the three treatment arms. Mean BCVA increased from baseline +4.9, +3.8, and +8.3 letters in the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly groups, respectively, at 12 months in the per-protocol analysis.[18] Mean BCVA increase in this analysis over the first 3 months was +6.8, +6.6, and +7.5 letters in the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly groups respectively with quarterly groups subsequently losing acuity after the baseline monthly loading doses.[18] The intent-to-treat analysis showed similar results as the per-protocol analysis. Both analyses show an initial and similar increase in VA over the first 3 months (with monthly dosing in all arms) with subsequent decreases in mean BCVA in the quarterly arms versus monthly arm at 12 months. Noninferiority could not be shown for the quarterly versus monthly treatment arms.[18]

VI. THE PHASE III, DOUBLE-MASKED, MULTICENTER, RANDOMIZED, ACTIVE TREATMENT-CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF 0.5 MG AND 2.0 MG RANIBIZUMAB ADMINISTERED MONTHLY OR ON AN AS-NEEDED BASIS (PRN) IN PATIENTS WITH SUBFOVEAL NEOVASCULAR AGE-RELATED DEGENERATION: THE HARBOR STUDY

The HARBOR study set out to evaluate a higher dose of ranibizumab in a monthly and

a PRN dosing regimen versus the standard dose in patients with wet AMD.

Study Design

This was a 24-month, Phase III, randomized, multicenter, double-masked, active treatment-controlled study evaluating the safety and efficacy of 0.5 mg and 2 mg dosing of intravitreal ranibizumab for CNV secondary to AMD[19]; 1,098 patients were randomly assigned in a 1:1:1:1 fashion to one of four treatment groups. Patients received either 0.5 mg ranibizumab monthly, 0.5 mg ranibizumab on an as-needed basis following 3 initial monthly doses, 2 mg ranibizumab monthly, or 2 mg ranibizumab as-needed following 3 initial monthly doses. Patients in the as-needed groups were evaluated for retreatment and treated if there was a ≥5 letters decrease in ETDRS BCVA or any "evidence of disease activity" on spectral-domain OCT.

Inclusion Criteria

- ETDRS BCVA of 20/40 to 20/320 (Snellen equivalent)
- Active subfoveal CNV with total lesion size <12 DAs

Exclusion Criteria

- History of vitrectomy in the study eye
- Prior treatment for neovascular AMD in the study eye

Primary Outcome

- Mean change in BCVA from baseline to 12 months

Key Secondary Outcomes

- Proportion of patients gaining ≥15 letters BCVA
- Mean number of ranibizumab injections
- Mean change from baseline in central foveal thickness
- Ocular and systemic side effects

Results

Mean change from baseline in BCVA was evaluated for all groups in a noninferiority comparison. The mean change in vision at month 12 for the 0.5 mg monthly group was +10.1 letters with +8.2 letters, +9.2 letters, and +8.6 letters gained in the 0.5 mg PRN, 2 mg monthly, and 2 mg PRN groups, respectively.[19] Comparison of the mean change in BCVA was evaluated for each group versus 0.5 mg monthly ranibizumab to evaluate for noninferiority. The margin of noninferiority was set at four letters. Noninferiority criteria were not met for the 0.5 mg PRN or the 2 mg PRN groups, nor was superiority criterion met for comparison of 0.5 mg monthly versus 2 mg monthly dosing.[19]

The proportion of patients gaining ≥15 letters was similar among all groups. The mean number of injections was 11.3 and 11.2 in the 0.5 mg monthly and 2 mg monthly groups, respectively.[19] The 0.5 mg PRN group had a mean of 7.7 injections with the 2 mg group having a mean of 6.9 injections.[19] Structural changes as per OCT were also reported as similar among all four groups.

Serious ocular AEs were similar across all groups. There were two cases of endophthalmitis in the 0.5 mg monthly group and one case of iridocyclitis and one retinal tear in the 2 mg monthly group, representing all reported ocular events.[19] Arterial thrombotic events were similar across all four groups, with the highest rate found in the 0.5 mg monthly group at 4.7%.[19]

At the time of writing, the results of the HARBOR trial are yet to be published in a peer-reviewed journal.

Figure 8B.3 shows the cumulative data from the above ranibizumab studies as well as the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) study showing mean change in VA for a particular dosing regimen.

VII. CATT

While ranibizumab was studied in clinical trials, clinicians began using the less expensive anti-VEGF agent, bevacizumab. The CATT study set out to evaluate ranibizumab versus bevacizumab with respect to visual outcomes.

With a large patient population, the CATT study was able to evaluate monthly and PRN dosing regimen for both medications. AE trends were also evaluated.

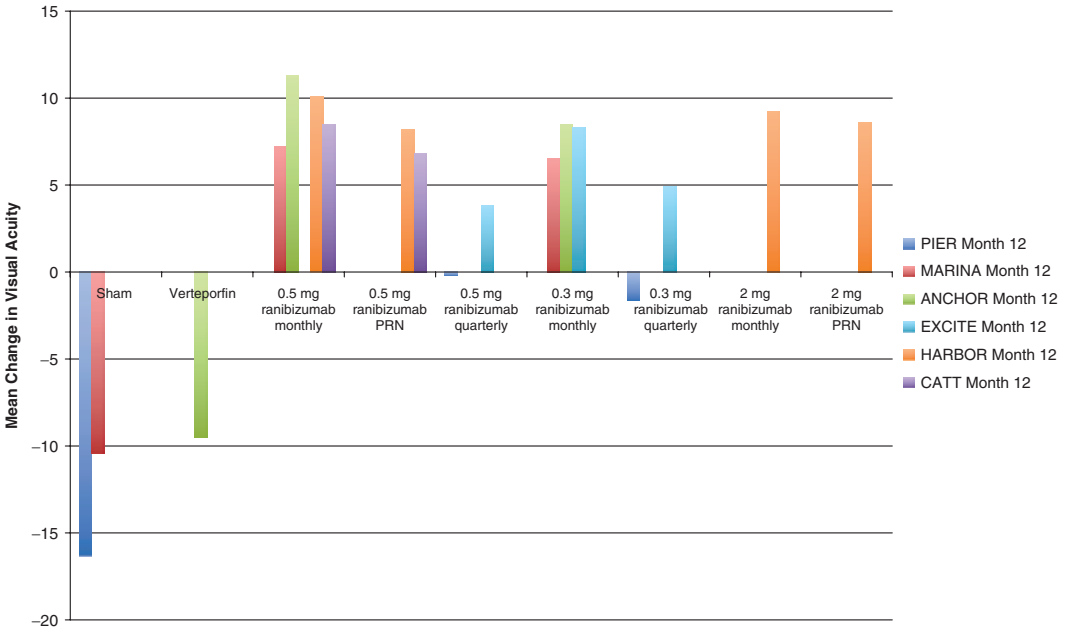


FIGURE 8B.3 Compilation of mean visual acuity changes from major ranibizumab trials.

Study Design

In the CATT trial,[20] 1,208 patients from 44 centers were randomly assigned to one of four treatment groups. Patients were treated with intravitreal injections of ranibizumab every 28 days, bevacizumab every 28 days, ranibizumab as needed (with "signs of active neovascularization"), and bevacizumab as needed. Patients received either 0.5 mg (0.05 ml) ranibizumab or 1.25 mg (0.05 ml) bevacizumab depending on their group. Patients were examined every 28 days, with the as-needed groups receiving time-domain OCT to evaluate macular thickness and for evidence of leakage, which would necessitate a reinjection. All patients in the as-needed group were dosed depending on evidence of "active neovascularization," using OCT, VA, fluorescein angiogram, and the presence of new or persistent hemorrhage as markers of active disease.

Major Inclusion Criteria

- Age ≥ 50 years
- One eye of untreated and active CNV
  - leakage seen on fluorescein angiogram, and
  - fluid seen on time-domain OCT within the retina or below the retinal pigment epithelium
- Vision of 20/30 to 20/320 as per electronic ETDRS testing

Primary Outcome

- Mean change in VA as measured by the ETDRS chart between baseline and 1 year

Secondary Outcomes

- Proportion of patients with <15 letters decrease in vision
- Number of injections
- Change in fluid and foveal thickness as measured by OCT
- Change in lesion size on FA
  - Ocular and systemic side effects
  - Annual drug cost

Results

1,185 of enrolled patients were included in the analysis. Greater than 90% of patients in each

group completed the study with approximately equal numbers of patients within each group.

All four study groups showed visual improvement at 1 year with the largest visual gains made within the first 6 months. The mean (±SE) change in BCVA from baseline at month 12 was +8.5±0.8, +8.0±10., +6.8±0.8, and +5.9±1.0 in the ranibizumab monthly, bevacizumab monthly, ranibizumab PRN, and bevacizumab PRN groups, respectively (Fig. 8B.4).[20] If the difference in mean VA change between two groups lay between plus and minus 5 letters with 99.2% confidence intervals, the groups were said to be noninferior or equivalent.[20] Comparisons between bevacizumab monthly and ranibizumab monthly and bevacizumab as needed and ranibizumab as needed showed equivalence.[20] Equivalence was also seen in comparison of ranibizumab as needed with ranibizumab monthly and ranibizumab as needed with bevacizumab monthly. Neither bevacizumab as needed compared to bevacizumab monthly or ranibizumab monthly and bevacizumab as needed showed equivalence as defined above.

One-year outcomes showed loss of less than 15 letters in 94.4% and 94.0% of the ranibizumab and bevacizumab monthly groups, respectively.[20] The ranibizumab as-needed group showed less than 15 letter loss in 95.4% and bevacizumab as-needed group had less than 15 letter loss in 91.5%.[20] There was no significant difference in these values per chi-squared testing with $P = 0.29$. Ranibizumab as-needed patients received significantly fewer treatments than the bevacizumab as-needed group (6.9 ± 3.0 vs. 7.7±3.5, respectively $P = 0.003$).[20]

Quantitative measurements using OCT showed a significantly greater decrease in macular thickness from baseline in the ranibizumab groups versus the bevacizumab groups (196±176 μm vs. 152±178 μm, respectively with $P = 0.03$).[20]

Safety

There was no significant difference in death rates between the two groups. There were, however, significantly more serious AEs in the bevacizumab group versus the ranibizumab

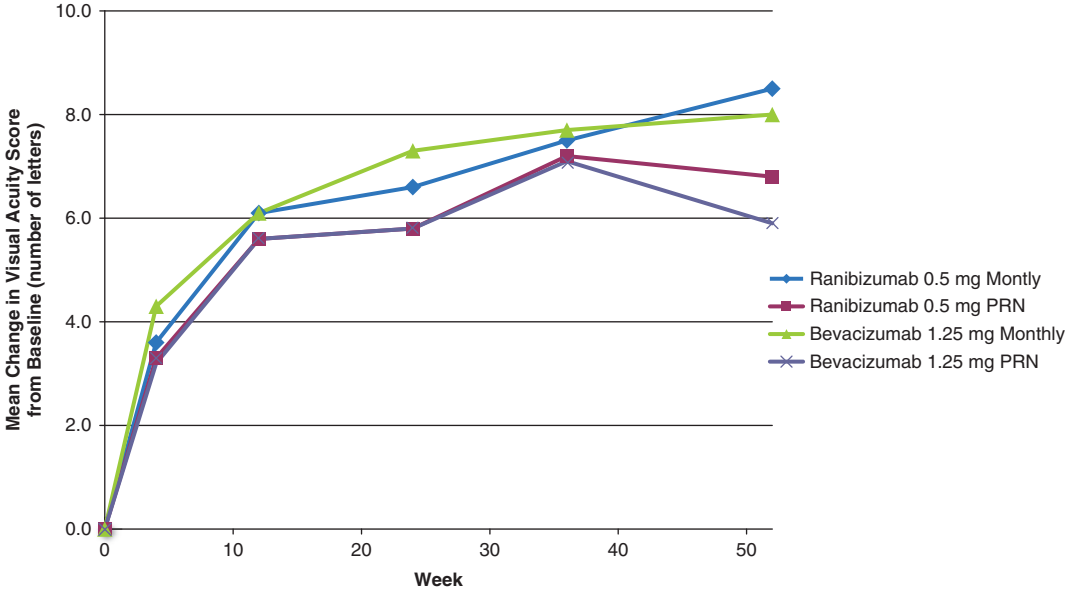


FIGURE 8B.4 Mean change in visual acuity score from baseline versus week of the CATT trial. (Reproduced from The CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364(20):1897–1908, with permission.)

group but with insufficient statistical power to adequately evaluate.[20] There were no significant differences in rates of arteriothrombotic or venous thrombotic events when the two medications were compared head to head.

VIII. CATT: TWO-YEAR RESULTS

Study Design

This study presented 2-year data from the original CATT study after completing its 1-year primary outcome. As described in the initial CATT study,[21] patients came into the second year of the study in one of the four treatment groups: ranibizumab monthly, ranibizumab as needed, bevacizumab monthly, or bevacizumab as needed. A second round of randomization was performed on the ranibizumab monthly and bevacizumab monthly treatment groups. Patients in these two groups were randomly assigned to continue with their initial treatment medication monthly or change to an as-needed treatment protocol with the same medication at 1 year (Fig. 8B.5). After randomization was completed at 1 year, patients were treated exactly as in the first year of study—dosing was held constant within groups and treatment decisions within the as-needed groups were not changed.

Inclusion Criteria

- Patients initially included and evaluated in the CATT study

Key Outcomes

- Mean change in VA
- Proportion of patients with <15 letters decrease in vision
- Number of injections
- Annual drug cost
- Presence and change in fluid and foveal thickness as measured by OCT
- Change in lesion size on FA
- Ocular and systemic side effects

Results

Statistical analysis was performed using an intent-to-treat analysis. The safety analysis was performed on all 1,185 patients previously evaluated in the first year, whereas only the 1,107 patients with a clinical visit within the second year were evaluated in the efficacy analysis. VA data was available for 93.0% of patients at the end of the 2-year study with an approximately equal and 3% to 5% rate of missed visits among the six treatment groups.

Patients who remained within a treatment regimen for the full 2 years were

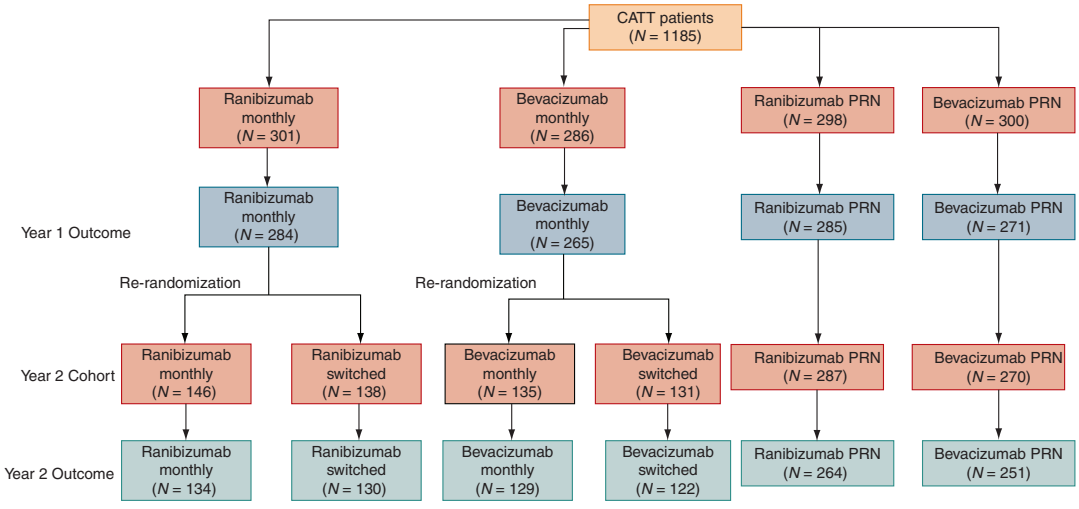


FIGURE 8B.5 CATT randomization scheme for year one and two (Modified from The CATT Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: Two-year results. *Ophthalmology*. 2012;119(7):1388–1398.)

compared after 2 years by drug (ranibizumab vs. bevacizumab) and by treatment regimen (i.e. bevacizumab plus ranibizumab monthly vs. bevacizumab plus ranibizumab as needed) for outcomes. Mean gains in VA in the patients remaining in their previous treatment regimen were +7.8, +8.8, +5.0, and +6.7 in the bevacizumab monthly, ranibizumab monthly, bevacizumab as-needed, and ranibizumab as-needed arms, respectively.[21] Interdrug comparison of mean change in VA showed no significant difference, whereas interregimen comparison did show significance (P = 0.21 and P = 0.046, respectively) with monthly better than as needed.[21]

There was no significant difference in patients losing less than 15 letters or more. There was a significant difference in number of injections given in the as-needed groups with ranibizumab as needed requiring 12.6±6.6 and bevacizumab as needed requiring 14.1±7.0 (P = 0.01).[21] Cost of the injections over the 2 years ranged from $705 for bevacizumab as needed to $44,800 for ranibizumab monthly.[21] Significant differences were also found in retinal thickness measurement on OCT with 29μm less in the monthly treatment groups versus as needed (P = 0.005).[21] The proportion of patients without fluid on OCT was significantly higher for the ranibizumab group versus bevacizumab (P = 0.0003).[21] The monthly regimens also had significantly higher proportion without fluid when compared to the as-needed groups (P < 0.0001).[21]

Patients who were reassigned randomly from the monthly group to an as-needed group were shown to have a significant decrease in mean VA with the ranibizumab group losing 1.8 letters and the bevacizumab group losing 3.6 letters from month 12 to 24 (P = 0.03).[21] For patients switching from monthly to as needed at month 12, VA at 24 months dropped toward similar acuities as those that were initially on an as-needed regimen (Fig. 8B.6). There was no significant change in the number of injections needed in the switched regimen patients. There was a small, however significant increase in the mean total retinal thickness in the as-needed groups versus monthly groups.[21]

Safety

Comparison in rates of death, arteriothrombotic events, and venous thrombotic events

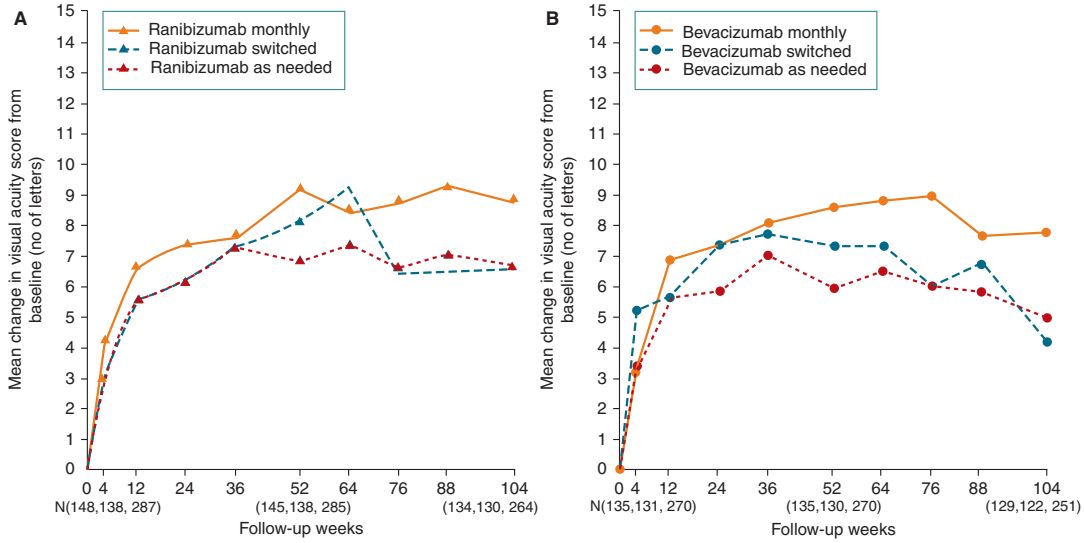


FIGURE 8B.6 The mean change in visual acuity from enrollment over time by dosing regimen within drug group: **(A)** ranibizumab and **(B)** bevacizumab. (Reproduced from The CATT Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: Two-year results. *Ophthalmology*. 2012;119(7):1388–1398, with permission.)

showed no significant differences between the drugs. However, there were a significantly greater proportion of patients in the bevacizumab-treated groups with one or more serious systemic AEs versus the ranibizumab-treated groups (bevacizumab 39.9% vs. ranibizumab 31.7%, $P = 0.004$).[21] Controlling for underlying illness, treatment with bevacizumab was found to be a significant risk factor for systemic side effects over 2 years (risk ratio 1.30 with 95% CI 1.07–1.57, $P = 0.009$).[21] These systemic events included side effects previously associated with anti-VEGF agents, namely, arteriothrombotic events, systemic hemorrhage, congestive heart failure, venous thrombotic events, hypertension, and vascular death. Gastrointestinal disorders, including hemorrhage, hernia, nausea, and vomiting, were significantly increased in patient groups receiving bevacizumab. There was no significant difference in rates of endophthalmitis or ocular AEs.

IX. IVAN

Similar to the CATT study, the IVAN study evaluated bevacizumab versus ranibizumab with respect to efficacy and safety. IVAN set out to evaluate other characteristics, including serum VEGF levels in an effort to evaluate the systemic implications of intravitreal anti-VEGF therapy.

Study Design

This is a 2-year randomized, noninferiority trial evaluating intravitreal injections of bevacizumab and ranibizumab in continuous and discontinuous regimens.[22] Patients with untreated neovascular age-related macular degeneration (nAMD) were randomly assigned to one of four groups receiving either 1.25 mg bevacizumab or 0.5 mg ranibizumab in either a continuous or discontinuous fashion. Masking was to medication and not to regimen. All patients were treated at their first three visits and were required to return for clinical visits every 28 to 35 days with OCT and fundus photography. Continuous treatment groups underwent monthly intravitreal injections where discontinuous therapy consisted of treatment only when clinical and OCT measurement criteria were met. Treatment criteria included subretinal fluid, increasing intraretinal fluid, or any new bleeding. Other treatment criteria included VA drop of greater than 10 letters or an increase of fluorescein leakage greater than 25%. Initiation of treatment in the discontinuous regimen necessitated a minimum of 3 monthly injections prior to reevaluation of treatment criteria.

Major Inclusion Criteria

- Age ≥ 50 years
- Previously untreated nAMD
- BCVA ≥ 25 letters on ETDRS chart
- FA evidence of nAMD
- Either subfoveal neovascularization, or
- Subretinal or serous pigment epithelial detachment component within 200 μm of the fovea

Exclusion Criteria

- Lesions with >50% area of fibrosis or blood

Primary Outcome

- BCVA as measured by ETDRS letters

Key Secondary Outcomes

- Adverse effects
- Cost of treatment
- Characteristics and measurements from FA and OCT
- Serum VEGF levels

Results

The primary endpoint of this study is at 2 years with preliminary outcomes published at 1 year. Data was evaluated with an intent-to-treat analysis; 628 patients were randomized to one of four treatment groups with 610 receiving at least one treatment.[22] At 1 year, mean visual acuities were similar across drugs and regimens with bevacizumab at 66.1 and ranibizumab at 69.0 letters and continuous treatment at 66.8 and discontinuous treatment at 68.4 letters.[22] The statistical

comparison between drugs was inconclusive (using a predefined 3.5 letter noninferiority limit), with a difference of mean visual acuities of just 1.99 letters (bevacizumab minus ranibizumab, 95% CI of –4.04 to 0.06).[22] No statistical significance was seen when comparing drug regimens with a difference of –0.35 letters (discontinuous minus continuous, 95% CI of –2.40 to 1.70).[22]

At 1 year, mean foveal retinal thickness as defined by time-domain OCT was significantly less in the continuous regimen versus discontinuous regimen (geometric means ratio [GMR] 0.91; CI, 0.86 to 0.97; $P = 0.005$).[22] No significance was seen when comparing retinal thickness between drugs. The continuous treatment showed significantly less leakage on FA versus discontinuous with 24% and 36%, respectively ($P = 0.002$) with no significance between drugs.[22]

All groups showed lower systemic VEGF levels at 1 year compared to baseline. Systemic VEGF levels were significantly lower in the bevacizumab group versus ranibizumab with levels of 83 pg/ml and 151 pg/ml respectively (GMR 0.47; 95% CI, 0.41 to 0.54) and significantly higher in the discontinuous versus continuous regimen (GMR 1.23; 95% CI 1.07 to 1.42).[22]

Cost analysis at 1 year showed significantly higher costs for ranibizumab versus bevacizumab ($P < 0.0001$) with continuous ranibizumab being the most expensive regimen followed by the ranibizumab discontinuous regimen.[22] Mean cost over the first year for continuous ranibizumab was £9,656, £6,398 for discontinuous ranibizumab, £1,654 for continuous bevacizumab, and £1,509 for discontinuous bevacizumab.[22] There was no significant difference between continuous versus discontinuous bevacizumab.

Safety

There was no significant difference in death rates comparing drug regimen or when comparing dosing regimen. There were fewer arteriothrombotic events or heart failure in the bevacizumab group versus ranibizumab (OR, 0.23; 95% CI 0.05 to 1.07; $P = 0.03$).[22] There was no significance in the rate of arteriothrombotic events or heart failure when comparing regimens. One or more serious systemic side effects occurred in 9.6% of the ranibizumab group members, 12.5% of the bevacizumab group, 9.7% of the continuous regimen, and 12.3% of the discontinuous regimen.[22] No significant difference was observed when comparing serious systemic side effects between drug given and between drug regimens.

X. VEGF TRAP-EYE: INVESTIGATION OF EFFICACY AND SAFETY IN WET AMD (VIEW 1, VIEW 2) OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: THE VIEW STUDY

Aflibercept is an FDA-approved, recombinant fusion protein comprised of key binding domains of the human VEGF 1 and 2 receptor extracellular domains fused to the Fc portion of the human IgG1 protein, formulated for intravitreal injection. Aflibercept binds all isoforms of VEGF-A, B, and placental growth factor (PGF).[23] It has a higher VEGF-binding affinity than ranibizumab or bevacizumab[24] and can theoretically maintain significant biologic activity in the vitreous 10 to 12 weeks after intravitreal injection.[25] The potential to decrease the intravitreal injection burden on patients with AMD by using a medication with longer therapeutic duration in the vitreous was the idea behind the pivotal VIEW 1 and VIEW 2 trials.

Study Design

VIEW 1 and VIEW 2 trials were parallel, Phase III, double-masked, randomized, multicentered, active controlled studies analyzing the safety and efficacy of intravitreal injections of aflibercept and ranibizumab for wet AMD. The VIEW 1 study took place in the United States and Canada and VIEW 2 in 26 countries throughout Europe, Asia, South America, and the Middle East[26]; 1,217 patients in VIEW 1[26] and 1,240 patients in VIEW 2[26] with new CNV secondary to AMD

were randomized in a 1:1:1:1 fashion to one of four dosing regimens. During the first year, patients received either 2 mg aflibercept every 4 weeks (2Q4), 0.5 mg aflibercept every 4 weeks (0.5Q4), 2 mg aflibercept every 8 weeks with a sham injection on visits between injections after 3 initial monthly doses (2Q8), or 0.5 mg ranibizumab every 4 weeks (RQ4). In the second year, no sham injections were given with patients receiving injections as frequently as every 4 weeks but at least every 12 weeks and according to prespecified as-needed dosing criteria. Dosing criteria in the second year of the study included

- Increase in CRT ≥ 100 μm as measured by OCT
- Loss of ≥ 5 ETDRS letters from previous visit with recurrent fluid on OCT
- New or persistent fluid on OCT
- New onset classic CNV
- New or persistent leak on FA
- New macular hemorrhage
- 12 weeks since previous injection

Inclusion Criteria

- Age ≥ 50 years
- Active subfoveal CNV secondary to AMD including juxtafoveal lesions affecting the fovea as per FA
- CNV at least 50% total lesion size
- ETDRS BCVA between 73 and 25 letters (~20/40 to 20/320 Snellen equivalent) in the study eye

Exclusion criteria

Key exclusion criteria included:

- Prior ocular or systemic treatment or surgery of nAMD, excluding vitamins or supplements
- Any prior or current investigational therapy to treat nAMD in the study eye
- Prior treatment with anti-VEGF agents in the study eye, prior treatment in the nonstudy eye less than 3 months prior to first study dose, prior systemic anti-VEGF treatment less than 3 months prior to first study dose
- Total lesion size >12 DA
- Subretinal hemorrhage >50% of total lesion size, or blood under the fovea 1 or more DAs in size
- Scar or fibrosis of >50% total lesion size
- Vitreous hemorrhage <4 weeks prior to first visit of study
- Presence of any other cause of CNV

Primary Outcome

- Noninferiority of intravitreal aflibercept regimens to ranibizumab as measured by proportion of patients maintaining vision at week 52 defined as losing less than 15 ETDRS letters from baseline

Secondary Outcomes

Key secondary outcomes include:

- Change in BCVA from baseline at week 52 as measured by ETDRS
- Number of injections over 52 weeks
- Anatomic findings on OCT

Results

The noninferiority margin of the primary outcome was set at 10% for the percent of patients losing less than 15 ETDRS letters at week 52 in the aflibercept groups compared with the monthly ranibizumab group.[26] Noninferiority was established for all groups in both VIEW 1 and VIEW 2 with 95.1 % of patients in the 2Q4 group, 95.0% of patients in the 0.5Q4, and 94.4% of patients in the 2Q8 group maintaining vision at week 52 versus 93.8% of patients in the RQ4 group. No groups were found to be superior to ranibizumab.[26] VIEW 1 showed a slightly higher mean change of BCVA at week 52 in the 2Q4 group versus RQ4 with +10.9 letters gained versus +8.1 letters gained, respectively.[26] This difference was not seen in any of the VIEW 2 groups. In both VIEW 1 and VIEW 2, patients received fewer overall injections in the 2Q8 groups versus RQ4 group; 2Q8 patients received an average of 7.5 and 7.7 injections (excluding sham injections) in VIEW 1 and 2, respectively, versus 12.1 and 12.7 injections in the respective RQ4 groups.[26] Similar reductions of CRT as measured by OCT were seen among all groups.

Safety

There were no significant safety concerns in the aflibercept groups with a similar safety profile to ranibizumab. Fewer patients in the ranibizumab group were found to have elevated intraocular pressure than in the aflibercept groups of VIEW 1 and 2. The incidence of systemic AEs, serious systemic AEs, specific arterial thromboembolic events as per the Anti-Platelet Trialists' Collaboration, and death were similar between the two medications.[26]

Combination Therapies

The DENALI and MONT BLANC studies set out to evaluate the use of combination therapy with PDT and ranibizumab versus ranibizumab alone in the treatment of CNV due to AMD.

XI. THE DENALI STUDY

The DENALI study set out to evaluate the efficacy and safety of ranibizumab and PDT combination versus ranibizumab monotherapy in the treatment of CNV due to AMD.

Study Design

This was a randomized, 12-month, Phase IIIb, prospective, multicenter, double-masked trial evaluating the safety and efficacy of 0.5 mg ranibizumab monotherapy versus verteporfin PDT combined with ranibizumab 0.5 mg for CNV secondary to AMD[27]; 321 patients were randomized in a 1:1:1 fashion to one of three treatment groups. Patients received either 0.5 mg ranibizumab in the monotherapy group, standard fluence (SF) verteporfin PDT (600 mW/cm^2) with ranibizumab, and reduced fluence (RF) verteporfin PDT (300 mW/cm^2) with ranibizumab. The monotherapy group received intravitreal injections on day 1 and monthly thereafter for 11 months along with sham verteporfin PDT. The verteporfin PDT combination groups received PDT on day 1 and then PRN for month 3 through 11 with at least 90 days between administrations along with ranibizumab at day 1, months 1 and 2, and PRN for months 3 through 11 with a 30-day interval. A treatment algorithm was devised for the combination groups. OCT and fluorescein angiogram were used in the algorithm to dictate treatment (Fig. 8B.7).

Inclusion Criteria

- Age ≥ 50 years
- Subfoveal CNV secondary to neovascular AMD
- BCVA between 73 and 24 letters (~20/40 to 20/320 Snellen equivalent)
- Maximum linear dimension of total lesion no greater than 5,400 μm
- Total CNV lesion area greater than 50% of total lesion area

Exclusion Criteria

- Any prior treatment for neovascular AMD in the study eye
- Uncontrolled glaucoma, angioid streaks, presumed ocular histoplasmosis syndrome, pathologic myopia, CNV secondary to causes other than neovascular AMD
- Fibrosis, pigment epithelial detachments, hemorrhage, or other hypofluorescent lesion obscuring >50% of the CNV lesion
- Retinal pigment epithelial tear

Primary Outcomes

- Mean change in BCVA (ETDRS) from baseline to month 12
- Proportion of patients in the combination groups with a ranibizumab treatment-free interval ≥ 3 months after month 2

Key Secondary Outcomes

- Time to first PRN ranibizumab treatment
- Number of ranibizumab and PDT treatments
- Effect of combination therapy versus monotherapy with respect to FA and OCT variables
- Ocular and systemic side effects

Results

Efficacy analysis was performed at month 12 using last observation carried forward; 89.1% of patients completed the 12-month study. At month 12, the mean change ± SD in BCVA was

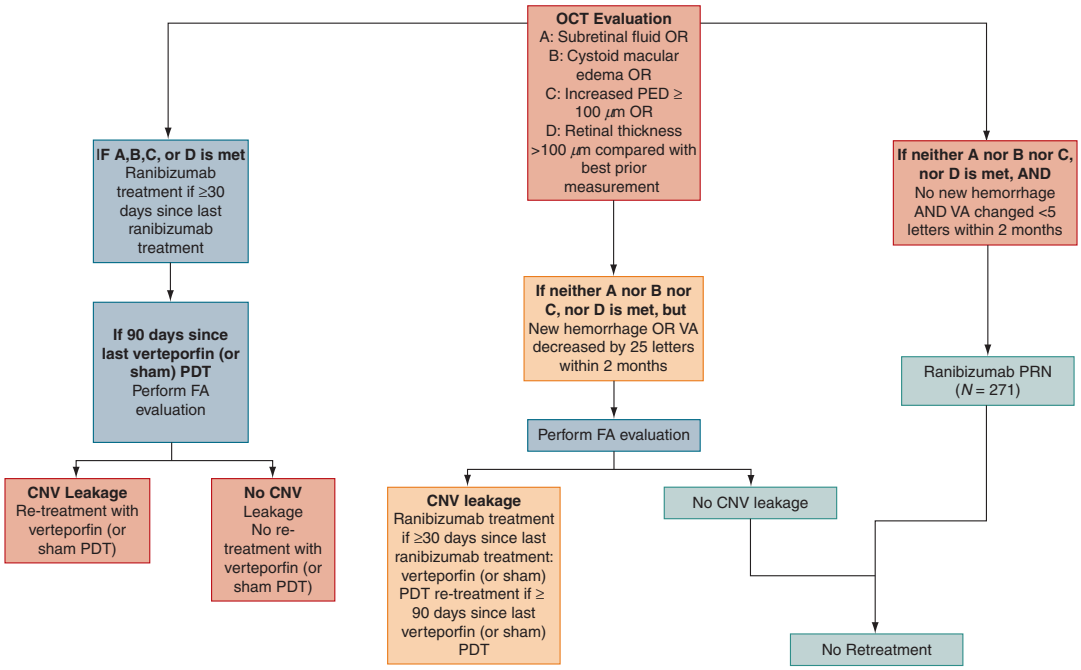


FIGURE 8B.7 The retreatment algorithm for the DENALI study group (Reproduced from Kaiser PK, Boyer DS, Cruess AF, et al. Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: Twelve-month results of the DENALI study. *Ophthalmology*. 2012;119(5): 1001–1010, with permission).

+8.1 ± 15.1 letters in the monotherapy group versus +5.3±15.7 letters and +4.4±15.5 letters in the SF and RF combination groups, respectively.[27] Comparison of the combination groups versus ranibizumab monotherapy did not meet noninferiority criteria of less than 7 letters difference ($P = 0.0666$ and $P = 0.1178$ for the verteporfin SF vs. ranibizumab and verteporfin RF vs. ranibizumab, respectively).[27] There was no significant difference in patients with a ranibizumab-free treatment period of >3 months when comparing the two combination groups. The mean number of ranibizumab retreatments after the initial three injections were 2.2 and 2.8 in the verteporfin SF and RF combination groups, respectively versus 7.6 in the monotherapy group.[27] There were 1.9 verteporfin treatments in the combination groups versus 1.5 sham PDT treatments in the monotherapy group.[27]

The monotherapy group had the largest decrease in CRT of all three groups. There was a significant decrease in the monotherapy versus verteporfin RF combination group with respect to CRT ($P = 0.050$).[27] There was significantly less leakage on FA in the monotherapy group versus the verteporfin SF combination group and no significant difference when comparing the monotherapy versus verteporfin RF group based on FA leakage.[27]

Safety

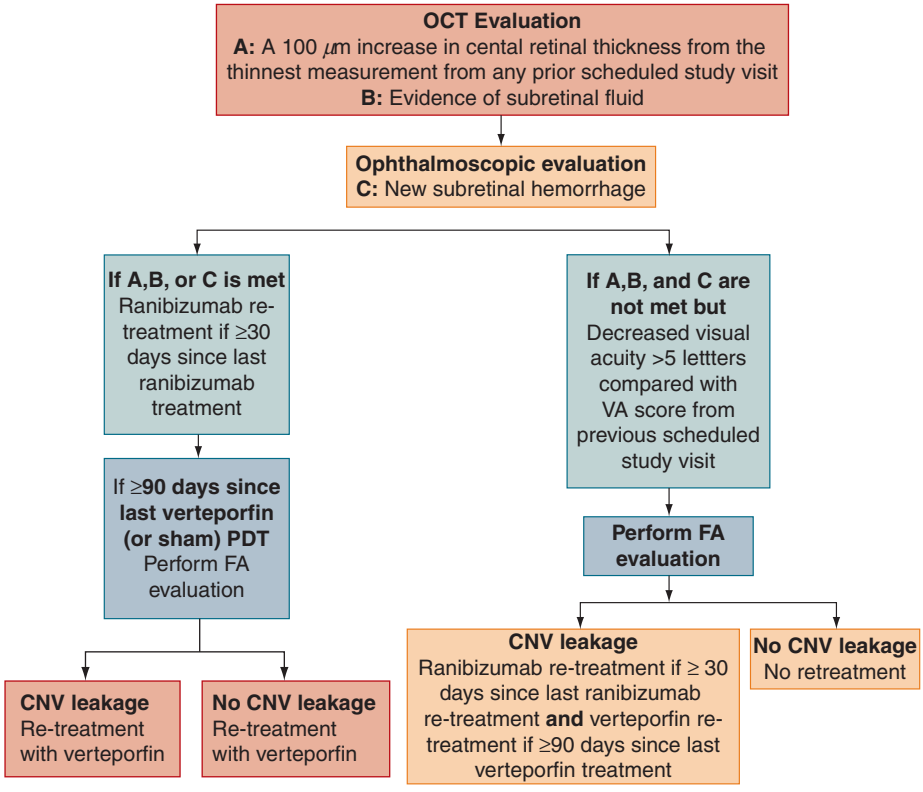
Safety profiles were similar among all groups.[27] Serious ocular events were seen in 3.8% and 0.9% of patients in the verteporfin SF and RF combination groups, respectively, versus 2.7% in the ranibizumab monotherapy group.[27] There were three cases of endophthalmitis, two in the monotherapy group and one in the verteporfin SF combination group.[27] Arterial thrombotic events were seen in 2.9% and 4.7% of patients in the verteporfin SF and RF combination groups, respectively, and in 6.3% of patients in the ranibizumab monotherapy group.

XII. VERTEPORFIN PLUS RANIBIZUMAB FOR CHOROIDAL NEOVASCULARIZATION IN AGE-RELATED MACULAR DEGENERATION: THE MONT BLANC STUDY

The MONT BLANC study set out to evaluate standard fluence verteporfin PDT combined with ranibizumab versus ranibizumab monotherapy to treat subfoveal CNV due to AMD in a European population.

Study Design

This was a multicenter, double-masked, randomized, active-controlled, phase II study evaluating the safety and efficacy of standard fluence verteporfin PDT combined with ranibizumab versus ranibizumab monotherapy[28]; 255 patients were randomized in a 1:1 ratio to either standard fluence verteporfin PDT (6 mg/m^2) combined with PRN 0.5 mg ranibizumab—the combination group—or to the PRN 0.5 mg ranibizumab group with sham PDT (5% dextrose infusion), the monotherapy group. The combination group received standard fluence verteporfin PDT and 0.5 mg ranibizumab intravitreal injection on day 1 with two subsequent ranibizumab injections at month 1 and 2. PDT and ranibizumab injections were then given on a PRN basis based on predetermined criteria at 90 and 30 day intervals, respectively (Fig. 8B.8). Retreatment criteria included CRT increase of ≥ 100 μm from



VA, visual acuity; FA, Fluorescein angiography; CNV, choroidal neovascularization

FIGURE 8B.8 The retreatment algorithm for the MONT BLANC study group. (Reproduced from Larsen M, Schmidt-Erfurth U, Lanzetta P, et al. Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: Twelve-month MONT BLANC study results. *Ophthalmology*. 2012;119(5):992–1000, with permission.)

the lowest previous value, presence of subretinal fluid or hemorrhage, BCVA decrease of >5 letters, and leakage on FA.

Inclusion Criteria

- Age ≥ 50 years
- Subfoveal CNV secondary to neovascular AMD
- BCVA between 73 and 24 letters (~20/40 to 20/320 Snellen equivalent)
- Maximum linear dimension of total lesion no greater than 5,400 μm
- Total CNV lesion area greater than 50% of total lesion area

Exclusion Criteria

- Any prior treatment for neovascular AMD in the study eye
- Uncontrolled glaucoma, angioid streaks, presumed ocular histoplasmosis syndrome, pathologic myopia, CNV secondary to causes other than neovascular AMD
- Fibrosis, pigment epithelial detachments, hemorrhage, or other hypofluorescent lesion obscuring >50% of the CNV lesion
- Retinal pigment epithelial tear

Primary Outcomes

- Mean change in BCVA (ETDRS) from baseline to month 12
- Proportion of patients in the combination groups with a ranibizumab treatment-free interval ≥ 3 months after month 2

Secondary Outcomes

- Number of ranibizumab injections after month 2
- Time to first ranibizumab injection after month 2
- Efficacy based on OCT and FA characteristics from baseline to month 12
- Ocular and systemic side effects

Results

Efficacy analysis was performed at month 12 using last observation carried forward; 94% of patients completed the 12-month study. The mean change in BCVA was +2.5 letters and +4.4 letters in the combination group and monotherapy group, respectively.[28] The confidence interval of the mean ± SE of the difference between the combination and monotherapy group at month 12 did not include a 7-letter difference and noninferiority was therefore reached[28]; 96% of patients in the combination group and 92% of patients in the monotherapy group had a treatment-free interval of ≥ 3 months after month 2,[28] which showed no significant difference. There was no significant difference in the number of ranibizumab injections with a mean of 4.8 and 5.1 injections in the combination and monotherapy groups, respectively.[28] The median time to the first ranibizumab retreatment after month 2 was 34 days later in the combination group versus the monotherapy group.[28]

There was no significant difference in the CRT between the two groups with a mean ± SE of –115.3±9.04 and –107.7±11.02 μm in the combination and monotherapy group, respectively.[28] The difference in CRT was not significant between the groups.

Safety

The rates of AEs between the two groups were similar.[28] There were no reports of endophthalmitis or uveitis in either group.[28] There were two patients in the combination group with serious ocular AEs and three patients in the monotherapy group.[28] AEs potentially related to systemic anti-VEGF therapy were comparable between the groups as well, with hypertension as the most common—8.2% in the combination group and 6% of the monotherapy group.[28] Arterial thrombotic events were uncommon in both groups with seven cases in the combination group and eight patients in the monotherapy group.[28]

XIII. CONCLUSIONS

Over the past 15 years, management of AMD has shifted from focal laser photocoagulation to ocular PDT and now to anti-VEGF injections. The current debate surrounds what is

the best treatment regimen for anti-VEGF agents—fixed dosing versus as-needed or PRN versus other more proactive regimens—and what is the best anti-VEGF agent in terms of safety and efficacy. Recent studies have proven the superiority of fixed dosing regimens; however, this comes at a cost to society as well as a burden to patients and caregivers. Nonetheless, the visual results are the best. When delivered using a fixed dosing schedule, the current anti-VEGF agents have similar visual efficacy. The winner in this case would be aflibercept since the fixed dosing schedule is every 2 months after a loading dose, compared to monthly ranibizumab and bevacizumab. Other comparison trials have shown similar efficacy between ranibizumab and bevacizumab when delivered on a fixed monthly schedule, but a significant difference is serious AEs. Now, these events are not usually associated with anti-VEGF agents, but the difference does give us pause. Finally, combination therapy has been shown to reduce the number of treatments required while maintaining visual gains, but not at a large enough delta to warrant its use outside of patients with polypoidal choroidal vasculopathy.

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9 Retinal Vein Occlusions

(Evidence-Based Eye Care)

Paul Hahn MD, PhD and Sharon Fekrat MD, FACS

Introduction

Retinal vein occlusion (RVO), including both branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), is a retinal vascular disorder with significant sight-threatening morbidity.[1–4] BRVO is three times more common than CRVO and second only to diabetic retinopathy as the most common retinal vascular cause of visual loss.[5–7] BRVO results from a blockage of blood flow in a branch retinal vein. This blockage typically occurs where a branch artery crosses over the branch retinal vein, resulting in a sectoral, wedge-shaped distribution of intraretinal hemorrhages, venous tortuosity and dilation, cotton wool spots, and/or cystoid macular edema (Fig. 9.1). In CRVO, a thrombus is suspected at the level of the lamina cribrosa, generally resulting in a sudden decrease in visual acuity (VA) with four quadrants of dilated tortuous retinal veins, intraretinal hemorrhages, cotton wool spots, optic disc swelling and hyperemia, and/or cystoid macular edema (Fig. 9.2).

The mechanism of RVO is multifactorial and poorly understood but is suggested by its associated risk factors, primarily systemic arterial disease such as hypertension, diabetes, hyperlipidemia, atherosclerosis, increased body mass index, and smoking.[8–15] RVO is commonly an age-related disease, and individuals less than 60 years of age may have a greater association with hypercoagulable states and inflammatory conditions compared with older persons with a higher incidence of systemic vascular disease risk factors.[16–18]

Primary causes of visual loss with RVO include macular edema and neovascularization, with secondary vitreous hemorrhage and/or neovascular glaucoma. Until recently, the standard of clinical management had been dictated for over 20 years by the Branch Retinal Vein Occlusion Study (BVOS) and the Central Retinal Vein Occlusion Study (CVOS). These landmark studies recommended grid-pattern laser photocoagulation for perfused macular edema in eyes with BRVO[5,19] and observation of macular edema in CRVO; panretinal laser photocoagulation (PRP) was recommended for the treatment of RVO-associated neovascularization.[5,19] Recent clinical trials investigating novel therapies have significantly expanded our understanding of RVO pathogenesis and our therapeutic options, setting a new standard of care for RVO-associated macular edema. This chapter reviews major clinical trials, focusing on currently available therapies that have recently advanced our treatment of RVO.

The Branch Retinal Vein Occlusion Study

The BVOS was a multicenter, prospective, randomized, controlled trial sponsored by the National Eye Institute (Fig. 9.3).[5,6] This trial was originally designed to study patients from 1977 to 1984 to determine whether peripheral argon laser photocoagulation can prevent the development of neovascularization and/or vitreous hemorrhage and whether grid-pattern laser photocoagulation can improve VA in eyes with perfused macular edema.

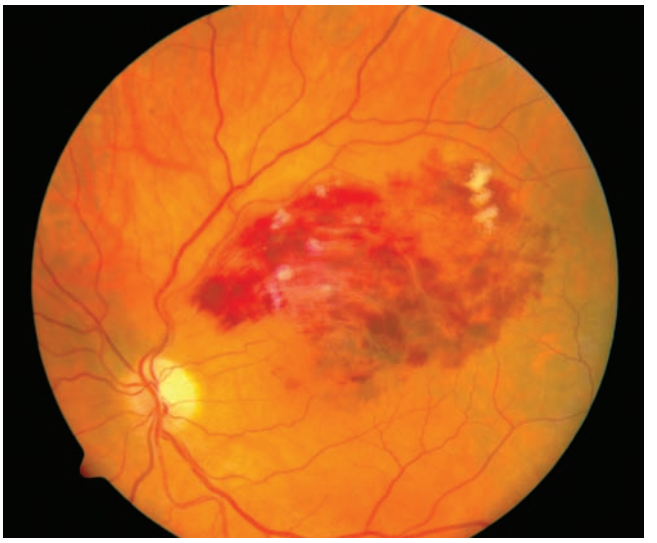

FIGURE 9.1 Fundus photograph of a branch retinal vein occlusion demonstrating typical features of sectoral intraretinal hemorrhages and cotton wool spots.

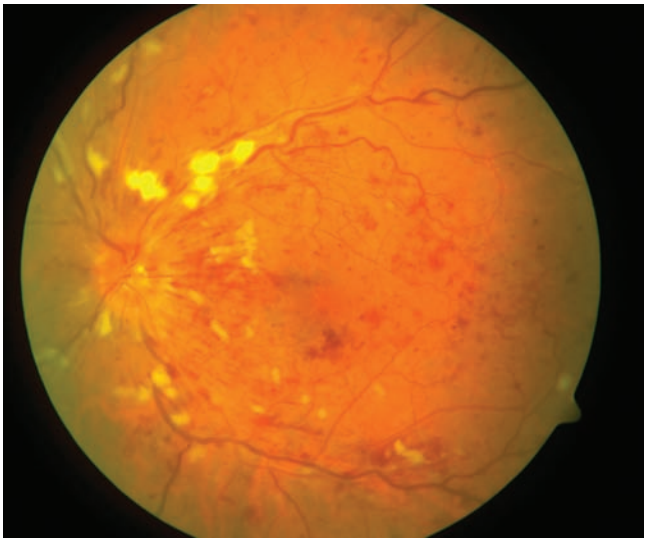

FIGURE 9.2 Fundus photograph of a central retinal vein occlusion demonstrating typical features of intraretinal hemorrhages, cotton wool spots, and venous tortuosity in four quadrants along with macular thickening.

In the BVOS, eyes with a BRVO were placed into four groups. Group I eyes had a BRVO without neovascularization but with pathology covering at least five disc diameters in diameter, which was felt to place these eyes at high risk for developing neovascularization. Eyes in this group were randomized to sector PRP or no laser treatment to determine whether PRP prevented the development of neovascularization. Group II eyes had a BRVO with neovascularization of the disc or within one disc diameter of the disc and were at risk for the development of vitreous hemorrhage. The eyes were randomized to sector PRP or no laser treatment to determine whether PRP could prevent vitreous hemorrhage. Group III eyes had a BRVO with reduced vision to 20/40 or less and perfused macular edema, characterized by <5 disc diameters of retinal capillary nonperfusion; these eyes were randomized to grid-pattern laser photocoagulation or no laser treatment. Finally, eyes in Group X, with inclusion criteria similar to Group I, were recruited only after Group I recruitment

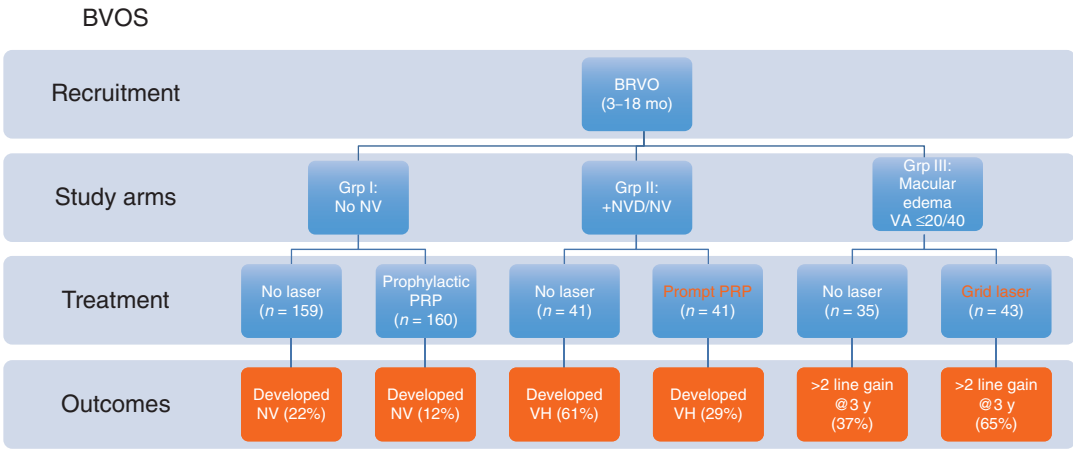

FIGURE 9.3 BVOS—statistically significant results are highlighted with orange boxes. BRVO, branch retinal vein occlusion; BVOS, Branch Retinal Vein Occlusion Study; PRP, panretinal laser photocoagulation; VA, visual acuity; NV, neovascularization; NVD, neovascularization at the disc; VH, vitreous hemorrhage.

was closed and were followed up primarily to obtain natural history information.

Spontaneous visual improvement in eyes with BRVO has been reported in smaller studies.[20–22] In the BVOS, VA in untreated BRVO eyes improved a mean of 0.23 lines over 3 years. Based on the BVOS, however, it is difficult to fully understand the natural history of eyes with a BRVO.[23] The BVOS natural history data involved only a small number of subjects, with 35 untreated eyes at 3 years.[5] Furthermore, eyes with BRVO duration ranging from 3 to 18 months were grouped together, and natural history was then determined from this group of eyes. Moreover, as BVOS enrollment required eyes to have had a BRVO of at least 3 months duration, no natural history data can be ascertained from the onset of BRVO to 3 months. Only BRVO eyes with perfused edema without foveal hemorrhage were enrolled, so no natural history information is available from the BVOS regarding eyes with ischemic edema or foveal hemorrhage.

Grid-Pattern Laser Photocoagulation

The BVOS evaluated grid-pattern laser photocoagulation for the treatment of perfused macular edema, recommending grid laser in those eyes with a BRVO of 3 to 18 months duration, a reduced VA ≤ 20/40, and without foveal hemorrhage.[5] The BVOS protocol involved focal laser in a grid-pattern in the area of leaking capillaries within two disc diameters of the foveal center but outside of the foveal avascular zone (Fig. 9.4). It is important to realize that eyes in the BVOS were not rigorously divided into categories of macular perfusion (i.e., perfused vs nonperfused macular edema) because the quality of the fluorescein angiograms was generally not adequate to differentiate.[24] However, patients with "distinct" areas of capillary nonperfusion in the macula were excluded. Although the BVOS is the largest randomized trial comparing laser treatment to observation for macular edema, with 71 treated and 68 untreated eyes, the reported 3-year data were only from 43 treated and 35 untreated eyes.[5] These small numbers and lack of precise angiographic differentiation of macular edema make the results difficult to interpret.

Nevertheless, the BVOS demonstrated a benefit of grid-pattern laser photocoagulation treatment for macular edema that met the criteria defined in the preceding text.[5] At 3 years, 65% of 43 treated individuals gained at least 2 lines of vision compared with 37% of 35 eyes in the untreated control group (Fig. 9.3).[5] This finding led to the recommendation that persistent BRVO-associated perfused macular edema and VA ≤ 20/40 be treated with grid-pattern laser photocoagulation, which had remained the standard of care until the recent development of intravitreal pharmacotherapy.

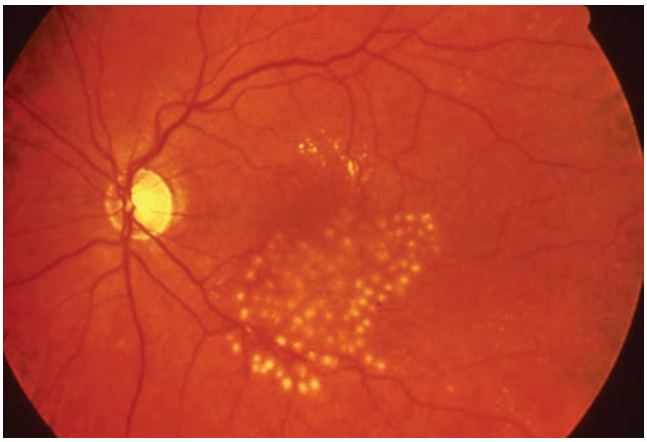

FIGURE 9.4 Fundus photograph of an inferotemporal branch retinal vein occlusion with macular edema treated in the Branch Retinal Vein Occlusion Study with grid laser photocoagulation.

Scatter Laser Photocoagulation

The data from BVOS groups I and II demonstrated that scatter argon laser photocoagulation in the affected distribution effectively reduces the development of retinal neovascularization and vitreous hemorrhage when compared with BRVO eyes in the untreated group. In group I, it was found that 12% of 160 laser-treated eyes developed retinal neovascularization compared with 22% of 159 untreated eyes. In group II, 29% of 41 treated eyes developed a vitreous hemorrhage as compared with 61% of 41 untreated eyes. Thus, it was concluded that scatter laser effectively decreases the likelihood of developing neovascularization and/or vitreous hemorrhage.[5,6] The BVOS did not directly address the optimal timing of PRP placement, but extrapolated data from both groups suggest that PRP placed after the development of neovascularization is as effective as prophylactic laser in reducing the incidence of vitreous hemorrhage. The BVOS therefore recommended that PRP be placed only after the development of neovascularization rather than prophylactically.

The Central Retinal Vein Occlusion Study

The CVOS was a multicenter, prospective, randomized, controlled clinical trial conducted between 1988 and 1992 (Fig. 9.5).[25,26] The CVOS sought to understand the natural history of perfused CRVO, to determine the role of grid-pattern laser photocoagulation in the treatment of macular edema, and to determine optimal timing of PRP treatment for CRVO-associated neovascularization.

In the CVOS, eyes were categorized into three groups according to perfusion status: perfused, nonperfused, or indeterminate. A nonperfused CRVO exhibited >10 disc areas of retinal capillary obliteration on fluorescein angiography based on a defined photographic protocol using a conventional wide-angle fundus camera with sweeps of the mid-periphery 30 seconds after intravenous injection of sodium fluorescein. Interestingly, in contrast to the preceding BVOS, which defined nonperfusion based on disc diameters, the CVOS defined nonperfusion based on disc areas. The CVOS only included eyes with onset of CRVO within the preceding 12 months. Eyes were excluded from the CVOS if they had previous laser photocoagulation for any retinal vascular disease in the affected eye, presence of diabetic retinopathy, new or old branch arterial/venous occlusion, retinal neovascularization, vitreous hemorrhage, peripheral anterior synechiae, or concurrent eye disease that decreased VA.

Natural History

Nine clinical centers participated in the CVOS, enrolling 714 CRVO-affected eyes from 711 patients. The number of male patients was slightly more than that of female patients, and over 50% of the patients were 65 years or older. Sixty-one percent of the

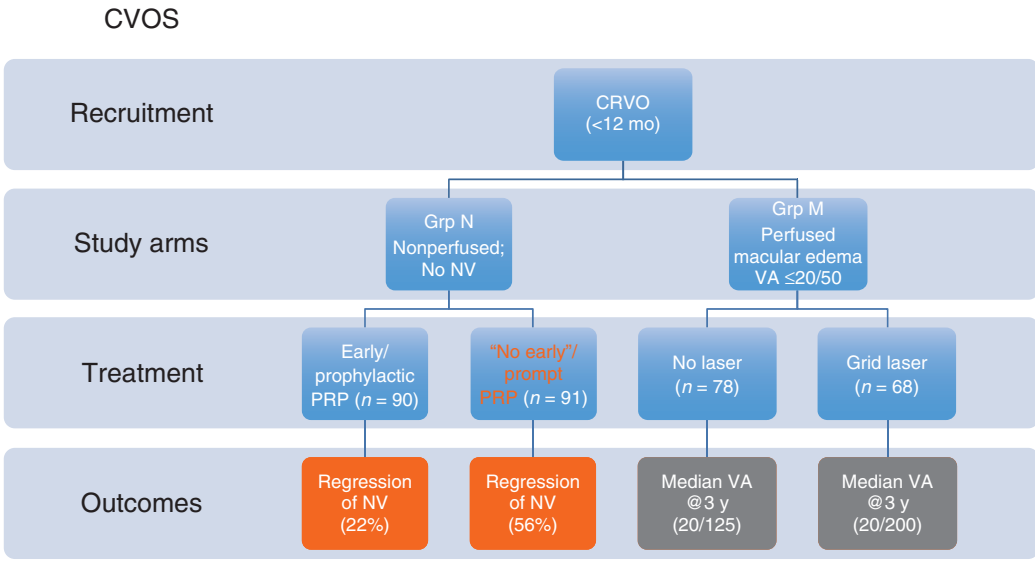

FIGURE 9.5 CVOS—statistically significant results are highlighted with orange boxes; gray boxes highlight nonsignificant, pertinent results. CRVO, central retinal vein occlusion; CVOS, Central Retinal Vein Occlusion Study; PRP, panretinal laser photocoagulation; NV, neovascularization; VA, visual acuity.

patients had some evidence of hypertension. At the initial visit, 546 eyes (76%) were classified as perfused on angiography. Of eyes that were initially classified as perfused, 34% (185 of 547 eyes) converted to nonperfused status by 3 years.[26] This progression was found to be strongly associated with duration of CRVO <1 month, VA worse than 20/200, and the presence of 5 to 9 disc areas of nonperfusion on the baseline fluorescein angiogram. Once a patient developed a CRVO in one eye, there was an annual risk of 0.9% of developing a CRVO in the fellow eye.[25,26]

Improvement in VA was strongly associated with the initial baseline acuity.[26] In the CVOS, presenting VA was variable: 29% were 20/40 or better, 43% were between 20/50 and 20/200, and 28% were 20/200 or worse; median baseline VA was 20/80. Of the eyes with an initial VA of 20/40 or better, 65% retained VA at this level over 3 years, while the remaining worsened. Among individuals with intermediate VA between 20/50 and 20/200, 41% maintained the same level over 3 years, 21% improved to better than 20/50, and 38% deteriorated to worse than 20/200. Eyes with an initial VA <20/200 had an 80% chance of maintaining poor vision without improvement over 3 years (Table 9.1).

TABLE 9.1 The Central Retinal Vein Occlusion Study

Presenting VA (median 20/80)	Final VA after 3 y		
	Improved	Stable	Worsened
>20/40 (29%)	N/A	65%	35%
20/50–20/200 (43%)	21%	41%	38%
<20/200 (28%)	20%	80%	N/A

VA, visual acuity.

The CVOS demonstrated that eyes with a nonperfused CRVO had a higher risk of developing neovascularization of the iris or angle (NVI/NVA).[26] Thirty-five percent of nonperfused eyes (61 of 176 eyes) developed NVI/NVA, compared with 10% (56 of 538) of perfused eyes. The median time to the development of NVI/NVA in nonperfused eyes was 61 days (range: 6 days to 8 months) after enrollment. The development of NVI/NVA was more likely in males and in eyes with a VA worse than 20/200 that had at least 30 disc areas of nonperfusion with moderate-to-severe venous tortuosity and retinal hemorrhage, or with CRVO duration <1 month.

Grid-Pattern Laser Photocoagulation

The CVOS Group M report investigated the role of grid-pattern argon laser photocoagulation in 155 eyes with perfused CRVO-associated macular edema and VA 20/50 or worse.[19] Treatment resulted in decreased macular edema as detected by fluorescein angiography, prior to the availability of optical coherence tomography (OCT) imaging. At 12 months, 21 of 68 treated eyes (31%) had no angiographic macular edema compared with 6 of 78 (8%) untreated eyes ($p < 0.0001$). Despite this anatomic improvement, grid-pattern laser photocoagulation did not improve VA in eyes with CRVO. Initial median visual acuities of 20/125 (observation) and 20/160 (laser treated) were comparable to final median visual acuities at 36 months of 20/160 (observation) and 20/200 (laser treated). Damage to the perifoveal vascular zone has been hypothesized to contribute to this lack of visual recovery despite anatomic improvement. Based on these results, the CVOS concluded that grid-pattern laser photocoagulation in eyes with CRVO-associated macular edema was not visually beneficial. Until the recent identification of novel therapies for CRVO-associated macular edema, the standard of care had been observation.

Panretinal Laser Photocoagulation

Despite the absence of any supporting clinical trial data prior to CVOS, prophylactic PRP had already been widely accepted as the standard of care for the prevention of NVI/NVA in nonperfused CRVO. The optimal timing of PRP treatment had not been established, however, and the CVOS Group N report therefore examined whether PRP treatment should be initiated on a prophylactic basis immediately following the diagnosis of CRVO or delayed until the development of any NVI/NVA.[27] Prophylactic PRP in eyes with nonperfused CRVO without neovascularization developed NVI/NVA in 18 of 90 treated eyes (20%), while 32 of 91 untreated eyes (35%) developed NVI/NVA; however, this difference was not statistically significant. Furthermore, once NVI/NVA developed, additional PRP was four times less effective in eyes that had already received prophylactic PRP (4 of 18 eyes; 22%) than control eyes (18 of 32 eyes; 56%) in inducing the regression of neovascularization. The CVOS therefore recommended prompt, but not prophylactic, PRP treatment immediately following the detection of anterior segment neovascularization.[27] Prophylactic PRP may be considered in patients with risk factors for developing NVI/NVA (male gender, short duration of CRVO, extensive retinal nonperfusion, and extensive retinal hemorrhage) or when close ophthalmologic follow-up is impossible or unlikely. Persistent neovascularization following PRP must be followed closely, and additional PRP may be needed to halt its progression.

Corticosteroid Therapy

Numerous case reports and case series have suggested the efficacy of corticosteroids in treating RVO-associated macular edema.[28–34] While the mechanism of action remains unknown, recent results from large, prospective, randomized, controlled clinical trials have demonstrated benefit of corticosteroids in treating RVO-associated macular edema. These trials include the National Eye Institute–sponsored **S**tandard Care vs **CO**rticosteroid for **RE**tinal Vein Occlusion (SCORE) study and the Allergan-sponsored **G**lobal **E**valuation of impla**N**table d**E**xamethasone in retinal **V**ein occlusion with macular edem**A** (GENEVA) trial, which investigated the role of intravitreal triamcinolone and a sustained-release intravitreal dexamethasone delivery system, respectively, for the treatment of RVO-associated macular edema.

SCORE Trial

Prior to the Food and Drug Administration (FDA) approval of pharmacotherapeutic agents for RVO, the SCORE study compared the efficacy and safety of an off-label intravitreal injection of 1 or 4 mg preservative-free triamcinolone acetonide (IVTA; Trivaris, Allergan, Inc., Irvine, CA) versus standard of care in the treatment of RVO-related macular edema.[35,36] Of note, this formulation of triamcinolone is not commercially available. In these trials, hemiretinal vein occlusion (HRVO) was categorized as BRVO. Key

inclusion criteria included VA between 20/40 and 20/400, RVO-associated macular edema on clinical exam, and central subfield retinal thickness ≥250 μm by OCT. Key exclusion criteria included eyes with foveal atrophy, significant cataract, or a recent history of laser treatment, ocular surgery, or intravitreal or peribulbar steroid administration. Eyes were retreated every 4 months during the 12-month study period unless specific criteria were met, including (1) significant improvement (central subfield OCT thickness ≤225 μm, VA ≥20/25, or significant interval improvement with presumed potential for continued improvement without treatment), (2) contraindication due to significant adverse effect (e.g., significant rise in intraocular pressure [IOP]), or (3) additional treatment considered futile due to no improvement following two consecutive injections.

Standard of care for RVO-associated macular edema at the time of the study had been defined by BVOS and CVOS, which recommended grid-pattern laser for perfused macular edema in eyes with BRVO (and HRVO) and observation for macular edema with CRVO. With these different standard of care treatments, the SCORE study was designed with two distinct arms to separately evaluate the role of IVTA compared with standard of care for macular edema secondary to BRVO (411 eyes) and secondary to CRVO (271 eyes).

SCORE-Branch Retinal Vein Occlusion Arm. The SCORE-BRVO arm (Fig. 9.6) randomized eyes to 1 mg IVTA ($n = 136$), 4 mg IVTA ($n = 138$), or grid-pattern laser ($n = 137$).[35] This study did not detect any difference in VA between eyes treated with IVTA or grid-pattern laser at 12 months. In the 1 mg IVTA, 4 mg IVTA, and grid-pattern laser groups, 29%, 26%, and 27%, respectively, gained ≥15 letters of VA at 1 year. A subgroup analysis of pseudophakic patients demonstrated a trend toward greater than 3 line gains in visual improvement with 1 mg (29%) or 4 mg (28%) IVTA compared with grid-pattern laser (20%), but these differences were not statistically significant. All treatments also resulted in equivalent improvement in mean VA of approximately 4 to 6 letters and similar reductions in macular edema as measured by OCT at 12 months.

The IVTA groups in SCORE-BRVO had an increased rate of side effects, particularly cataract progression and increased IOP, compared with the standard of care group. Cataract progression was noted in 25% of eyes in the 1 mg IVTA group and 35% in the 4 mg IVTA group compared with only 13% in the grid-pattern laser group. IOP-lowering medication was required in 7% and 41% of eyes in the 1 mg and 4 mg IVTA groups, respectively, compared with only 2% of eyes in the grid-pattern laser group. Endophthalmitis and retinal

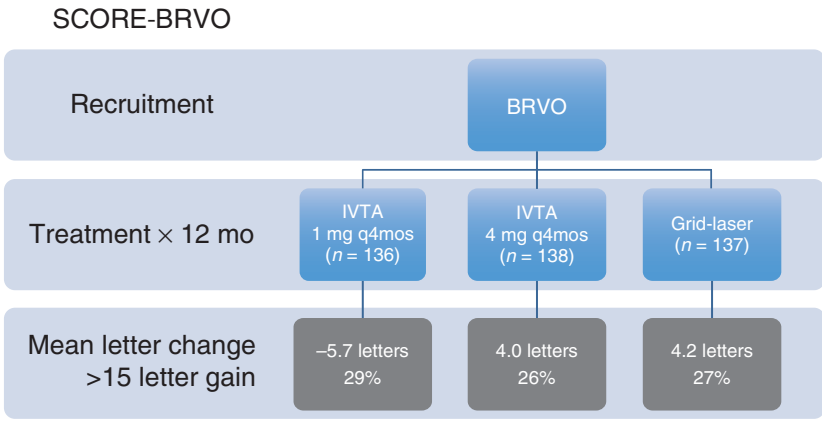

FIGURE 9.6 SCORE-BRVO—gray boxes highlight nonsignificant, pertinent results. BRVO, branch retinal vein occlusion; IVTA, intravitreal triamcinolone acetonide; SCORE, Standard Care vs COrticosteroid for REtinal Vein Occlusion.

detachment occurred in <1% of patients in all groups. There was no difference in systemic adverse events across all groups.

Given the absence of any improvement in visual outcomes with IVTA compared with laser, particularly with a less favorable side-effect profile following IVTA treatment, the SCORE-BRVO trial recommended that grid-pattern laser remain the standard of clinical practice for treatment of BRVO-associated perfused macular edema.

SCORE-Central Retinal Vein Occlusion Arm. In the parallel SCORE-CRVO arm (Fig. 9.7), intravitreal injection of 1 mg IVTA (92 eyes) or 4 mg IVTA (91 eyes) was found to confer significant visual benefit in the treatment of CRVO-associated macular edema compared with observation (88 eyes).[36] At 1 year, 27% (1 mg) and 26% (4 mg) of patients treated with IVTA gained ≥15 letters compared with 7% of untreated patients. Mean change in VA was a loss of only 1.2 letters in both IVTA groups compared with a loss of 12.1 letters in the observation group. Improvements in central foveal thickness by OCT were only significant following treatment with 4 mg IVTA at 4 months, with a median change of –196 μm in the 4 mg IVTA group compared with –77 μm in the 1 mg IVTA group and –125 μm in the observation group.

An increased rate of cataract formation through 12 months was identified in the 4 mg IVTA group (33%) compared with the 1 mg IVTA group (26%) and the observation group (18%). Over 2 years, 23% of eyes from the 4 mg group required cataract surgery compared with 3% of eyes in the 1 mg group and no eyes from the observation group. A subgroup analysis of pseudophakic eyes revealed a mean gain in VA of 2 letters in the 1 mg IVTA group and a mean loss of VA of 1 letter in the 4 mg group, compared with a loss of 14 letters in the observation group. In these pseudophakic eyes, a 3 or more line gain was achieved in 20% of both IVTA groups compared with 6% in the observation group.

Apart from cataract formation, the most notable primary ocular adverse event was elevated IOP, which was observed over 12 months in 20% and 35% of eyes in the 1 mg and 4 mg IVTA groups, respectively, compared with 8% in the observation group. While most elevations were successfully treated with topical IOP-lowering eyedrops, glaucoma tube shunt surgery during a 2-year period was performed in 2% of eyes in the 4 mg group but in no eyes in the 1 mg or observation groups. There were no cases of endophthalmitis or retinal detachment in any group at 12 months. There was no difference in systemic adverse events across all groups.

Given the improvements in treating vision loss with IVTA compared with observation for CRVO-associated macular edema, and

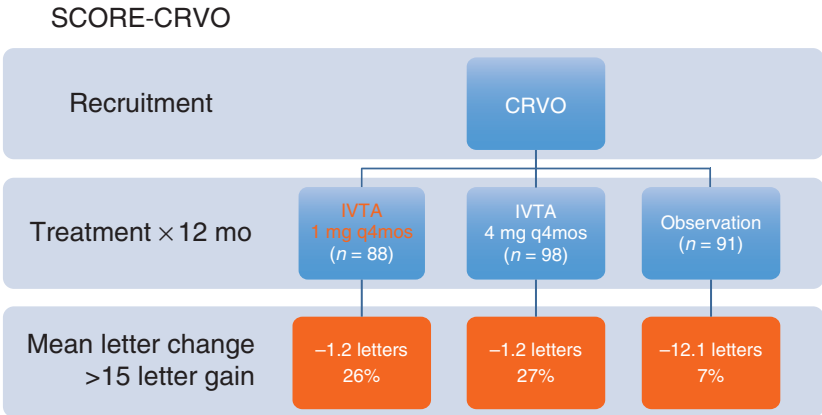

FIGURE 9.7 SCORE-CRVO—statistically significant results are highlighted with orange boxes. CRVO, central retinal vein occlusion; IVTA, intravitreal triamcinolone acetonide; SCORE, Standard Care vs **CO**rticosteroid for **RE**tinal Vein Occlusion.

given the superior side-effect profile of the 1 mg dose compared with the 4 mg dose, the SCORE-CRVO trial recommended consideration of 1 mg IVTA at 4-month intervals in the treatment of CRVO-associated macular edema.

GENEVA Trial

In 2009, a sustained-release intravitreal 0.7 mg dexamethasone delivery system, Ozurdex (Allergan), became the first FDA-approved treatment for macular edema secondary to RVO. This approval was based on results of the multicentered international 6-month GENEVA study at 167 sites in 24 countries investigating the effect of a single 0.35 mg or 0.7 mg Ozurdex injection compared with sham injection for the treatment of macular edema in eyes with RVO (Fig. 9.8A).[37] Key inclusion criteria included clinically detectable RVO-associated macular edema, best-corrected VA between 20/50 and 20/200, and central subfield retinal thickness ≥300 µm by OCT; additionally, the duration of macular edema was required to be between 6 weeks and 12 months in eyes with BRVO and

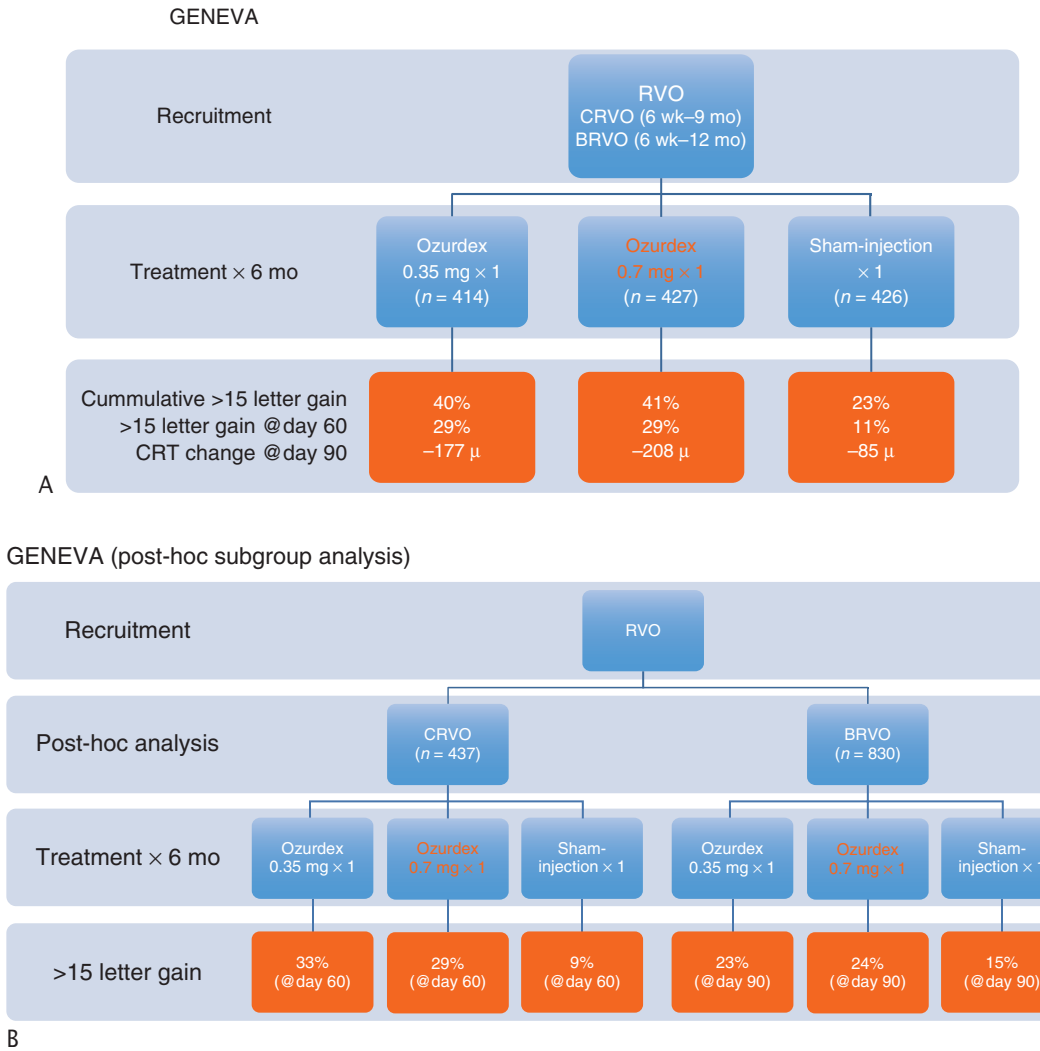

FIGURE 9.8 GENEVA **(A)** and post hoc subgroup GENEVA analysis **(B)**—statistically significant results are highlighted with orange boxes. BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; GENEVA, **G**lobal **E**valuation of impla**N**table d**E**xamethasone in retinal **V**ein occlusion with macular edem**A**. CRT, central subfield retinal thickness.

6 weeks and 9 months in eyes with CRVO. Key exclusion criteria included the presence of any neovascularization, the presence of any diabetic retinopathy, a history of glaucoma or steroid-induced IOP elevations, or the presence of "any ocular condition in the study eye that, in the opinion of the investigator, would prevent a 15-letter improvement in visual acuity."[37]

Primary outcomes were reported for all RVO eyes grouped together. Eyes with BRVO and eyes with CRVO were not evaluated separately. The Ozurdex implant resulted in decreased mean time to ≥15 letter improvement, increased rate of ≥15 letter gain through day 90 (but not at day 180), improved mean VA, lower rate of ≥15 letter, and greater decrease in central subfield retinal thickness through day 90.

Post hoc subgroup analysis was performed on 830 BRVO eyes and 437 CRVO eyes injected with Ozurdex (Fig. 9.8B). In BRVO eyes, the 0.7 mg group demonstrated significant gains of ≥15 letters compared with the sham control at up to 90 days (24% vs 15%) but not at 180 days. Among CRVO eyes, the 0.7 mg group demonstrated significant gains of ≥15 letters compared with the sham control at up to 60 days (29% vs 9%) but not at 90 or 180 days. Unlike in the SCORE study, corticosteroid administration was compared with sham injection and not with standard of care; Ozurdex was therefore not compared with grid-pattern laser photocoagulation, and comparative efficacies of these treatment options are unknown.

Following the initial 6 month study period, a 6 month open-label extension was continued. All RVO eyes with persistent macular edema were eligible for an additional Ozurdex 0.7 mg injection 6 months following initial treatment and were followed for an additional 6 months for a total of 1 year from study enrollment.[38] At the conclusion of this 12 month follow-up, the results of primary endpoints from the second injection were similar to the first, with an approximate 10 letter VA gain and maximal improvement peaking at 60 days following injection.

Primary ocular adverse effects following Ozurdex administration included cataracts and increased IOP. While no significant risk of cataract formation was identified in the initial 6 month prospective study after a single injection,[37] 29.8% of eyes receiving two injections 6 months apart developed cataract by the 12 month endpoint compared with 5.7% of sham-treated eyes.[38] The initial 6 month study period may have been too short to observe the presence of significant cataract formation.

Ocular hypertension was detected in 4% of Ozurdex-treated eyes compared with 0.7% of sham-injected eyes within 6 months after a single Ozurdex injection and was generally managed with topical medications alone. Increases in IOP peaked at 60 days. Following a single injection of Ozurdex, 12.6% of eyes developed ≥10 mmHg increase in IOP at 60 days, and 15.4% of eyes developed a similar increase in IOP 60 days following a second Ozurdex injection 6 months after the first. Two retinal detachments occurred in the 6 month study, one in the sham group and one in the 0.7 mg group. No cases of endophthalmitis were reported at 12 months. There was also no difference in nonocular adverse events among groups.

Anti–Vascular Endothelial Growth Factor Therapy

Vascular endothelial growth factor (VEGF) is a proangiogenic protein that has been hypothesized to cause capillary endothelial cell proliferation leading to progressive vascular closure and nonperfusion in RVO.[39] Elevated levels of VEGF in the vitreous of eyes with RVO have suggested that VEGF plays an important role in RVO pathogenesis.[40–42] Anti-VEGF therapy may improve blood flow, decrease intravenous pressure, and normalize venous diameter and tortuosity.[39]

Ranibizumab – BRAVO/CRUISE Trials

Recently, two parallel, double-masked, multicenter, randomized, controlled phase 3 clinical trials demonstrated the efficacy of intravitreal anti-VEGF therapy with ranibizumab (Lucentis, Genentech, Inc.; San Francisco, CA) for the treatment of RVO-associated macular edema. The RanibizumaB for the Treatment of Macular Edema

after B**RA**nch Retinal Vein **O**cclusion: Evaluation of Efficacy and Safety (BRAVO) and the Ranibizumab for the Treatment of Macular Edema after **C**entral **R**etinal Vein Occl**U**s**I**on **S**tudy: **E**valuation of Efficacy and Safety (CRUISE) trials demonstrated the superiority of monthly intravitreal ranibizumab compared with sham injection for the treatment of macular edema secondary to BRVO and CRVO, respectively.[43,44] In these trials, HRVO was categorized as BRVO. These results definitively demonstrated a role for VEGF in the pathogenesis of RVO, prompting FDA approval of ranibizumab in 2009 for the treatment of both BRVO and CRVO.

These trials prospectively compared monthly intravitreal injections of 0.3 mg or 0.5 mg ranibizumab to sham-injected controls in the treatment of macular edema secondary to BRVO (397 patients) and CRVO (392 patients). Key inclusion criteria included RVO diagnosed within 12 months of enrollment, BCVA between 20/40 and 20/320, and central subfield thickness ≥250 μm by OCT. Key exclusion criteria included prior episode of RVO, brisk afferent pupillary defect, recent history of spontaneous improvement in VA, and a history of recent laser photocoagulation, anti-VEGF treatment, or intraocular corticosteroid injection. Eyes were treated with 0.3 mg or 0.5 mg ranibizumab or with sham injection on a monthly basis for 6 months[43,44] followed by a 6 month observation period, in which monthly ranibizumab was administered to all groups on an as-needed basis.[45,46] In the BRAVO trial, eyes were eligible for rescue grid-pattern laser treatment following 3 months of enrollment if sufficient clearing of hemorrhages had occurred without significant visual or anatomic improvement.[45,46]

BRAVO. The BRAVO study demonstrated anatomic and VA benefits in ranibizumab-treated eyes compared with sham-treated eyes with BRVO-associated macular edema (Fig. 9.9).[43] Eyes treated with 0.3 mg and 0.5 mg ranibizumab gained 16.6 and 18.3 letters, respectively, at 6 months compared with a gain of 7.3 letters in the sham group. When treated with ranibizumab, 55% (0.3 mg) to 61% (0.5 mg) gained ≥15 letters from baseline compared with 29% in the sham group. The mean change in central foveal thickness was –337 μm in the 0.3 mg group and –345 μm in the 0.5 mg group compared with –158 μm in the sham group. Rescue grid-pattern laser treatment was administered in 18.7% (0.3 mg) and 19.8% (0.5 mg) of ranibizumab-treated eyes compared with 54.5% of sham-treated eyes. These improvements in VA and foveal thickness were statistically significant at 6 months.

Adverse events were rare. The sham group included no cases of endophthalmitis or retinal detachment. There was one case of retinal detachment in the 0.3 mg group and one

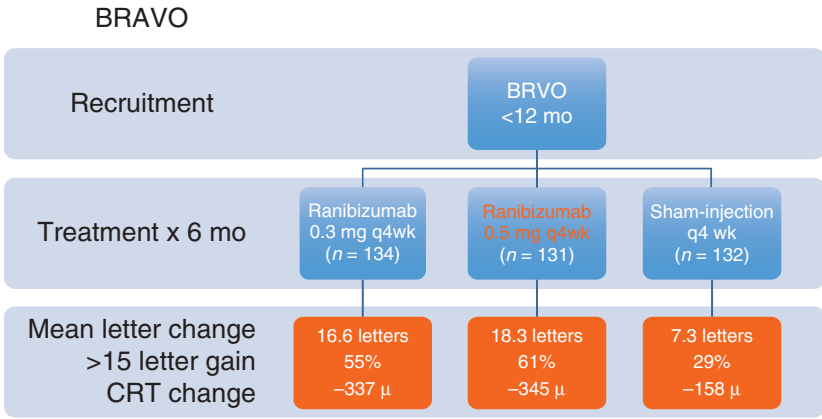

FIGURE 9.9 BRAVO—statistically significant results are highlighted with orange boxes. BRAVO, Ranibizuma**B** for the Treatment of Macular Edema after B**RA**nch Retinal **V**ein **O**cclusion: Evaluation of Efficacy and Safety; BRVO, branch retinal vein occlusion; CRT, central subfield retinal thickness.

case of endophthalmitis in the 0.5 mg group. There was one case of stroke in the sham group and 0.5 mg group. Additionally, there was one myocardial infarction in the 0.5 mg ranibizumab group.

CRUISE. Conducted in parallel with the BRAVO trial, the CRUISE trial similarly demonstrated anatomic and VA benefits in ranibizumab-treated eyes compared with the sham-treated eyes with CRVO-associated macular edema (Fig. 9.10).[44] Eyes treated with 0.3 mg (132 eyes) and 0.5 mg ranibizumab (130 eyes) gained 12.7 and 14.9 letters, respectively, at 6 months compared with a 0.8 letter gain in the sham group (130 eyes). Additionally, 46.2% (0.3 mg) and 47.7% (0.5 mg) of eyes treated with intravitreal ranibizumab gained ≥15 letters from baseline compared with only 16.9% in the sham group. The mean change in central foveal thickness was –434 μm (0.3 mg) and –452 μm (0.5 mg) in the treatment groups compared with –168 μm in the sham group. These improvements in VA and foveal thickness were statistically significant at 6 months.

There were no cases of retinal detachment or endophthalmitis in any of the groups. Systemic adverse events were also rare. There were no reported strokes in any of the groups. One transient ischemic attack occurred in the 0.5 mg group, and one myocardial infarction occurred in each of the groups.

Following the initial 6 month treatment period in both BRAVO and CRUISE, all groups, including the control group, were eligible to receive monthly ranibizumab for macular edema on an as-needed basis over the following 6 months. The benefits with ranibizumab in VA and anatomy observed in the first 6 months were generally maintained at 1 year.[45,46] RVO eyes initiating as-needed monthly ranibizumab after 6 months of sham injection treatments exhibited significant visual and anatomic benefits, but the magnitude of these improvements was less than that of either ranibizumab-treated group, suggesting that delayed treatment may result in diminished response to therapy.[45,46]

Bevacizumab (Avastin)

Much of our understanding of the role of anti-VEGF agents in treating retinal disease comes from studies with bevacizumab (Avastin; Genentech, Inc.). Prior to the FDA approval of ranibizumab, the low cost and ready availability of bevacizumab resulted in rapid growth in its ophthalmic use despite its off-label indication. Numerous anecdotal reports and case series have demonstrated improvement in RVO-associated macular edema with intravitreal bevacizumab (Fig. 9.11).[39,47–54] Improvements in macular edema and VA following intravitreal bevacizumab for RVO are greater than would be expected by the natural history alone and have been reported in both ischemic and nonischemic RVO.[50] In a study following a single

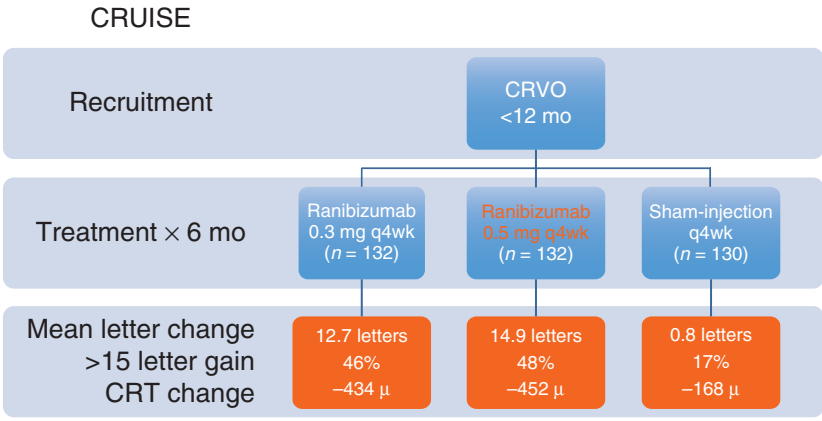

FIGURE 9.10 CRUISE—statistically significant results are highlighted with orange boxes. CRUISE, Ranibizumab for the Treatment of Macular Edema after **C**entral **R**etinal Vein Occl**U**s**I**on **S**tudy: **E**valuation of Efficacy and Safety; CRVO, central retinal vein occlusion; CRT, central subfield retinal thickness.

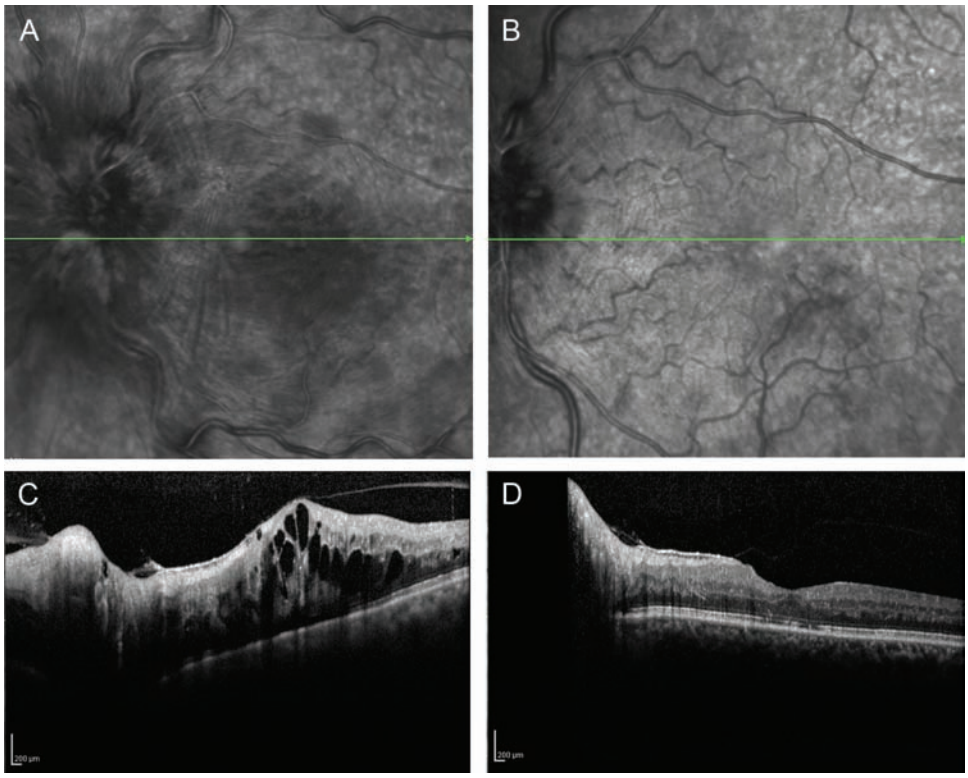

FIGURE 9.11 A 65-year-old male with central retinal vein occlusion–associated macular edema treated with a single intravitreal injection of 1.25 mg bevacizumab. Preinjection scanning laser ophthalmoscopy **(A)** and spectral domain optical coherence tomography (SDOCT) **(B)** demonstrate prominent optic nerve and retinal thickening with inner and outer retinal cysts. Ten weeks postinjection, scanning laser ophthalmoscopy **(C)** and SDOCT **(D)** demonstrate dramatic resolution of retinal thickening and return of normal foveal contour. Similar resolution of macular edema can be observed with intravitreal injections of corticosteroids or other anti–vascular endothelial growth factor agents.

injection of bevacizumab, the peak increase in VA was achieved between 3 and 6 weeks after the injection, followed by a return of macular edema with decreased VA.[49] In most case series, repeated treatments with bevacizumab have been administered at 4- to 8-week intervals to minimize the recurrence of macular edema. Intravitreal bevacizumab has additionally been associated with rapid resolution of anterior segment neovascularization,[55] indicating that neovascular complications of RVO, including neovascular glaucoma, may be effectively temporized by anti-VEGF agents.

The off-label use of intraocular bevacizumab and the lack of large, randomized, controlled clinical trials limit the safety profile data on bevacizumab for rare events. It is difficult to quantify the systemic risks such as myocardial infarction and stroke. In retrospective studies, the side-effect profile of bevacizumab was similar to that of ranibizumab, with an equivalent rate of endophthalmitis of 0.2%.[56] In another study, the most common adverse events were conjunctival hyperemia and subconjunctival hemorrhage at the injection site.[47] A recent randomized, blinded study comparing bevacizumab and ranibizumab in the treatment of age-related macular degeneration demonstrated that bevacizumab may be comparable to ranibizumab in efficacy.[57] It is unclear if these results are generalizable to the treatment of RVO or other retinal disorders. Despite these limitations, the ophthalmic use of bevacizumab quickly grew and remains the most widely used treatment modality for retinal disease.[58,59]

Aflibercept – COPERNICUS Trial

Aflibercept (VEGF Trap-Eye or Eylea; Regeneron Pharmaceutics, Inc., Tarrytown, NY) has been recently FDA-approved for the treatment of CRVO based on 6 months results from the COntrolled Phase 3 Evaluation of Repeated iNtravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety (COPERNICUS) trial (Fig. 9.12).[60] In this multicentered, prospective, randomized, controlled Phase 3 trial investigating the role for aflibercept in the treatment of CRVO-associated macular edema, 189 eyes with CRVO-associated macular edema were randomized 3:2 to receive six monthly injections of either 2 mg aflibercept (115 eyes) or sham (74 eyes). At 6 months, eyes treated with aflibercept gained a mean of 17.3 letters compared to a 4.0 letter loss in the sham group. Additionally, 56.1% of eyes treated with intravitreal aflibercept gained ≥15 letters from baseline compared to only 12.3% in the sham group. The mean change in central foveal thickness was −457.2 μm in the aflibercept group compared to −144.8 μm in the sham group. These improvements in visual acuity and foveal thickness were statistically significant at 6 months. Serious adverse events, both systemic and intraocular, attributable to the treatment itself were rare and balanced between groups. Aflibercept has recently been FDA-approved in September 2012 for the treatment of CRVO. There have not yet been published reports studying aflibercept for treatment of BRVO.

Other Anti–Vascular Endothelial Growth Factor Agents (Pegaptanib)

Pegaptanib (Macugen; Eyetech, Inc., Cedar Knolls, NJ) is currently the only other FDA-approved intravitreal anti-VEGF agent, which received approval for the treatment of neovascular age-related macular degeneration in 2004. Similar to other anti-VEGF agents, the use of pegaptanib for treatment of retinal diseases, including RVO, has been investigated and remains off-label. Use of pegaptanib has been studied for treatment of BRVO-associated macular edema in a prospective, uncontrolled, randomized dose-finding study, demonstrating visual and anatomic improvements with injection of 0.3 mg and 1 mg pegaptanib.[61] In a Phase II double-masked, multicenter, randomized trial, patients with CRVO-associated macular edema receiving off-label intravitreal injection of 0.3 mg or 1 mg pegaptanib every 6 weeks for 24 weeks were prospectively compared to sham-injected controls.[62] While there was no significant difference in gain of ≥15 letters among groups, patients treated with pegaptanib had decreased risk of ≤15 letter loss, greater mean letter improvement, and greater anatomic improvement. The use of pegaptanib for RVO-associated macular edema may prove to be an alternative to bevacizumab, ranibizumab, or aflibercept, and its utility is currently being investigated.

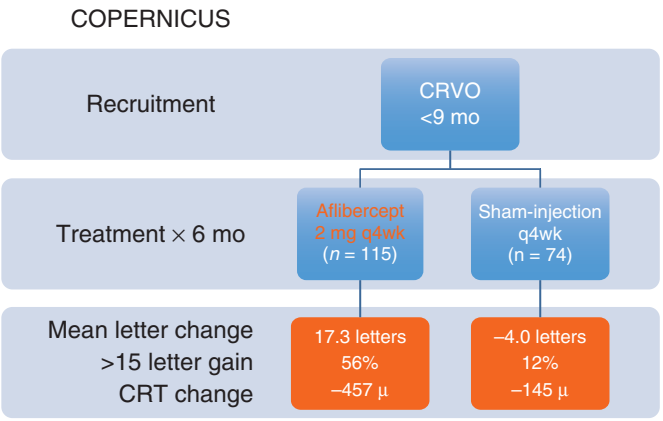

FIGURE 9.12 COPERNICUS—statistically significant results are highlighted with orange boxes. COPERNICUS, **CO**ntrolled **P**hase 3 **E**valuation of **R**epeated i**N**travitreal administration of VEGF Trap-Eye **I**n **C**entral retinal vein occlusion: **U**tility and **S**afety; CRVO, central retinal vein occlusion.

Treatment of Systemic Medical Conditions

Systemic vascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, atherosclerosis, increased body mass index, smoking, and, less commonly, hypercoagulability, have been strongly associated with RVO.[8–17,63] In patients presenting with RVO, identification and treatment of any underlying conditions are of paramount importance. It is unclear if systemic anticoagulation, as with aspirin, can prevent or change the natural history of RVO,[64] but prophylactic use of anticoagulants may help prevent nonocular thrombotic events, especially in individuals with known systemic vascular disease. Close coordination with the internist is always recommended.

Alternative Treatments

Pars plana vitrectomy may be helpful in treating visual loss associated with nonclearing vitreous hemorrhage that can occur in eyes with RVO. Vitrectomy with internal limiting membrane peeling has also been investigated for the treatment of RVO-associated macular edema. Reported outcomes have been inconsistent,[65,66] indicating the need for further investigation with large-scale, randomized trials. The pharmacokinetics of intravitreal pharmacologic agents are altered following vitrectomy, which results in reduced duration of effect. Particularly given the development of effective and less invasive intravitreal therapies, the potential benefits of vitrectomy in the treatment of RVO (and other retinal diseases) must always be carefully balanced against the expected reduction in efficacy of intravitreal pharmacotherapy.

Treatments targeting macular edema and neovascularization typically address the sequelae of RVO and not the underlying pathology. Alternative treatments have attempted to address the pathogenic vascular occlusion. Administration of recombinant tissue plasminogen activator through a systemic approach, locally with intravitreal injection, or directly through cannulation of the retinal vein has been reported to dissolve the offending thrombus in some cases.[67–71] Creation of a chorioretinal anastomosis between a retinal vein and the choroidal circulation has also been attempted in efforts to bypass the occlusion. Chorioretinal anastomoses have been created through a surgical transretinal venipuncture technique[72,73] or, more commonly, through argon or neodynium:yttrium aluminum garnet (Nd:YAG) to rupture the posterior branch retinal vein wall and adjacent Bruch's membrane.[74–76] Arteriovenous sheathotomy has been performed for the treatment of BRVO in attempts to restore venous outflow by severing the common adventitial sheath between a retinal vein and artery.[77–79] Radial optic neurotomy has been described for the treatment of CRVO, in which a radial incision is performed on the nasal edge of the optic nerve head to incise the scleral ring and, in theory, decompress the scleral outlet and central retinal vein.[80–85]

Success using each of these alternative techniques has been described, but these successes have not been highly reproducible among different groups. Each of these techniques is also associated with a significant complication profile. Particularly following the recent development of effective intravitreal pharmacotherapy, these alternative approaches have been largely abandoned.

Summary

The recent development of intravitreal pharmacotherapy has transformed the treatment of retinal diseases, including RVO. Prior to the development of these intravitreal agents, available options for the management of RVO were limited. The standard of care for macular edema had long been guided by BVOS and CVOS, which recommended grid-pattern laser for BRVO-associated perfused macular edema and observation for CRVO-associated macular edema. These studies recommended management of documented ocular neovascularization with sectoral scatter laser photocoagulation or PRP, which remains the standard of care.

A sustained-release dexamethasone implant (Ozurdex) and an anti-VEGF agent, ranibizumab (Lucentis), were FDA approved for the treatment of RVO-associated macular edema in 2009 and 2010, respectively, validating the widespread but off-label use of preservative-free triamcinolone and bevacizumab (Avastin) for RVO. Another intravitreal anti-VEGF agent, aflibercept (Eylea), has recently completed phase 3 trials evaluating the safety and efficacy of the treatment of RVO. While the results of the BRVO arm of this trial are not yet published, recent FDA-approval of aflibercept in 2012 for treatment of CRVO further expands treatment possibilities.

In the absence of prior robust treatment options for RVO, the remarkable efficacy and favorable side-effect profiles of these intravitreal agents have quickly led to their widespread use for the treatment of RVO-associated macular edema.[86,87] Optimal treatment protocols and indications, however, are still being investigated. Because of differences in study design, patient populations, and primary outcome measures, results from individual trials cannot be directly compared to determine relative efficacies of each intravitreal agent when compared with another. There are currently no large prospective, randomized trials comparing the use of anti-VEGF agents to corticosteroids or to laser in the management of RVO, and the specific indications for each of these modalities, their comparative efficacies, and the efficacy of combined therapy are currently being investigated.[88–93] Additionally, as these agents have only recently become available, their long-term role is unknown and is being actively studied.[94] Further understanding of duration of effect and frequency of injections will be important in optimizing dosing of corticosteroids and particularly anti-VEGF agents. Despite these shortcomings, the profound improvements noted with intravitreal pharmacotherapy has shifted the standard of care toward use of these agents.

For the management of visually significant RVO-associated macular edema, the authors advocate administration of anti-VEGF agents as first-line therapy. Anti-VEGF agents, bevacizumab, ranibizumab, and aflibercept, are generally administered at 4-week intervals or longer in some eyes to avoid recurrence of macular edema. Given the increased risk of cataract and IOP elevations with steroids, the authors typically reserve corticosteroid use for pseudophakic patients without glaucoma unresponsive to anti-VEGF agents. This paradigm is straightforward for the treatment of CRVO-associated macular edema, for which the previous standard of care per the CVOS had been observation. In the treatment of BRVO-associated macular edema, FDA-approved Ozurdex and ranibizumab have not been rigorously compared with grid-pattern laser photocoagulation or with each other. Without firm evidence-based guidelines, the authors recommend anti-VEGF agents as first-line therapy for BRVO-associated macular edema, with grid-pattern laser for consolidating therapy of recurrent edema and reserving steroids for refractory cases in pseudophakic patients without glaucoma.

Ocular neovascularization and particularly neovascular glaucoma remain important complications of retinal venous occlusive disease for which vigilance is critical, especially in eyes with widespread capillary nonperfusion. The management of ocular neovascularization secondary to RVO has generally remained unchanged since BVOS and CVOS, which demonstrated a significant reduction in vitreous hemorrhage and neovascular glaucoma following sectoral scatter laser photocoagulation or PRP.[6,27] These studies recommended prompt laser treatment following identification of neovascularization, which has remained the gold standard of treatment. Although anti-VEGF agents may also result in rapid regression of neovascularization and otherwise alter the natural history of RVO,[95] the authors recommend use of these agents only as a temporizing measure, when needed, until definitive treatment can be administered with scatter laser placement.

Fundamentally, RVOs likely arise from a block in venous drainage. Optimal therapy of RVO needs to address the underlying occlusion, but thus far, attempts to do so with vitrectomy, administration of recombinant tissue

plasminogen activator, creation of a chorioretinal anastomosis, arteriovenous sheathotomy, and radial optic neurotomy have had limited therapeutic success. The development of intravitreal pharmacotherapy has significantly improved our ability to treat RVO, and continued experience with these agents will likely further optimize our evolving treatment protocols. These treatments, however, are directed toward downstream sequelae of RVO and serve as temporizing, albeit effective, treatments against a chronic disease. While intravitreal pharmacotherapy has significantly advanced our treatment of RVO, treatment paradigms of RVO will ultimately need to address the principal occlusive pathophysiology.

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10 Evidence-Based Ophthalmology: Clinical Trials and Beyond Retinal Detachment and Proliferative Vitreoretinopathy

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I. INTRODUCTION

The management of rhegmatogenous retinal detachment has evolved over the last century as a result of advances made in surgical techniques and surgical instruments and with the advent of vitreous substitutes.

The "Custodis" method of segmental scleral buckle to seal the retinal break, without drainage of subretinal fluid (SRF), allowing for spontaneous resorption of SRF, the earliest technique, was only suitable for isolated small tears. Encircling scleral buckles offered a more effective, though more invasive, alternative for more extensive detachments and breaks. With the introduction of pneumatic retinopexy by Dominguez,[1] followed by the popularization of pars plana vitrectomy (PPV) by Machemer, the strategies for tackling retinal detachments have become more sophisticated, especially with the advent of vitreous substitutes, the use of long-acting gases, and more recently wide-angle viewing systems and high-speed state-of-the-art vitreous cutters. Despite the significant advances in techniques, proliferative vitreoretinopathy (PVR) remains the most common cause of failure for primary rhegmatogenous retinal detachment.

Randomized controlled trials (RCTs) have been designed to ask several important questions regarding retinal detachment management. The question of pneumatic retinopexy as a safe and effective alternative to scleral buckle was addressed by the Retinal Detachment Study group. The Silicone Oil study was designed to test the hypothesis that silicone oil offered an advantage over the various gas tamponades in the management of advanced PVR. The question of vitrectomy versus scleral buckle in primary uncomplicated retinal detachment continues to be controversial; however; new evidence is emerging that may clarify this issue. Randomized trials have been conducted to address this question in a group of patients with pseudophakic and aphakic retinal detachment (PARD).

II. PNEUMATIC RETINOPEXY VERSUS SCLERAL BUCKLE: THE RETINAL DETACHMENT STUDY GROUP

Pneumatic retinopexy was first introduced by Dominguez in 1984 and popularized by Hilton and Grizzard in 1985 for a nonincisional repair of retinal detachment.[1,2] Pneumatic retinopexy is based on the principle that an inert long-acting gas, when injected into the vitreous cavity, is capable of sealing a retinal break by positioning the gas bubble against the retinal tear to create an internal tamponade. The surface tension of the gas prevents continued ingress of liquid vitreous, thus allowing the SRF to be naturally absorbed by the Retinal pigment epithelium (RPE) pump. Typically, the fluid that has accumulated under the retina will be reabsorbed within 1 to 2 days depending on the chronicity and the extent of the SRF. Given that gas will disappear from the eye within 1.5 to 6 weeks, it is necessary to create a more permanent seal surrounding the retinal tear.[2] The choices in performing retinopexy include laser and cryopexy. Transconjunctival cryopexy can be performed prior to the injection of the gas bubble or on a subsequent day after resolution of the SRF. Laser photocoagulation requires attached retina and thus reabsorption of the

SRF in the area of the break and therefore is performed following gas injection.

Sulfur hexafluoride (SF_6) and perfluoropropane (C_3F_8) are the gases most frequently used in pneumatic retinopexy.[3] Sterile room air can also be used.[4] The type of gas selected is based on surgeon preference, the size of the retinal breaks, the number of breaks, the chronicity of detachment, the ability of the patient to position properly, and the duration of tamponade required. A gas bubble of 0.3 ml covers more than 45° of arc of the retina. To cover 80° to 90°, a bubble of 1.2 ml is required.[5] Generally, 1.0 ml is sufficient to cover all breaks simultaneously or alternately. This requires an injection of 0.5 ml of pure SF_6 and 0.3 ml of pure C_3F_8, and if sterile room air is injected, 0.6 to 0.8 ml is recommended. Sterile air, because of the requisite large volume of gas injected, will require a large volume paracentesis or multiple paracenteses to normalize intraocular pressure (IOP) following injection.

Patient selection and compliance are essential for success with pneumatic retinopexy. Patients with back or neck problems may not be ideal candidates. The location of the retinal breaks will determine the position that must be maintained. Breaks between 11 and 1 o'clock are easiest to target. Generally, the break should have tamponade maintained for 3 to 5 days.[6] This allows for resolution of the SRF and maturation of the chorioretinal adhesion. Restrictions that must be adhered to while gas is present in the eye include no travel above 4,000 ft and no air travel due to decreases in atmospheric pressure leading to bubble expansion and an unsafe rise in IOP. In addition, patients should not have anesthesia that requires the use of nitrous oxide. Nitrous oxide is more soluble in blood and rapidly diffuses into the vitreous gas bubble, also leading to an unsafe rise in IOP. Phakic patients should also be instructed not to lay flat on their back until the bubble dissipates to avoid prolonged contact with the lens that may accelerate formation of cataract.

Prior to pneumatic retinopexy, the primary operation for repair of retinal detachment had been scleral buckling (SB), with single surgery success rates between 75% and 88%.[7,8] However, there had been no RCT to compare the two procedures. The controversy concerning the safety, efficacy, and indications for pneumatic retinopexy led to the conduct of the Pneumatic Retinopexy Study.

Study Objectives

The Pneumatic Retinopexy Study was conducted to determine the efficacy of pneumatic retinopexy in comparison with SB for selected retinal detachments.

Inclusion/Exclusion Criteria

Patients were eligible for the study if they had

1. Single break no larger than 1 clock hour located in the superior 8 clock hours, or a group of small breaks within 1 clock hour of each other.
2. Media sufficiently clear to rule out other retinal breaks, determine macular attachment, and not significantly reduce visual acuity.
3. Availability for follow-up for at least 6 months.
4. History of good vision before retinal detachment.
5. Macula-on eyes corrected visual acuity of 20/50 or better.
6. Macula-off eyes corrected visual acuity of 20/50 or worse.
7. Shortest diameter of detachment at least 6DD.

Exclusion criteria included the following:

1. PVR, grade C or D.
2. Uncontrolled glaucoma or cup-disc ratio exceeding 0.6.
3. Retinal breaks in inferior 4 clock hours.
4. Inability to maintain required postoperative head position.

Treatment Groups/Trial Design

Prior to randomization, retinal detachments were stratified into two separate groups:

1. Macula-on
2. Macula-off

Outcome Measures

The primary outcome measures were anatomic and functional success following surgical intervention:

1. Single operation success was strictly defined as retinal reattachment at 6 months after one surgical intervention or injection of gas with one laser and/or cryotherapy performed immediately or within 72 hours.

Important Methodologic Aspects

Pneumatic Retinopexy

Pneumatic retinopexy was performed in accordance with a specific protocol (see below). The type and volume of gas injected, the number of cryopexy or laser photocoagulation applications, paracentesis, IOP at 5, 10, 20, 30, and 60 minutes were noted. The patients were not randomized to the type of gas used for the procedure.

Summary of Protocol

1. Transconjunctival cryotherapy of retinal break.
2. Eyelid speculum.
3. Topical Betadine solution with equal parts balanced salt solution, wait 3 minutes.
4. Dry injection site 3 to 4 mm posterior to limbus with cotton-tipped applicator.
5. Briskly inject sterile (millipore filter) C_3F_8 (0.3 ml) or SF_6 (0.6 ml) with a 30-gauge needle in the uppermost pars plana (supine patient with head turned 45° to side; Table 10.1).
6. Cover conjunctival perforation with sterile cotton-tipped applicator as needle is withdrawn and turn head to move gas bubble away from injection site.
7. Observe central retinal artery: if artery is closed, wait up to 10 minutes; if artery does not pulsate, use paracentesis or vitreous aspiration.
8. "Steamroller maneuver," if indicated, is done at this time.
9. Monitor IOP and central retinal artery for 60 minutes.
10. Topical antibiotics and eye pad.
11. Diamox (250 mg four times daily for 3 days) if patient will drive to a higher altitude not exceeding 4,000 ft.

Scleral Buckling

When SB was used, the surgeons were asked to perform the surgery using their usual and customary techniques. The surgeon recorded the type of buckling material, number of cryopexy applications, drainage or SRF, paracentesis, and the type and volume of gas injected.

Follow-up

Follow-up was done on days 1, 3, 7, 14, 30, 60, 120, and 180. Visual acuity was obtained using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart in a masked manner. Refractions were performed at 1 and 6 months after surgery. The macula was examined for holes, pucker, and edema. The peripheral retina was examined for new tears, SRF or blood, PVR, and choroidal detachment.

TABLE 10.1 Expansion and Duration of Intraocular Gases

Gas	Final volume	Time to final volume (hours)	Duration of effective size	Duration of bubble
Air	Injected volume	Immediate	1–3 d	1 wk
SF_6	Doubles	36	7–10 d	10–12 d
C_3F_8	Quadruples	72	4–5 wk	6 wk

C_3F_8, perfluoropropane; SF_6, sulfur hexafluoride.

Modified from Lincoff H, Haft D, Ligget P, et al. Intravitreal expansion of perfluorocarbon bubbles. *Arch Ophthalmol.* 1980;98:1646.

TABLE 10.2 Summary of the Pneumatic Retinopexy Study[12]

Outcome	Scleral buckle (%)	Pneumatic retinopexy (%)
Reattachment with one operation	82	73
Reattachment with one operation and postoperative laser/cryo	84	81
Final attachment	98	99
Visual acuity better than 20/50 with preoperative macular detachment	56	80

Summary of Major Results

1. A total of 198 eyes were followed for a minimum of 6 months, 145 (81%) were followed for 1 year.
2. In the scleral buckle group, most cases were managed with the drainage of SRF and an encircling buckle. In one-third, gas was injected.
3. In the pneumatic group, most cases were managed with C_3F_8, and approximately one quarter required paracentesis.
4. Average cryotherapy applications were similar in both groups.
5. With one operation, retinal reattachment was slightly higher in the SB group (82% with scleral buckle vs. 73% with pneumatic retinopexy), but the difference was not statistically significant. The addition of postoperative laser photocoagulation or cryotherapy resulted in similar reattachment rates (84% with scleral buckle and 81% with pneumatic retinopexy).
6. With reoperations, the final reattachment rate was 98% in the SB group and 99% in the pneumatic retinopexy group.
7. If the detachment did not include the macula, the 6-month final visual acuity was similar for both groups.
8. If the detachment included the macula for 14 days or less, final visual acuity was significantly better in the pneumatic retinopexy group ($p = 0.01$); 80% of cases treated with pneumatic retinopexy had better than 20/50 visual acuity compared with 56% with scleral buckle.
9. Phakic eyes had similar cure rates when treated by either procedure. Aphakic/pseudophakic eyes also had similar success rates by both procedures. However, as a group, aphakic/pseudophakic eyes have a lower cure rate than phakic eyes regardless of the procedure used.
10. New/missed retinal breaks occurred with significantly greater frequency in the pneumatic retinopexy group.
11. PVR developed in 5% of the SB group and 3% of the pneumatic retinopexy group. This difference was not statistically significant.
12. Complications were similar in both groups.

III. INTERPRETATION OF RESULTS AND IMPLICATIONS FOR CLINICAL PRACTICE

Multiple methods exist to successfully repair retinal detachments. Success of surgery is measured by anatomic reattachment and final visual outcome. Pneumatic retinopexy, due to its relatively noninvasive nature, is less likely to be associated with complications including anisometropia and diplopia compared to scleral buckle. Pneumatic retinopexy can restore vision more quickly with lower morbidity than other retinal operations; therefore, in selected patients, it offers certain advantages over other more invasive techniques of retinal detachment repair. The Pneumatic Retinopexy Trial demonstrated that patients with a preoperative macular detachment of less than 2 weeks duration had a significantly better chance of achieving 20/50 or better visual acuity when treated with pneumatic retinopexy compared to scleral buckle.[6] This finding has not been found in other retrospective, comparative series where no difference in final visual acuity was noted between scleral buckle and pneumatic retinopexy.[9,10]

Although single operation pneumatic retinopexy success is desirable because it is associated with the highest level of visual acuity return, the evidence suggests that a failed pneumatic attempt does not disadvantage ultimate anatomic correction of the retinal detachment. In the Pneumatic Retinopexy Study, the single procedure success rate was lower with pneumatic retinopexy compared to scleral buckle; however, the final anatomic success rate was similar.[6] Similar findings have been observed in retrospective, comparative studies of pneumatic retinopexy versus scleral buckle.[9–11] Higher single procedure failure rates with pneumatic retinopexy are ascribed to reopening of the original break, missed retinal breaks, and new retinal breaks. In a retrospective study of 213 eyes undergoing pneumatic retinopexy based on the Pneumatic Retinopexy Study Group inclusion criteria, the single procedure success rate was significantly lower in patients with preoperative vitreous hemorrhage or retinal detachment greater than 4.5 clock hours.[12] Mean visual acuity was significantly better in patients achieving retinal reattachment with single procedures (mean visual acuity 20/30) compared to those requiring a secondary procedure (visual acuity 20/60).

Success with pneumatic retinopexy depends upon case selection and surgical technique. Most favorable cases include phakic eyes with less extensive detachment, secondary to a superior retinal break less than 1 clock hour in size, and no PVR. Retrospective series of pneumatic retinopexy suggest that patients with a single retinal break and a retinal detachment in the superior two-thirds of the fundus have a single procedure success rate as high as 97%.[11] Factors negatively influencing single operation anatomic success include pseudophakia, an increased number of retinal breaks, and a greater area of detached retina. Factors not influencing outcome include the presence of lattice degeneration (less than 3 clock hours), the type of retinal break, the type or volume of gas used, the type of retinopexy (laser or cryotherapy), the sequence of gas insertion versus retinopexy application, the status of the posterior capsule, and gender.

With increased attention to health care costs, the ability to treat retinal detachments with a minimally invasive, office-based procedure may make pneumatic retinopexy increasingly important in management. Estimates have suggested that pneumatic retinopexy may cost 25% to 50% less than SB surgery when operating room and anesthesia costs are considered.[11]

Controversies and Future Use of Pneumatic Retinopexy

Increased familiarity and comfort with pneumatic retinopexy has led to expanded usage of this technique in the management of retinal detachment. Technique modifications have been suggested to improve the outcomes of pneumatic retinopexy.

Tamponade during pneumatic retinopexy is largely determined by surgeon preference. Options include sterile air, SF_6, and C_3F_8. There are limited data comparing tamponade agents' effects on procedure success rate. A randomized, noninferiority trial has been conducted comparing sterile air to C_3F_8.[13] This study demonstrated a single procedure success rate of 60% in the sterile air group and 73% in the C_3F_8 group, which was not a statistically significant difference. The final reattachment rate was 92% in the air group and 96% in the C_3F_8 group, with similar final visual acuities suggesting that sterile air is a reasonable alternative to C_3F_8. Of note in this study, 0.3 cc of tamponade was injected in each group, which is a lower volume than what many practitioners have advocated for procedures using sterile air.

Inferior retinal detachment was initially considered to be an exclusion for treatment with pneumatic retinopexy.[6] Inverted positioning required to tamponade the inferior retinal breaks was considered to be impractical. In addition, concerns have arisen regarding the practicality of prolonged inverted positioning required to achieve adequate reabsorption of SRF and chorioretinal adhesion. Inverted pneumatic retinopexy had been previously used to successfully reattach the retina following recurrent retinal detachment after scleral buckle.[14] Recent case series have revisited and

expanded the role of inverted pneumatic retinopexy. In one series of recurrent inferior retinal detachment following encircling scleral buckle, 17 patients underwent inverted positioning.[15] Positioning was achieved with 10° Trendelenburg, 10° neck extension, and 10° ocular supraduction. Tamponade was achieved with injection of 0.3 to 0.8 ml of intraocular gas. Patients maintained strict positioning for 48 hours and part-time positioning for 1 week; 88% of patients achieved lasting retinal reattachment with a median follow-up of 1.3 years (0.1 to 11.5 years). A second case series of 11 patients, including 5 primary inferior retinal detachments, achieved an 82% single procedure success rate with inverted pneumatic retinopexy.[16] Patients were positioned with their head dependent in a prone position for 8 hours. No further positioning was required. This series suggests that limited positioning in selected patients may allow inferior retinal reattachment. No comparative trials exist to determine the true efficacy of inverted pneumatic retinopexy in a larger population versus scleral buckle.

The lower single procedure success rate observed with pneumatic retinopexy has been ascribed to the frequent development of new retinal breaks. The majority of these breaks occur within 1 month of the procedure.[6] The majority will occur in the superior fundus, often in relative proximity to the initial retinal break. It is postulated that the gas bubble may shift the vitreous, leading to new areas of vitreo-retinal traction. One attempt to reduce the rate of new retinal breaks is the application of 360° laser retinopexy. In one retrospective case series, prophylactic laser was suggested to reduce the rate of new retinal breaks.[17] These findings have not been validated in prospective studies nor have the potential complications of extensive laser been fully explored.

The popularity and comfort of surgeons with PPV has prompted many to treat primary uncomplicated retinal detachment with primary vitrectomy. A RCT to compare pneumatic retinopexy to primary pars plana vitrectomy (PPPV) would help answer these questions further and elucidate whether the risk of an operating room procedure with its added cost is justified by the potential benefits of earlier rehabilitation, enhanced primary success, and faster and more complete visual recovery.

IV. VITRECTOMY VERSUS SCLERAL BUCKLE FOR PRIMARY RHEGMATOGENOUS RETINAL DETACHMENT

Introduction

The surgical choice of treatment for patients with primary retinal detachment uncomplicated by PVR remains controversial. Traditionally, the initial management of retinal detachment has been scleral buckle. Increased experience with vitrectomy, improvements in surgical instrumentation, the advent of high-speed cutters, and the introduction of wide-field viewing systems have led to an increased utilization of vitrectomy in the management of primary retinal detachment. Medicare data in the United States indicates an 80% increase in the use of vitrectomy to repair retinal detachment and a 70% decrease in SB since 1997. Potential advantages of primary vitrectomy include removal of vitreous opacities and capsular remnants, possibly faster and increased rate of foveal reattachment in macula-off retinal detachments, and avoidance of complications associated with SB including refractive shifts, extraocular muscle imbalance, and buckle extrusion.[18,19]

Data published to date suggest that vitrectomy compares favorably with SB. The two primary outcome measures of success in retinal detachment repair cited in most studies are anatomic retinal reattachment and visual acuity. The overall retinal reattachment rate for PPV in a recent review was 85%, compared to 71% to 95% reattachment rate achieved in retrospective reports of SB procedures.[20,21]

Evaluation of the literature to determine the true efficacy of primary vitrectomy compared with SB is difficult for several reasons. There is a lack of uniform inclusion criteria in the studies, including different configurations of retinal detachment, duration of detachment, and preoperative lens status that could significantly influence the results.[22,23] While the bulk of the literature on the primary repair

of retinal detachment is composed of case series, there are several comparative trials; however, in not all of these studies were the subjects truly randomized, and thus, selection bias may influence the stated results.[24] In addition, many randomized studies lack an a priori sample size calculation and thus it is difficult to determine whether the study enrollment had adequate power to detect a true difference in treatment efficacy. Duration of follow-up varies between studies. In some cases, a lack of long-term follow-up makes the results of the studies difficult to compare.

In general, vitrectomy has been compared to SB in two separate groups: pseudophakic/aphakic retinal detachment and phakic retinal detachment. In addition, some literature has examined the role of primary vitrectomy compared to combination vitrectomy/scleral buckle.

Primary Vitrectomy versus Scleral Buckle in Primary Pseudophakic and Aphakic Retinal Detachment

Capsular opacities, poor dilation, vitreous debris, and the presence of small retinal breaks have been cited as reasons for failure of primary scleral buckle in cases of PARD. Primary vitrectomy has become increasingly popular in the management of these cases due to the ease of improving visualization of small retinal breaks and the lack of induced myopia secondary to the presence of a scleral buckle. In addition, these cases are not subject to the primary complication of vitrectomy, cataract.

Several case series have been conducted examining the role of primary vitrectomy alone in the management of PARD.[24–29] These series report a primary retinal reattachment success rate ranging from 88% to 94% and a final reattachment rate of 96% to 100%. The rate of final visual acuity better than 20/50 is reported to be 69% to 79%.

Nonrandomized, comparative series have studied vitrectomy versus scleral buckle in patients with pseudophakic retinal detachment.[29] Similar primary and final retinal reattachment rates as well as visual acuities were reported. A meta-analysis of 29 published studies on the management of pseudophakic retinal detachment from 1966 to 2004 demonstrated a higher single procedure reattachment rate with vitrectomy alone (odds ratio [OR] 1.69 [1.07–2.68]) or combined PPV/SB (OR 3.54 [1.57–7.97]) compared with scleral buckle alone.[26]

Two RCTs have compared primary vitrectomy with scleral buckle in the management of pseudophakic retinal detachment.[30,31] One study was a single-center trial conducted with a single surgeon.[30] The other was conducted as a multicentered trial.[31] Both studies benefited from clear inclusion and exclusion criteria, a priori sample size calculations to ensure adequate statistical power, and a defined randomization schedule.

In the single-center RCT, 150 patients with pseudophakic retinal detachment were randomized to an encircling silicone scleral band (240 style, 2.5 mm) versus a conventional 20-gauge three-port vitrectomy, retinal reattachment with perfluoro-n-octane (PFO), and gas tamponade with 20% SF_6.[30] Results from this study indicated that vitrectomy was associated with a significantly higher single procedure anatomic reattachment rate (94% with PPV vs. 83% with SB). Operative time was significantly shortened with vitrectomy. The number of unidentifiable retinal breaks was significantly higher in the scleral buckle group, which partially accounted for the better observed single procedure success rate of vitrectomy. Final retinal reattachment rates were similar in both groups (95% in the SB group vs. 99% in the PPV group). No difference in final visual acuity was observed. Axial length was significantly increased in the scleral buckle group postoperatively.

The Pseudophakic and Aphakic Retinal Detachment Study

The PARD study group recently reported their 6-month results comparing vitrectomy to SB in the management of primary aphakic or pseudophakic retinal detachment.[31] PARD is a multicenter, prospective RCT. Eligible patients had retinal detachment following cataract extraction with or without intraocular lens implantation. A total of 225 eyes of 225 patients were enrolled in six centers, of whom 64% were pseudophakic. Patients who were eligible for the study were randomized to one of the following treatment groups:

Scleral Buckle Group

- Meridional sponge with encircling 240 band was used if fishmouthing was anticipated or if encircling was not feasible
- If no identifiable break:
  - encircling 276 tire for patients with total retinal detachment with 240 band
  - localized 276 tire to cover detached quadrants with encircling 240 band in cases with incomplete retinal detachment
- If breaks identified, cryotherapy was applied, otherwise 360° laser treatment was applied on the buckle within 1 week postoperatively
- Drainage of SRF was performed unless the retinal detachment was shallow with scant SRF

Primary Pars Plana Vitrectomy Group

- Three-port PPV without debulking of the vitreous base
- Perfluorocarbon liquid was used to assist drainage of SRF
- Endolaser was applied to identifiable breaks, otherwise two to three rows of laser was applied postoperatively to the vitreous base
- Air–fluid exchange followed by SF_6 20%
- Prone positioning for 5 days

The findings of the PARD study demonstrated a comparable single procedure, anatomic reattachment rate (68% in the SB group vs. 62.6% in the PPV group). The final success rate was similar in both groups (85% in the SB group and 92% in the PPPV group). The percentage of patients achieving 20/40 or better acuity at 6 months was equivalent in both groups (12.8% in the SB group and 11.3% in the PPV group). Myopia was associated with a significantly higher redetachment rate at 6 months in both groups ($p = 0.04$). No statistically significant difference in incidence of complications was observed between the two groups.

The differences between the results of these two RCTs likely reflect differences in the populations studied. The PARD group at enrollment had 84% of eligible eyes with hand motions or light perception visual acuity compared with a 40% to 45% rate of eyes in the single-center study with baseline acuity less than 20/400. Thus, the lower single procedure success rate and lower rates of visual recovery observed in the PARD group reflect the presence of more extensive retinal detachment and possibly detachments of longer duration.

The Scleral Buckle versus Primary Vitrectomy in Rhegmatogenous Retinal Detachment Study

The Scleral Buckle versus Primary Vitrectomy in Rhegmatogenous Retinal Detachment Study (SPR Study) conducted in Europe included both a phakic and a pseudophakic arm in a prospective RCT of scleral buckle versus PPV in primary retinal detachment[32]; 134 pseudophakic patients were randomized to scleral buckle and 132 were randomized to PPV. Patients randomized to PPV could receive an encircling buckle at the discretion of the surgeon. The details of the inclusion and exclusion criteria are listed in the section below.

A significantly higher single procedure success rate was noted in the PPV group compared to the scleral buckle group, with a 72% single procedure reattachment rate with PPV and 53.4% with scleral buckle. The final reattachment rates were similar at 94%. Visual acuity improved in both groups, with no significant difference in acuity noted at 1 year follow-up.[33]

The choice between scleral buckle and vitrectomy for the management of primary retinal detachment in pseudophakic eyes continues to be determined by surgeon preference. Improvements in vitrectomy technology, increased emphasis on refractive outcomes in vitreo-retinal surgery, and attention to cost issues including operative time will likely lead to continued increases in popularity of vitrectomy as the initial choice for management of these retinal detachments.

Primary Vitrectomy versus Scleral Buckle in Phakic Patients

One potential concern with performing vitrectomy as a method of primary repair of retinal detachment in phakic patients is the high

rate of cataract formation. Improvements in cataract surgery techniques have made lens extraction a commonplace outpatient surgical procedure. Thus, cataract formation as a complication of retinal detachment repair has been viewed by some surgeons as a minor problem that does not create a significant disadvantage to vitrectomy. This is particularly true when the complications of vitrectomy are weighed against the potential complications of SB such as anisometropia and diplopia.

Several retrospective case series have examined the role of vitrectomy in the repair of primary retinal detachment in phakic patients.[22,23,34] Many of these series did not specifically include only phakic patients. In series that contained both phakic and pseudophakic patients, the anatomic reattachment rates were not separated by preoperative lens status. It is, therefore, difficult to clearly answer the question of whether preoperative lens status significantly affects the outcome of vitrectomy.

The primary anatomic reattachment rate ranged from 64% to 89%, with final reattachment rates ranging from 92% to 100%. Final visual acuity better than 20/50 was reported in 41% to 76% of cases, though the rate of preoperative macula-off retinal detachment varied significantly between the series, making interpretation of the visual acuity data difficult.

The Scleral Buckle versus Primary Vitrectomy in Rhegmatogenous Retinal Detachment Study

The SPR Study was a randomized trial of vitrectomy versus SB in the management of primary retinal detachment.[32,33] The study consisted of two parallel trials stratified by preoperative lens status; 203 phakic patients underwent SB procedures and 206 underwent primary vitrectomy at 25 centers in Europe.

The inclusion criteria were as follows:

1. Phakic retinal detachment with well-demonstrated pathologic retinal breaks.

The exclusion criteria were as follows:

1. Posterior retinal breaks or breaks that cannot be supported by a scleral buckle
2. Greater than grade B PVR
3. Other ocular diseases that would influence final visual outcome
4. Myopia greater than 7 diopters
5. Previous intraocular surgery

The primary outcome measure was the following:

1. Change in best corrected visual acuity from baseline

The secondary outcome measures were as follows:

1. Retinal reattachment posterior to the equator
2. Development of cataract based on Lens Opacities Classification System (LOCS) III grading system
3. Development of PVR
4. Number of retinal procedures

The study randomized patients to

1. Scleral buckle performed in the preferred technique of the operating surgeon.
2. Vitrectomy with removal of traction on the retinal tear, retinopexy, and gas tamponade. Encircling scleral buckle may be included at the surgeon's discretion.

The 1-year outcome data demonstrated a nonsignificant difference in the single procedure retinal reattachment rate of 63.6% in the scleral buckle group and 63.8% in the PPV group. The final reattachment rate was 96% in both groups. Significantly better visual acuity was found in the scleral buckle group (logMar 0.33/approximately 20/40) compared to the PPV group (logMar 0.48/approximately 20/60) though no difference in final visual acuity or final reattachment rate was noted between groups. A significantly higher rate of cataract was noted in the vitectomy group, with 77% of PPV patients showing progression of lens changes compared with 46% of scleral buckle patients. The authors felt that the visual acuity outcomes were independent of cataract progression as patients with "significant" cataracts

were excluded from the final analysis and surgeons were encouraged to perform cataract surgery during the postoperative follow-up.

The use of vitrectomy in the management of phakic retinal detachment continues to increase. Further investigations will be required to validate its use as primary therapy. One factor not considered in the SPR study and other retrospective studies of PPV in phakic retinal detachment is the preoperative status of the vitreous. The presence or absence of preoperative complete posterior vitreous detachment may influence the anatomic outcomes and complication rates in cases treated with PPV.[33]

Combination Primary Scleral Buckle and Vitrectomy versus Primary Vitrectomy Alone

SB has been combined with vitrectomy in cases of unrelieved vitreo-retinal traction such as PVR. In addition, encircling bands were once popular during vitrectomy to provide support to the vitreous base and possibly avoid postoperative retinal breaks resulting from vitreous incarceration in the sclerotomies. The advent of wide-field viewing systems has led to a decline in the use of encircling bands in vitrectomy cases. Some authors have suggested adding an encircling scleral band to vitrectomy in the management of primary retinal detachment, particularly pseudophakic retinal detachment.[35–37] The case for scleral buckle in addition to vitrectomy has been traditionally made in cases of inferior retinal breaks where the buckle may provide support in areas difficult to tamponade with intraocular gas.[38,39] The single procedure success rate reported in these studies ranges from 92% to 100%. The final reattachment rates were 93% to 100%.

No randomized trials have been conducted to compare these interventions. Two nonrandomized, comparative studies have been conducted.[39,40] In both studies, the single procedure and final reattachment rates observed were similar between the two groups. Final visual outcomes were similar between the two groups. As one would expect, the addition of a scleral buckle significantly increases the rate of postoperative myopia. The SPR study did allow surgeons to include an encircling buckle at the time of primary vitrectomy. This intervention was not randomized. An encircling buckle was used in 66.7% of pseudophakic detachment patients and 50.7% of phakic detachment patients. Redetachment rates in phakic patients undergoing vitrectomy did not seem to be influenced by the placement of an encircling buckle. The recurrence rate was 29.5% with a buckle and 20.6% without a scleral buckle. In the pseudophakic group, a greater benefit to adjunct scleral buckle was noted, with a redetachment rate of 11.4% with a buckle versus 40.9% without a scleral buckle.[33]

Overall, the value of the addition of a scleral buckle to vitrectomy in the primary management of retinal detachment remains unclear. Evidence from nonrandomized series questions whether the buckle adds significant benefit to vitrectomy in the age of wide-field viewing systems. Currently, the Vitrectomy plus Encircling Band versus Vitrectomy Alone for the Treatment of Pseudophakic Retinal Detachment Study (VIPER) study is recruiting patients in Europe. Patients will be randomized to vitrectomy with or without adjunct scleral buckle.

V. VITREOUS SUBSTITUTES: SILICONE OIL SILICONE STUDY

Introduction and Study Objectives

PVR is the leading cause of failure in retinal detachment surgery. Development of preretinal membranes results in progressive traction on the retina leading to redetachment. PVR is observed in 5% to 10% of cases of retinal detachment[8] and is characterized by the growth of cellular membranes composed of metaplastic retinal pigment epithelial cells and glial cells. These membranes adhere to the retina and subsequent contraction prevents complete retinal reattachment.[41]

The management of PVR requires removal of the vitreous, dissection of preretinal membranes to relieve retinal traction, application of retinopexy to close the pathologic retinal breaks, and maintenance of retinal reattachment to allow maturation of the chorioretinal adhesion. In cases of severe retinal contracture, creation of a relaxing retinotomy or retinectomy may be required to achieve retinal reattachment.

Intraocular tamponade at the end of surgery is a crucial component in achieving long-term attachment. Tamponade may be achieved with long-acting gas or silicone oil. Long-acting gases provide temporary tamponade but are ultimately reabsorbed. Silicone oil provides long-term tamponade and generally must be surgically removed in a separate procedure. Prior to the Silicone Oil Study, the prevailing attitude was that the anatomic results of vitrectomy in cases of severe PVR would be better with silicone oil than with gas, but that the complications associated with this modality would jeopardize the visual outcomes. The concerns about the safety and efficacy of the various methods of long-term tamponade were the primary impetus for the study.

Study Objectives

1. To compare the anatomic and visual outcomes in cases of severe PVR treated with long-acting gas versus silicone oil.
2. To compare the frequency of complications between silicone oil and long-acting gas.

Inclusion/Exclusion Criteria

1. Patients 18 years and older
2. PVR at least grade C3 or higher by the Retina Society Classification (Table 10.3; Figure 10.1)[42]
3. Sufficient retinal contracture to warrant intraocular dissection
4. Visual acuity better than light perception

TABLE 10.3 Retina Society Classification of Proliferative Vitreoretinopathy[37]

Grade	Name	Clinical features
A	Minimal	Vitreous haze and pigment
B	Moderate	Wrinkling of the inner retinal surface, rolled edge to retinal break, retinal stiffness, vessel tortuosity
C	Marked	Full-thickness fixed folds
C1		One quadrant
C2		Two quadrants
C3		Three quadrants
D	Massive	Fixed folds in four quadrants
D1		Wide funnel retinal detachment
D2		Narrow funnel retinal detachment
D3		Closed funnel retinal detachment

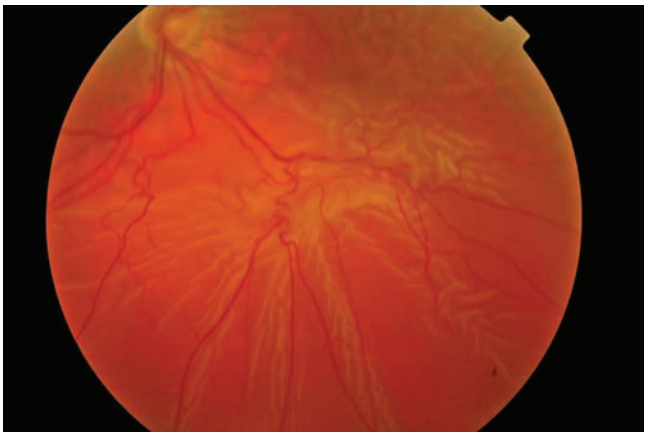

FIGURE 10.1 Photo of recurrent retinal detachment involving the macula with grade C proliferative vitreoretinopathy.

5. No concomitant eye disease including giant retinal tears and proliferative diabetic retinopathy
6. No prior penetrating trauma
7. No blunt trauma within 3 months of enrollment

Study Conduct

A total of 404 eyes were included in the study. Randomization was stratified into two groups: group 1 had no previous vitrectomy; group 2 had at least one prior unsuccessful vitrectomy with gas tamponade. From 1985 to 1987, eyes were randomized to receive either silicone oil or 20% SF_6 gas. From 1987 to 1990, eyes were randomized to receive either silicone oil or 14% C_3F_8 gas.

All eyes underwent vitrectomy with removal of epiretinal membranes and intraoperative reattachment of the retina prior to administration of the tamponade. Retinal breaks were treated with laser or cryopexy. An encircling scleral buckle was placed at the discretion of the surgeon. Lensectomy was performed as needed.

Outcome Measures

1. Anatomic reattachment was defined as continuous attachment of the macula (with or without attachment of the retina posterior to the encircling scleral buckle).
2. Functional success was measured by visual acuity 5/200 or better.
3. Complications measured were
   a. Elevation of IOP greater than 25 mmHg
   b. Hypotony (IOP less than 5 mmHg)
   c. Keratopathy including edema, localized opacity, or band keratopathy

VI. RESULTS

Phase 1 of the silicone study compared 20% SF_6 tamponade to silicone oil (Table 10.4). Eyes treated with silicone oil had a higher rate of anatomic success and better functional outcome. In eyes treated with SF_6, 50% had total retinal attachment at 36 months and 60% had macular reattachment. In the silicone oil group, 60% to 70% achieved total reattachment and 80% had macular reattachment. Correspondingly, visual acuity results were better in the silicone oil group, with 50% to 60% achieving better than 5/200 compared to 30% to 40% in the SF_6 group; 35% to 40% of eyes without prior vitrectomy (group 1) required additional surgery. In eyes with macular reattachment, keratopathy was more common in SF_6 eyes, whereas no difference was observed in cases with persistent macular detachment. Hypotony was infre-

TABLE 10.4 Phase 1 Silicone Study Results

Group	Visual acuity >5/200	*p*	Retinal attachment	*p*	Hypotony	Keratopathy
Group1						
SF_6	30–40%		Macula 60% Total 50%		Macula-on <5% Macula-off 40–50%	Macula-on 25–30% Macula-off 55–60%
Silicone oil	50–60%	<0.05	Macula 80% Total 60–70%	<0.05	Macula-on <5% Macula-off 25–30%	Macula-on 10–15% Macula-off 55–60%
Group 2						
SF_6	31%		46%		20%	23%
Silicone oil	64%		71%		20%	41%

SF_6, sulfur hexafluoride.

TABLE 10.5 Phase 2 Silicone Study Results

Group	Visual acuity >5/200 (%)	*p*	Retinal attachment	*p*	Hypotony (%)	*p*	Keratopathy (%)
Group 1							
C_3F_8	43		Macula 81% Total 73%	NS <0.05	30	<0.05	33
Silicone oil	45	NS	Macula 78% Total 64%		16		30
Group 2							
C_3F_8	38		Macula 76% Total 73%	NS	42	<0.05	45
Silicone oil	33	NS	Macula 77% Total 62%		22		43

C_3F_8, perfluoropropane.

quent in both groups with macular reattachment. Hypotony was more common in eyes with persistent macular detachment treated with SF_6.[43]

Phase 2 of the study compared the outcomes in eyes treated with 14% C_3F_8 and those treated with silicone oil. No statistically significant difference was found in the anatomic or functional outcomes between the two groups (Table 10.5). Total reattachment was achieved in 73% in both groups treated with C_3F_8 and 64% of group 1 eyes and 61% of group 2 eyes treated with silicone oil. Macular attachment rates were similar. Accordingly, visual acuity results were similar (81% of C_3F_8 eyes and 78% of silicone oil eyes in group 1 achieving better than 5/200 and 38% of C_3F_8 eyes and 33% of silicone oil eyes in group 2); 30% to 35% of eyes required reoperation. No difference in the rate of keratopathy was observed. Hypotony was statistically more frequent in eyes treated with C_3F_8.[44]

Analysis of all group 1 eyes compared to group 2 eyes treated with silicone oil or C_3F_8 (SF_6 eyes were excluded from this analysis) demonstrated no difference in the rates of complete retinal reattachment (67% group 1 vs. 67% group 2), macular attachment (78% vs. 77%), and visual acuity better than 5/200 (44% vs. 39%; Table 10.6).[45] No differences in the rates of hypotony were noted; however, keratopathy was more common in group 2 eyes. Eyes requiring more than one surgery were less likely to regain visual acuity better than 5/200.

Postoperative elevations of IOP occurred in 5% of eyes. It was more common in silicone oil eyes (8% silicone oil vs. 2% C_3F_8). Hypotony occurred in 24% of eyes. It was more prevalent in C_3F_8 eyes (31%) compared to silicone oil eyes (18%). Eyes were more likely to have

TABLE 10.6 Outcomes of Groups 1 and 2 Silicone Study Results

Group	Visual acuity >5/200 (%)	Retinal attachment	Hypotony (%)	Keratopathy (%)
1	44	Macula 78% Total 67%	20	29
2	39	Macula 77% Total 67%	19	46

chronic hypotony with a persistent macular detachment (48% with macular retinal detachment vs. 16%). This was true in both the silicone oil (42% vs. 10%) and C_3F_8 groups (54% vs. 21%). Preoperative predictors of hypotony included preoperative hypotony, chronic retinal contraction anterior to the equator, rubeosis, and large retinal breaks. Chronic hypotony was associated with poor visual acuity, persistent retinal detachment, corneal opacity, and abnormal anterior chamber depth.[46]

Corneal abnormalities occurred in 27% of eyes postoperatively. No difference in the rate of corneal abnormality was observed between the treatment groups. The predictors of corneal abnormalities were preoperative rubeosis, preoperative aphakia or pseudophakia, postoperative aqueous flare, and reoperations. Corneal abnormalities were associated with poor visual acuity and hypotony.[47]

Macular pucker was present in 64% of eyes at baseline. At 6 months follow-up, 15% of eyes had evidence of macular pucker; 31% of these were new. No difference in the rate of macular pucker was observed in the treatment groups. Preoperative predictors of macular pucker formation were preoperative aphakia or pseudophakia, absence of focal posterior or intravitreal contraction, and larger sized retinal breaks (>2 disc diameters). Functional success, with visual acuity better than 5/200, was more common in eyes without macular pucker.[48]

Retinotomies are performed in cases of severe retinal contracture not relieved by removal of the preretinal membranes. Relaxing retinotomy was performed in 29% of eyes. It was required more commonly in group 2 eyes (42%) compared to group 1 eyes (20%). Relaxing retinotomy was required more frequently in eyes with more severe anterior retinal traction including those with diffuse anterior contraction, anterior retinal displacement and subretinal membranes. Eyes not requiring relaxing retinotomies were significantly more likely to achieve posterior retinal reattachment (69% vs. 50% in group 1 and 75% vs. 48% in group 2), visual acuity better than 5/200 (60% vs. 32% in group 1 and 63% vs. 20% in group 2), and less hypotony (35% vs. 17%). Silicone oil reduced the rate of hypotony in group 1 eyes but not in group 2.[49]

Silicone oil may be removed in some eyes. In the silicone study, 45% of eyes randomized to silicone oil had the oil removed at a median time of 6 months postoperatively. Eyes having the oil removed were more likely to have an attached retina, a successful visual outcome, and no hypotony. Eyes with the oil removed were more likely to experience visual improvement; however, they were also more likely to experience recurrent retinal detachment.[50]

The study also included the creation of a new grading system for PVR that included both anterior and posterior contraction. The prior Retinal Society classification emphasized pathology posterior to the equator. The Silicone Oil grading system described six patterns of retinal contracture and their location relative to the equator (Table 10.7).[51]

Implications for Clinical Practice

The Silicone Study demonstrated that silicone oil and C_3F_8 are equivalent methods of achieving retinal tamponade following surgery for severe PVR. Silicone oil and C_3F_8 offered similar visual and anatomic outcomes, with a slightly higher rate of hypotony associated with C_3F_8. Both are superior to SF_6 in the treatment of retinal detachment and PVR. This observation is likely the result of the shorter duration of tamponade offered by SF_6.

The Silicone Study achieved macular reattachment in approximately 80% of cases. Improvements in surgical experience, technique, and instrumentation have led to continued improvement in the success of PVR surgery. The primary goal of surgery in these cases continues to be anatomic success with a single procedure. The Silicone Study confirmed that, regardless of the tamponade used, single procedure success offers the best results.

Given the equivalence of C_3F_8 to silicone oil demonstrated by the Silicone Study, the choice of tamponade rests upon the surgeon's clinical decision. Factors that may favor silicone oil include preoperative hypotony, anterior PVR, intraoperative retinotomy, need for rapid visual recovery, or inability to position postoperatively.

Inferior PVR remains one area of continued difficulty for surgeons. The silicone oil

TABLE 10.7 Silicone Study Proliferative Vitreoretinopathy Classification[38]

Type number	Type of contraction	Location	Clinical signs
1	Focal	Posterior	Starfold
2	Diffuse	Posterior	Confluent irregular retinal folds in the posterior retina; remainder of retina drawn posterior; optic nerve may not be visible
3	Subretinal	Posterior	"Napkin ring" around disc or "clothes line" elevation of retina
4	Circumferential	Anterior	Irregular folds in anterior retina; series of radial folds more posterior; peripheral retina within vitreous base stretched inward
5	Perpendicular	Anterior	Smooth circumferential fold of retina at insertion of posterior hyaloid
6	Anterior	Anterior	Circumferential fold of retina at insertion of posterior hyaloid pulled forward; trough of peripheral retina anteriorly; ciliary processes stretched with possible hypotony; iris retraction
Grade		Clinical signs	
A		Vitreous haze and vitreous pigment	
B		Inner retinal wrinkling, rolled edge to break	
P P1: one quadrant P2: two quadrants P3: three quadrants P4: four quadrants		Starfold and/or diffuse contraction in posterior retina and/or subretinal membrane	
A A1: one quadrant A2: two quadrants A3: three quadrants A4: four quadrants		Circumferential and/or perpendicular and/or anterior traction in anterior retina	

PVR, proliferative vitreoretinopathy.

that is currently available has a specific gravity less than water and therefore floats. It is exceptionally difficult to achieve a 100% oil fill and therefore the inferior retina cannot be adequately tamponaded with standard silicone oil. Fluorinated silicone oil with a specific gravity heavier than water has been developed, but widespread use has been limited by complications. Perfluorocarbon liquids also possess a higher specific gravity than water. While these have become useful intraoperative tools, concerns about retinal toxicity has limited their use in long-term retinal tamponade. Newer, partially fluorinated alkanes may provide a safer, heavier than water tamponade. Early series utilizing a mixture of 30% perfluorohexyloctane and 70% polydimethylsiloxane 1,000 (silicone oil) have demonstrated efficacy in providing inferior retinal tamponade without significant complications such as ocular hypertension and keratopathy.[52] Future investigations will be required to establish the efficacy and safety of these alternative tamponade agents.

Pharmacologic Prevention of Proliferative Vitreoretinopathy

PVR results in the development of contractile membranes on the retinal surface leading

to recurrent retinal detachment. Numerous agents including dexamethasone, retinoic acid, colchicine, daunorubicin, low-molecular-weight heparin, and 5-fluorouracil (5-FU) have been suggested as possible pharmacologic agents capable of reducing the formation and contracture of PVR membranes. To date, few of these agents are routinely used in clinical practice.

5-FU is a pyrimidine analogue that inhibits DNA synthesis. Its effects are predominantly in proliferating cells. It has been shown to inhibit fibroblast activity and PVR formation in animal models.[53] Studies of retinal morphology and Electroretinogram (ERG) in animal models have not shown evidence of toxicity with single and multiple injections.[54] Studies of single injections of 5-FU in cases of human retinal detachment have not been shown to improve the outcomes of surgery.[55] It has been hypothesized that prolonged exposure to 5-FU is necessary to achieve inhibition of fibroblasts.

A prospective controlled trial of 5-FU has been conducted in cases of retinal detachment at high risk for PVR.[56] In this study, adjuvant low-molecular-weight heparin (5 IU/ml) was combined with 5-FU (200 μg/ml). Low-molecular-weight heparin may reduce fibrin formation and act synergistically with 5-FU. Patients enrolled in the study underwent vitrectomy for repair of retinal detachment and were considered at high risk for PVR. High-risk patients had uveitis, aphakia, previous cryotherapy, more extensive retinal detachment, vitreous hemorrhage, and preoperative PVR. The risk factors used were based on a previous risk factor study conducted at the same institution.[57] Patients enrolled could have had prior therapy for peripheral retinal pathology including retinopexy and scleral buckle in 11% to 15% of cases. Patients were randomized to saline infusion during vitrectomy versus an infusion fluid containing low-molecular-weight heparin and 5-FU. A total of 174 patients were enrolled in the study and had a similar distribution of PVR risk factors at baseline. The primary outcome measure was PVR of grade CP1 or worse by the new Retina Society Classification system. The rate of PVR was significantly lower in the treated group (12.6% vs. 26.4%). Primary retinal reattachment was achieved with one procedure in 78% of treated patients and 71% of placebo patients (no significant difference). A trend toward higher reoperation rate for PVR was noted in the placebo group (18.4% vs. 10.3%) though this did not reach statistical significance. PVR was associated with a significantly poorer visual outcome. Ten patients developed postoperative hyphemas. No difference in hyphema rate was noted between the two groups. No other significant complications were noted.

5-FU has also been studied in the management of active PVR to prevent recurrent retinal detachment.[58] A total of 157 patients with grade C anterior or posterior PVR involving at least 1 clock hour were enrolled. Patients with giant retinal tears, penetrating trauma, and proliferative diabetic retinopathy were excluded. Patients were randomized to standard infusion or an infusion containing 200 μg/ml 5-FU and 5 IU/ml of low-molecular-weight heparin. The study infusion was continued for 1 hour. In cases of longer duration, the infusion fluid was changed to the standard infusion solution. All patients underwent vitrectomy with removal of epiretinal membranes. Relaxing retinotomies were performed as required. All patients had 1,000 cSt silicone oil placed at the time of surgery, with planned removal at 3 months. The primary outcome measure was stable attachment of the posterior pole without silicone oil at 6 months. Due to improved anatomic outcomes with advances in vitreo-retinal surgery, the investigators sought a more rigorous measure of success to determine the utility of adjuvant pharmacologic therapy.[58]

At the 6-month follow-up, 84% of eyes achieved total retinal reattachment and 94% had attachment of the posterior pole. At 6 months follow-up, there was no significant difference in the primary outcome measure (posterior retinal reattachment without silicone oil) between the treatment and control group (56% vs. 51%). There was a trend toward a lower rate of macular pucker in the treated group; however, this did not meet statistical significance.[58]

5-FU inclusion in the infusion solution of patients undergoing vitrectomy for retinal detachment at high risk for PVR may reduce the rate of PVR and recurrent retinal detachment. The drug is relatively inexpensive and may provide a significantly cost-effective intervention for the prevention of PVR. In general, its use has not been widely adopted due to concerns of potential toxicity and drug dosage errors at the time of infusion. In addition, clinical data supporting its usage remain limited. Nonetheless, PVR remains the primary reason for failure of retinal detachment surgery. Future investigations will likely focus on adjuvant therapies that specifically target precise steps in the pathogenesis of PVR. Gene transfer has been studied in experimental PVR and may provide options for clinical disease.[59,60] Further investigations will be necessary to better understand the role of pharmacologic agents in the prevention of PVR.

VII. VITREOUS SUBSTITUTES: PERFLUOROCARBON LIQUIDS

Perfluoron Multicenter Clinical Trial

Perfluorocarbon liquids have become an indispensable tool in the management of complex retinal detachments. Their physical properties include a high specific gravity (1.76 for PFO) and immiscibility in water. These properties can be utilized to facilitate anterior displacement of SRF or blood, unfold giant retinal tears, and provide countertraction and retinal stabilization during membrane peeling in PVR. Unlike silicone oil, their low viscosity (0.69 for PFO at 25°C) makes their injection quite simple, without a need for pressurized systems. As discussed previously, the long-term use of Perfluorocarbon liquid (PFCLs) in inferior PVR remains controversial, with conflicting reports of retinal toxicity in animals and humans.[61]

The utility and safety of heavy liquids in retinal surgery have been explored in two prospective, multicentered, collaborative studies.[62,63]

Perfluoroperhydrophenanthrene (Vitreon) was studied in 162 eyes with retinal tears of greater than 90°. Vitreon was used as a surgical adjunct to achieve intraoperative retinal reattachment. In 97.5% of cases, intraoperative retinal reattachment was achieved; 49% of the eyes experienced recurrent retinal detachment with a final reattachment rate of 90%. Complications observed in the series included cataract, macular pucker, corneal decompensation, and hypotony. Complications were not felt to be the result of the usage of Vitreon intraoperatively. In 9.9% of cases, Vitreon was left in the eye to provide long-term tamponade with a mean duration of 87 days. Cases with prolonged Vitreon exposure had similar outcomes to the remainder of the cases.[62]

The Perfluoron Study Group was a multicenter, nonrandomized study of PFO usage as an intraoperative adjunct in cases of retinal detachment complicated by PVR.[63] Eligible patients were 15 months or older and underwent surgery for retinal detachment with PVR using intraoperative Perfluoron. No attempts were made to define indications of use of Perfluoron other than surgeon preference. The study was undertaken before PFO was approved by the Food and Drug Administration and sought to explore the visual and anatomical outcomes associated with its use, as well as the rate of complications.

The study included 555 patients, followed up for a median of 5.6 months, with PVR grade C3 or higher in 73%. Postoperative visual acuity was 20/200 or better in 25% of patients, compared to 10% preoperatively. Overall, postoperative acuity improved in 60%, remained stable in 23%, and worsened in 18% of patients. Preoperative characteristics that were associated with final acuity of 20/200 or better included preoperative acuity of 5/200 or better, no diabetes mellitus, no prior vitrectomy, prior SB, no silicone oil tamponade, and no relaxing retinotomy.

Complete retinal reattachment was achieved intraoperatively in 91% of eyes and at the last follow-up in 77% of eyes. Recurrent retinal detachment was associated with significantly poorer visual outcome; 20/200 or better acuity was achieved in 12% of patients with recurrent retinal detachment,

compared with 35% of patients without recurrence ($p < 0.001$). Operative characteristics significantly associated with recurrent retinal detachment, in univariate and multivariate analysis, included female gender, creation of a relaxing retinotomy, and the use of SF_6, air, or no tamponade compared with C_3F_8 or silicone oil tamponade.

Retained PFO was noted in 7.4% of patients, corneal edema in 7%, elevated IOP in 2%, and hypotony in 15%. Significant cataract or cataract surgery was noted in 92% of phakic eyes without significant cataract preoperatively.

In summary, perfluorocarbon liquids appear to be safe and useful adjuncts in vitrectomy for complicated retinal detachments, with an acceptable complication profile and success rate. While the Vitreon collaborative group included a small number of patients with longer term retinal tamponade, little information currently exists about longer term tamponade using perfluorocarbon liquids. Future investigations will focus on the safety and efficacy of longer term usage of perfluorocarbons.

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11 Evidence-Based Medicine: The Prophylaxis and Treatment of Endophthalmitis

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In spite of significant advances in the management of endophthalmitis over the past two decades, numerous issues remain unresolved. There is no doubt that approximately 20 years ago, the advent of intravitreal antibiotics paved the way for notably improved visual and anatomic outcomes. In the mid-1990s, the Endophthalmitis Vitrectomy Study (EVS) addressed the role of vitrectomy versus vitreous tap in the treatment of postoperative endophthalmitis, and documented that patients with hand motion or better vision fared equally well with either a complete pars plana vitrectomy or a vitreous tap.[1] In a subgroup analysis it was noted that in patients with a visual acuity of light perception the outcome was better in the vitrectomy group. Both procedures employed intravitreal antibiotics consisting of vancomycin and amikacin. This study provided ophthalmologists with evidence-based outcomes in the management of postoperative endophthalmitis for the first time.

The EVS also provided ophthalmologists with very important data regarding the pathogens that most commonly cause postoperative endophthalmitis (see Fig. 11.1). Additionally, the study determined that there was no apparent benefit from the use of intravenous antibiotics (cephalosporins and aminoglycosides).[1] The systemic antibiotics chosen in the EVS were the best available at the time; however, several studies following the completion of the EVS revealed that systemically administered cephalosporins and aminoglycosides do not readily achieve therapeutic intraocular concentrations in the vitreous cavity.[2,3]

Unfortunately, even within the confines of a well-conceived and well thought-out multicenter, prospective clinical trial like the EVS, a number of pertinent issues remain unresolved or were not fully addressed in the original study. These include the choice of the intravitreal antibiotics (ceftazidime was not employed, and today it has virtually replaced intravitreal amikacin), the management of types of endophthalmitis not specifically studied in the EVS (filtering bleb–associated, posttraumatic, indolent, postintravitreal injection and fungal endophthalmitis), the role of intravitreal corticosteroids, and inpatient versus outpatient management of infection.

Additionally, since the completion of the EVS, new antibiotics such as the fourth-generation fluoroquinolones have been developed, and these agents will most likely play a key role in the treatment of proven infection or in the prophylaxis against infection in the near future (as described in the following text).

The Endophthalmitis Vitrectomy Study

In the late 1980s, the EVS group set out to determine the role of vitrectomy versus vitreous tap in the treatment of postoperative endophthalmitis, and to address the role of intravenous antibiotics versus no intravenous antibiotics in treating endophthalmitis. Vitrectomy was introduced in the 1970s and many surgeons began to employ it in conjunction with intravitreal antibiotics for treating endophthalmitis. There were several theoretical advantages to vitrectomy including the removal of the infecting organisms and

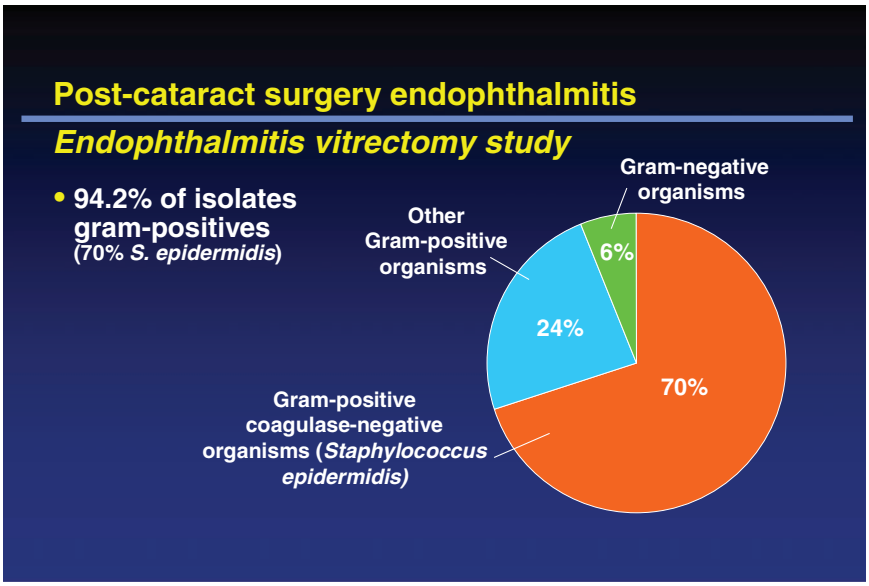

FIGURE 11.1 Endophthalmitis Vitrectomy Study confirmed growth isolates. (Reprinted from Endophthalmitis Vitrectomy Study Group. Results of the Endophthalmitis Vitrectomy Study: a randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative bacterial endophthalmitis. *Arch Ophthalmol.* 1995;113:1479–1496, with permission.)

their toxins, better distribution of antibiotics, clearing of tractional membranes that could lead to retinal detachment, clearing of opacities in the vitreous, and providing a good volume of vitreous material for microbiologic culture. Before the EVS, small human studies were inconclusive regarding the benefits of vitrectomy and in previous studies it appeared that only the most advanced cases of endophthalmitis underwent vitrectomy. Therefore, visual outcomes were poor and it was uncertain if vitrectomy would yield superior outcomes in eyes with better presenting vision. In the late 1980s, the role of vitrectomy in the management of endophthalmitis remained quite controversial. During this time, the role and benefit of systemic intravenous antibiotics in the management of endophthalmitis was also uncertain. It was the "standard of care," yet it was questioned whether the theoretical benefit outweighed the systemic side effects of antibiotics used at the time. Additional factors included an analysis of the costs of the antibiotics and hospitalization for administration of these drugs. These unresolved issues served as the impetus for the largest prospective study on endophthalmitis management to date.[4]

Clinical centers in 25 US cities enrolled 420 patients over a 3 1/2-year time frame. Entry criteria were stringent and were limited to patients who had a clinical diagnosis of endophthalmitis within 6 weeks of cataract extraction or secondary intraocular lens (IOL) placement and had a vision worse than 20/50 but at least light perception. Additionally, patients were required to have a hypopyon and clouding of the anterior chamber or vitreous media sufficient to obscure clear visualization of second-order retinal arterioles. Patients who did not have a cornea and anterior chamber clear enough to visualize at least a portion of their iris were excluded. Furthermore, the cornea needed to be clear enough to allow the possibility of pars plana vitrectomy.[4]

All eyes in the EVS underwent immediate cultures of the anterior chamber and vitreous. Intravitreal amikacin and vancomycin were administered, as were subconjunctival vancomycin and ceftazidime. Topical vancomycin,

amikacin, and cycloplegics were administered in all patients as well.[1]

Patients were randomized to the following groups: (a) Three-port pars plana vitrectomy with intravenous antibiotics (ceftazidime and amikacin); (b) three-port pars plana vitrectomy without intravenous antibiotics; (c) vitreous tap with intravenous antibiotics; and (d) vitreous tap without intravenous antibiotics.[1] The vitreous tap could be performed with or without a cutting type instrument, with a tap defined as removal of <0.3 ml of vitreous fluid.

The EVS found no difference in outcomes between immediate three-port pars plana vitrectomy and vitreous tap/biopsy for patients with hand motion or better vision (Fig. 11.2). In a subgroup analysis it was noted that in patients with a visual acuity of only light perception, improved visual results occurred in the immediate three-port pars plana vitrectomy group as compared to the vitreous tap/biopsy group. These patients were three times more likely to achieve >20/40 vision (33% vs. 11%), two times more likely to achieve >20/100 vision (56% vs. 30%), and less likely to incur a vision <5/200 (20% vs. 47%) (Fig. 11.3). No difference in final visual acuity or media clarity was noted, whether or not systemic antibiotics were employed.[1]

Confirmed bacterial growth isolates were more likely to be positive in the vitreous compared to aqueous specimens. Figure 11.1 demonstrates that 94.2% of confirmed growth isolates were gram-positive organisms (the vast majority due to one organism alone *Staphylococcus epidermidis*—70%). Gram-negative

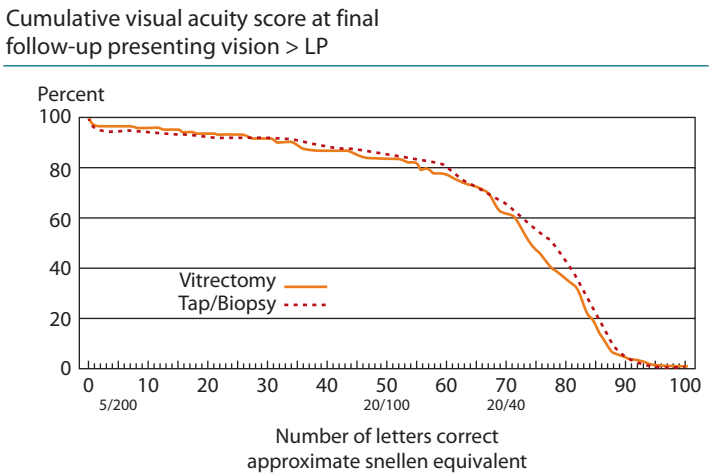

FIGURE 11.2 Immediate PPV was of no benefit for patients presenting with HM or better V_A.

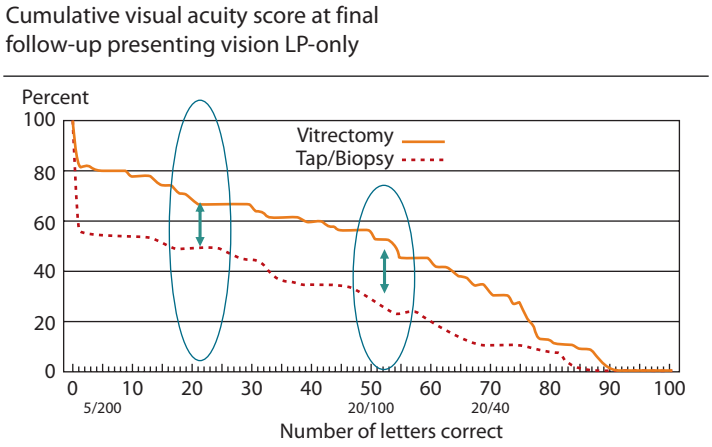

FIGURE 11.3 In patients with LP only V_A, PPV increased rate of V_A of 20/100 or better (56% vs. 30%) and >5/200 (80% vs. 53%).

organisms only comprised 5.9% of confirmed growth isolates. At the time of the EVS, all gram-positive organisms were sensitive to vancomycin. However, 2 of the 19 gram-negative organisms were resistant to both amikacin and ceftazidime.[5–8]

An analysis was performed to determine the causes of <20/40 vision after endophthalmitis. The following etiologies were found: pigmentary degeneration of the macula (18%), macular edema (17%), unclear etiology (14%), and miscellaneous causes (10%). Epiretinal membranes, presumed optic nerve damage, corneal opacity, phthisis, posterior capsular opacity, retinal detachment, macular ischemia, and vitreous opacities each accounted for <10% of causes for <20/40 vision after endophthalmitis.[1]

A subset analysis of patients with diabetes included in the EVS resulted in two interesting findings. First, diabetes was associated with a higher yield of *S. epidermidis*. Second, only 39% of patients with diabetes had a final visual outcome of >20/40 as compared to 55% of patients without diabetes. As a group, patients with diabetes fared worse and attained a less desirable visual outcome as compared to patients without diabetes.[1]

Retinal detachment occurred with an overall incidence of 8.3%. There was a minimal difference in the rates between the three-port vitrectomy group (7%) and the vitreous tap/biopsy group (9%). Retinal detachment repair was attempted in 66% of patients. The likelihood of obtaining a final visual outcome of >20/40 was 55% without a retinal detachment as compared with only 26% of patients who had a retinal detachment.[1]

The EVS answered some of the most controversial issues surrounding the management of endophthalmitis at the time. It was a well-designed study that utilized antibiotics that were the best available in the late 1980s. Additionally, the EVS taught us valuable information regarding the spectrum of causative organisms in postoperative endophthalmitis. The EVS clearly was a landmark study that provided ophthalmologists with evidence-based outcomes for managing postoperative endophthalmitis.

European Society of Cataract and Refractive Surgeons (ESCRS) Study of Prophylaxis of Postoperative Endophthalmitis after Cataract Surgery

In March of 2008, the European Registry of Quality Outcomes for Cataract and Refractive Surgery (EUREQUO) commenced. The ESCRS became the lead partner with 11 national societies as associated partners. The aims of this monumental effort were to improve treatment and standards of care for cataract and refractive surgery and to develop evidence-based guidelines for cataract and refractive surgery across Europe. The database contained data on 820,000 cataract surgeries roughly 3 years after commencing the project. Analysis included many variables spanning from outpatient versus inpatient surgery to type of IOLs chosen to same-day bilateral surgery. Of interest to this review is the European data regarding use of antibiotics in the setting of cataract surgery.[9]

The ESCRS multicenter study of the prophylaxis of endophthalmitis after cataract surgery study began in September 2003 and was terminated early in January 2006. The study included 24 ophthalmology centers in Austria, Belgium, Germany, Italy, Poland, Portugal, Spain, Turkey, and the United Kingdom. This randomized, placebo-controlled, multinational clinical study sought to evaluate prospectively the prophylactic effect of intracameral cefuroxime injection and/or perioperative levofloxacin eyedrops on the incidence of endophthalmitis after phacoemulsification cataract surgery.[10,11]

By the end of 2005, complete follow-up records had been received for 13,698 study patients. Such a clear beneficial effect from the use of intracameral cefuroxime had been observed that it was agreed it would be unethical to continue the study and to wait for the completion of all follow-up procedures before reporting this important result. If total reported cases of endophthalmitis are considered, the incidence rate observed in those treatment groups not receiving cefuroxime prophylaxis (23 cases in 6,862 patients) was almost five times as high as that in the groups

receiving this treatment (5 cases in 6,836 patients). If only cases proved to be due to infection are considered, the rate was more than 5 times as high in the treatment groups not receiving cefuroxime. Although the use of perioperative levofloxacin eyedrops as prophylaxis was also associated with a reduction in the observed incidence rate of postoperative endophthalmitis, this effect was smaller and was not statistically significant. The study group strongly recommended that intracameral cefuroxime administered at the time of surgery significantly reduced the risk for developing endophthalmitis after cataract surgery.[10]

By the time of the 2007 report, the study had recruited 16,603 patients. The study was based on a 2 × 2 factorial design, with intracameral cefuroxime and topical perioperative levofloxacin factors resulting in four treatment groups. The comparison of case and noncase data was performed using multivariable logistic regression analyses. Odds ratios (ORs) associated with treatment effects and other risk factors were estimated.[11]

Twenty-nine patients presented with endophthalmitis, of whom 20 were classified as having proven infective endophthalmitis. The absence of an intracameral cefuroxime prophylactic regimen at 1 mg in 0.1 ml normal saline was associated with a 4.92-fold increase (95% confidence interval [CI], 1.87–12.9) in the risk for total postoperative endophthalmitis. In addition, the use of clear corneal incisions (CCIs) compared to scleral tunnels was associated with a 5.88-fold increase (95% CI, 1.34–25.9) in risk and the use of silicone IOL optic material compared to acrylic with a 3.13-fold increase (95% CI, 1.47–6.67). The presence of surgical complications increased the risk for total endophthalmitis 4.95-fold (95% CI, 1.68–14.6), and more experienced surgeons were more likely to be associated with endophthalmitis cases. When considering only proven infective endophthalmitis cases, the absence of cefuroxime and the use of silicone IOL optic material were significantly associated with an increased risk, and there was evidence that men were more predisposed to infection (OR 2.70; 95% CI, 1.07–6.8)[11] (Tables 11.1 and 11.2).

Since the release of this data, numerous controversies have been discussed including the risks of administering an incorrect concentration of antibiotic into the eye. The procedure for mixing appropriate dose and volume of cefuroxime can be complex, and incorrect dosing is possible. Errors are rare, but if the incorrect cefuroxime dose is administered, it may have serious consequences for the eye. Furthermore, it was found that the use of topical antibiotics did not seem to offer a prophylactic benefit. Topical agents were not administered postoperatively until the day after surgery, and levofloxacin, a third-generation fluoroquinolone, was employed in this study. Discussions have taken place as to whether or not a fourth-generation fluoroquinolone topical agent could have been more beneficial. Additionally, one should consider if installation of topical antibiotics on the day of surgery, rather than the day after, could have shown a prophylactic effect.

Lastly, generalizability of this data has been discussed. Rates of endophthalmitis, as well as causative organisms, vary throughout the world. Therefore, concern exists as to whether or not the ESCRS data is relevant to parts of the world where baseline rates of endophthalmitis are lower or higher.

Regardless, the ESCRS Study was the largest study of an antibiotic in medical history. The results were impressive and recommendations strong. However, as with any good clinical trial, controversies exist. These mainly revolve around antibiotics chosen, timing of dosing, and applicability of trial data to non-European parts of the world. Currently, approximately one-third to one-half of cataract surgeons around the world employs cefuroxime prophylaxis in cataract surgery.

Potential New Treatment Regimens

Topical Fluoroquinolones

While topical antibiotics were not specifically studied in the EVS, they may soon play an increasingly important role in the management of and prophylaxis against ocular

TABLE 11.1 **Study design and bacteriological results relating to all endophthalmitis cases (proven and non-proven) in patients recruited to the study[11]**

Group A **Placebo vehicle drops × 5[a]** **No intracameral Injection**	**Group B** **Placebo vehicle drops × 5[a]** **Intracameral cefuroxlme injection**
2 *Streptococcus pneumoniae*	2 *Staphylococcus epidermidis*
1 *Streptococcus salivarius*	
1 *Streptococcus suis*	
1 *Streptococcus mitis, Staphylococcus epidermidis*	
1 *Staphylococcis aureus, Staphylococcus epidermidis, Propionibacterium acnes*	
3 *Staphylococcus epidermidis*[b]	
1 *Propionibacterium acnes*	
4 Non-proven	1 Non-proven
Group C **Levofloxacin drops 0.5% × 5[a]** **No intracameral injection**	**Group D** **Levofloxacin drops 0.5% × 5[a]** **Intracameral cefuroxime injection**
1 *Streptococcus salivarius*	1 *Staphylococcus warneri*
1 *Streptococcus sanguinis*	
1 *Streptococcus oralis*	
1 *Staphylococcus aureus*	
2 *Staphylococcus epidermidis*	
1 *Staphylococcus hominis/haemolyticus*	
3 Non-proven	1 Non-proven

[a]One drop 1 hour before surgery, 1 drop half an hour before surgery, 1 drop immediately postoperation, 1 drop 5 minutes later, and 1 drop 5 minutes later again. All groups received povidone—iodine 5% (Betadine) before surgery and were prescribed levofloxacin 0.5% eyedrops from days 1 to 6 after surgery 4 times daily.
[b]One removed for *PP* analysis

Reprinted from Endophthalmitis Study Group, European Society of Cataract & Refractive Surgeons. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. *J Cataract Refract Surg*. 2007;33:978–988, with permission.

infection. Although the ESCRS study did not support the use of topical antibiotics after cataract surgery, the antibiotic chosen at the time was levofloxacin, which now is considered to be an older-generation antibiotic.[11] In the early 1990s, topical ciprofloxacin was released as the first ophthalmic fluoroquinolone—this agent was embraced by corneal, cataract, and refractive surgeons as a powerful weapon against ocular infection. Other topical fluoroquinolones were subsequently released; however, some of our most powerful weapons have lost a portion of their effect because of increasing levels of resistant organisms each year, especially against the gram-positive organisms. A serious clinical problem could arise if current trends of resistance to older-generation fluoroquinolones continue. The rise in resistant organisms has challenged empiric monotherapy, creating the need for newer topical antibiotics with a broader spectrum of coverage and less risk of resistance.

During the spring of 2003, topical gatifloxacin 0.3% (Zymar by Allergan Pharmaceuticals) and topical moxifloxacin 0.5% (Vigamox by Alcon Laboratories) were released for clinical use (see Fig. 11.4. These fourth-generation fluoroquinolones have been engineered to be effective against a number of currently resistant organisms; thus, theoretically they should be able to delay the development of new

TABLE 11.2 **Total Patient Numbers and Endophthalmitis Incidence Rates in Each of the 4 Groups in the Study Based on Intent to Treat and Per Protocol Analysis (CI= Confidence Interval)[11]**

Group A	Group B
Intent to treat	**Intent to treat**
Number of patients 4,054	Number of patients 4,056
Incidence rates (%)	***Incidence rates (%)***
Total: 0.345 (95% CI, 0.119–0.579)	Total: 0.074 (95% CI, 0.015–0.216)
Proven: 0.247 (95% CI 0.118–0.453)	Proven: 0.049 (95% CI, 0.006–0.178)
Per protocol	**Per protocol**
Number of patients 3,990	Number of patients 3,997
Incidence rates (%)	***Incidence rates (%)***
Total: 0.326 (95% CI, 0.174–0.557)	Total: 0.075 (95% CI, 0.016–0.219)
Proven:0.226 (95% CI, 0.103–0.428)	Proven: 0.050 (95% CI, 0.006–0.181)
Group C	**Group D**
Intent to treat	**Intent to treat**
Number of patients 4,049	Number of patients 4,052
Incidence rates (%)	***Incidence rates (%)***
Total: 0.247 (95% CI, 0.119–0.454)	Total: 0.049 (95% CI, 0.006–0.178)
Proven: 0.173 (95% CI, 0.070–0.356)	Proven: 0.025 (95% CI, 0.001–0.137)
Per protocol	**Per protocol**
Number of patients 3,984	Number of patients 4,000
Incidence rates (%)	***Incidence rates (%)***
Total: 0.251 (95% CI, 0.120–0.461)	Total: 0.050 (95% CI, 0.006–0.181)
Proven: 0.176 (95% CI, 0.071–0.362)	Proven: 0.025 (95% CI, 0.001–0.139)

Reprinted from Endophthalmitis Study Group, European Society of Cataract & Refractive Surgeons. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. *J Cataract Refract Surg.* 2007;33:978–988, with permission.

resistant strains more effectively than their older-generation predecessors.

The structures of gatifloxacin and moxifloxacin give these drugs the capacity to delay resistance through a two-pronged approach that inhibits both the prokaryotic DNA gyrase and topoisomerase. The structure increases hydrophobicity, which decreases the resistance due to efflux pumps. Overall, the fourth-generation fluoroquinolones have enhanced gram-positive and atypical coverage while retaining gram-negative coverage, in a manner that is essentially identical to that of the older-generation fluoroquinolones.[12]

Topical fourth-generation fluoroquinolones are poised to be a powerful weapon for the corneal, cataract, and refractive surgeon for various anterior segment indications. Unfortunately, there is limited data regarding the intraocular penetration of these new-generation agents in humans. Several prior studies of earlier-generation agents have demonstrated that topically administered agents do not achieve adequate intraocular concentrations to be effective against the pathogens most commonly responsible for bacterial endophthalmitis.[13]

We completed an investigation to determine the intraocular penetration of moxifloxacin 0.5% in humans to see if therapeutic concentrations of drug can be achieved in the aqueous and vitreous after topical administration.[14]

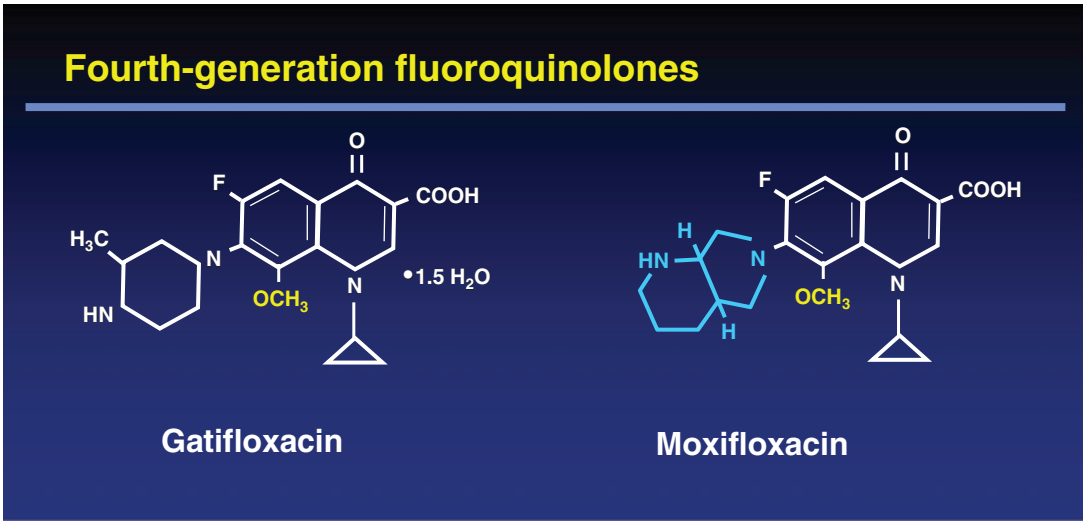

FIGURE 11.4 Graphic structures of gatifloxacin and moxifloxacin.

In this study we obtained aqueous and vitreous samples in phakic, noninflamed eyes after topically administering moxifloxacin 0.5%, either every 2 hours (Q2H) or every 6 hours (Q6H), for 3 days before surgery. We found that mean moxifloxacin concentrations in the Q2H group for the aqueous (n = 9) and vitreous samples (n = 10) were 2.28 ± 1.23 μg/ml and 0.11 ± 0.05 μg/ml, respectively. Mean moxifloxacin concentrations in the Q6H group for the aqueous (n = 10) and vitreous (n = 9) samples were 0.88 ± 0.88 μg/ml and 0.06 ± 0.06 μg/ml, respectively (see Fig. 11.5). MIC_{90} levels (minimum inhibitory concentration of antibiotic required to kill 90% of isolates) were far exceeded in the aqueous sample for a wide spectrum of key pathogens. Concentration of moxifloxacin in the vitreous did exceed the MIC_{90} for several organisms; however, the MIC_{50} (minimum inhibitory concentration of antibiotic required to kill 50% of isolates) was exceeded in the Q2H group for *S. epidermidis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Bacillus cereus*, and other gram-negative organisms.

Further studies will determine the precise role of topically administered moxifloxacin 0.5% in the management and/or prophylaxis of intraocular infections. This data may be of significance when considering prophylaxis against the development of infection in such settings as intravitreal injections that are discussed later in the chapter.

Oral and Intravenous Antibiotics

While intravitreal antibiotic injections are clearly the most effective way to achieve therapeutic antibiotic levels in the vitreous, the use of certain orally administered antibiotics can be a potential alternative/adjunct as they have been shown to achieve vitreous concentrations exceeding the MIC_{90} level for the organisms most commonly involved in bacterial endophthalmitis. Hence, the use of oral antibiotics has important implications for the ophthalmologist, particularly in the prophylaxis and/or management of postoperative, posttraumatic, or bleb-associated bacterial endophthalmitis.

As previously noted, the EVS investigated the use of intravenous amikacin and ceftazidime in conjunction with intravitreal antibiotic injection for managing acute postoperative endophthalmitis and found no improved outcomes with the use of systemic antibiotics.[1] According to studies published later, amikacin and ceftazidime were found to have very limited intravitreal penetration.[2,3]

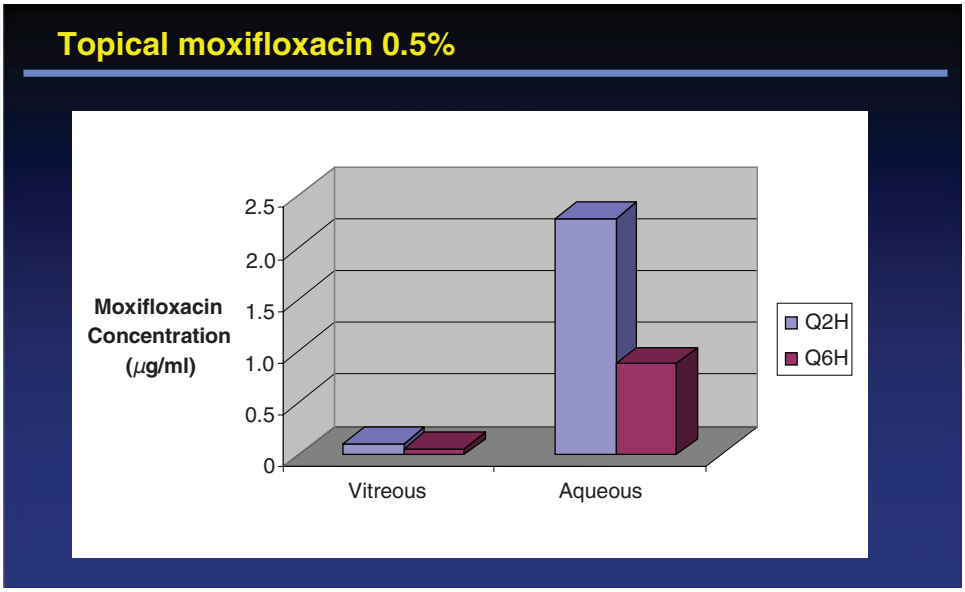

FIGURE 11.5 Intraocular concentrations of moxifloxacin after topical administration (Q2H = one drop every 2 hours for 3 days; Q6H = one drop every 6 hours for 3 days). (Reprinted from Hariprasad SM, Blinder KJ, Shah GK, et al. Penetration pharmacokinetics of topically administered 0.5% moxifloxacin ophthalmic solution in human aqueous and vitreous. *Arch Ophthalmol.* 2005;123:39–44, with permission.)

Therefore, the only conclusion that can be inferred from the EVS data regarding systemic antibiotic use is that intravenous amikacin and ceftazidime specifically have no apparent role in managing postoperative endophthalmitis. Therefore, does EVS data still apply, given the recent advancements in the development of antimicrobials? The answer is, most likely, it does not.

Over the past 10 years there has been mounting evidence in the literature that agents in the fluoroquinolone class of antibiotics are able to achieve effective concentrations in the vitreous after oral administration (see Table 11.3).[15–20] Our group has reported that orally administered gatifloxacin (Tequin by Bristol-Myers Squibb, Inc.) can achieve therapeutic aqueous and vitreous levels in the noninflamed human eye and the activity spectrum appears to appropriately encompass the most frequently encountered bacterial species involved in the various causes of endophthalmitis.[15,16] The fourth-generation fluoroquinolones, gatifloxacin, and moxifloxacin have high oral bioavailability of >90% and reach peak plasma concentrations 1 to 2 hours after oral dosing. Unfortunately, it was announced in the spring of 2006 that gatifloxacin would no longer be marketed as it caused glucose dysregulation in certain patients.

We designed a prospective, nonrandomized clinical study of 24 patients scheduled for elective pars plana vitrectomy surgery to investigate the aqueous and vitreous concentration of gatifloxacin achieved after oral administration of two 400 mg tablets taken 12 hours apart before surgery. The percentages of plasma gatifloxacin concentration achieved in the vitreous and aqueous were 26.17% and 21.02%, respectively. Mean inhibitory vitreous and aqueous MIC_{90} levels were achieved against a wide spectrum of bacteria (e.g., the vitreous concentration of gatifloxacin achieved with this dosing regimen exceeded the MIC_{90} for *S. epidermidis* by > fivefold).

Garcia-Saenz et al. reported that orally administered moxifloxacin (Avelox by Bayer) can achieve therapeutic levels in the human aqueous; however, vitreous concentration data was not obtained in this study.[20] To address this, we designed a second prospective, nonrandomized clinical study of 15 patients

TABLE 11.3 **In Vitro Susceptibilities of Moxifloxacin, Gatifloxacin, Levofloxacin, Ofloxacin, and Ciprofloxacin Showing Minimum Inhibitory Concentration at Which 90% of Isolates Are Inhibited (μg/ml)**

	Moxifloxacin[18]	Gatifloxacin[15]	Levofloxacin[17]	Ofloxacin[13]	Ciprofloxacin[19]
Mean vitreous penetration	1.34 ± 0.66 μg/ml	1.34 ± 0.34 μg/ml	2.39 ± 0.70 μg/ml	0.43 ± 0.47 μg/ml	0.56 ± 0.16 μg/ml
Gram-positive organisms					
Staphylococcus epidermidis	0.13	0.25	0.50	0.50	1.00
Staphylococcus aureus (MSSA)	0.06	0.13	0.25	0.50	0.50
Streptococcus pneumonia	0.25	0.50	2.00	2.00	2.00
Streptococcus pyogenes	0.25	0.50	1.00	2.00	1.00
Bacillus cereus	0.13	0.25	—	0.50	—
Enterococcus faecalis	1.00	2.00	2.00	4.00	4.00
Gram-negative organisms					
Proteus mirabilis	0.25	0.25	0.25	0.125	0.06
Pseudomonas aeruginosa	32.0	32.0	32.0	4.00	0.78
Haemophilus influenza	0.06	0.016	0.06	4.00	0.016
Escherichia coli	0.008	0.008	0.03	0.125	0.016
Klebsiella pneumonia	0.13	0.13	0.13	0.50	0.06
Neisseria gonorrhoeae	0.016	0.016	0.016	0.06	0.008
Anaerobic organisms					
Bacteroides fragilis	2.00	1.00	2.00	4.00	8.00
Propionibacterium acnes	0.25	0.50	0.75	1.50	—

—, Data not available.

MSSA, methicillin-sensitive *S. aureus*.

scheduled for elective pars plana vitrectomy surgery to investigate the aqueous and vitreous concentration of moxifloxacin achieved after oral administration of two 400 mg tablets taken 12 hours apart before surgery. The percentages of plasma moxifloxacin concentration achieved in the vitreous and aqueous were 37.6% and 44.3%, respectively. Mean inhibitory vitreous and aqueous MIC_{90} levels were achieved against a wide spectrum of bacteria.[18]

Moxifloxacin has an inherent advantage over gatifloxacin for gram-positive organisms. Table 11.1 reviews the mean vitreous penetration of several fluoroquinolones along with their respective MIC_{90} levels for the organisms we are most concerned about in endophthalmitis. From this table, it is readily apparent that moxifloxacin has roughly 50% lower MIC_{90} levels compared to gatifloxacin for gram positives. Although our studies have

shown similar vitreous penetration of the two agents after oral administration, moxifloxacin may have a theoretical advantage, given its activity against gram-positive organisms.

On the basis of previous studies, we can conclude reasonably that significant intraocular penetration of an antibiotic after oral administration may be a property unique to the new-generation fluroquinolones. For example, a recently published study demonstrated that cefepime administered orally does not achieve therapeutic levels in the noninflamed human eye.[21]

To demonstrate proof of the principle that orally administered fourth-generation fluoroquinolones could be used to treat intraocular infection in humans, we assessed the use of oral gatifloxacin in the treatment of localized filtering bleb infection in six consecutive patients with blebitis. These six patients were treated with oral gatifloxacin 400 mg tablets for 1 week (b.i.d. loading dose for 1 day followed by q.d. thereafter) in conjunction with a topically administered antibiotic q.i.d. (ofloxacin, ciprofloxacin, fortified ceftazidime, or fortified tobramycin). Excluded were those patients with frank bleb-associated endophthalmitis. Cultures of the superior conjunctiva were obtained in two patients revealing *S. pneumoniae* in one and *S. aureus* in the other. All patients had prompt resolution of bleb purulence, none developed clinical features of endophthalmitis, and all patients tolerated the treatment regimen well.[22]

The ideal oral antiinfective agent has several characteristics: it offers a broad spectrum of coverage for the organisms of concern, is bactericidal, is well tolerated, has excellent bioavailability with oral administration, and has rapid kill curves. We believe that these properties are intrinsic to the fourth-generation fluoroquinolones. Experience with these agents over time and further investigations will help elucidate the precise role of oral antibiotics in the management of endophthalmitis.

Intravitreal Injections

With the exponential rise in the number of intravitreal injections over the last several years, much interest exists in determining the most effective technique for prophylaxis against infection in this setting. Although practices can vary widely among physicians, an expert panel published recommendations based on areas of strong agreement and areas in which consensus was not achieved.[23]

The areas of strong agreement are as follows:

- Povidone-iodine for ocular surface, eyelids, and eyelashes
- Use of a speculum and avoiding contamination of the needle with eyelashes or eyelid margin
- Avoidance of extensive massage of the eyelids either preinjection or postinjection (to avoid expressing meibomian glands)
- Avoidance of injecting patients who have active eyelid or ocular adnexal infection
- Using adequate anesthetic for each patient (topical drops and/or subconjunctival injection)
- Dilating the eye
- Avoiding prophylactic or postinjection anterior-chamber paracentesis

Consensus was not found on the following points:

- Most did not want to use a povidone-iodine flush and preferred drops; no benefits were attributed to drying.
- Most did not use a sterile drape.
- Most advocated the use of gloves.
- Regarding the use of preinjection or postinjection antibiotics, there is a paucity of published scientific data to support a reduction in endophthalmitis.
- Regarding an intraocular pressure (IOP) check following injection, there is no consensus on the IOP level at which physicians are comfortable discharging patients.
- No consensus was reached about patient competency to self-report signs and symptoms of endophthalmitis or other adverse events.
- No consensus was reached on the need for clinical follow-up exams versus telephone exchanges with a physician or nurse.

At the present time, most ophthalmologists no longer employ preinjection or postinjection prophylactic antibiotics, and care is taken

regarding potential contamination of the surgical field from the mouth or nose (the ophthalmologist and the patient do not speak during the procedure).[24]

If infection develops after an intravitreal injection, most follow the treatment guidelines of postoperative endophthalmitis described earlier in this chapter. If the eye is eventually stabilized, a greater challenge remains in determining whether or not to continue intravitreal injections in that eye if the underling condition warrants treatment.

Great concern exists over the development of resistance to commonly used antimicrobials, especially when used repeatedly/intermittently after ocular procedures. Recent studies have shown rapid emergence of resistance of ocular surface flora following topical antibiotics and a significant prevalence of resistance in the patients being treated.[25–30]

Oral and Intravitreal Antifungal Agents

Although fungal endophthalmitis is rare in the grand scheme of intraocular infection, it remains an important clinical problem in ophthalmology because of the potentially devastating consequences resulting from these infections. Additionally, ocular fungal infections have traditionally been very difficult to treat because of limited therapeutic options both systemically and intravitreally.

In the past few years there have been major strides in the development of antifungal agents, and their potential use in the treatment of fungal endophthalmitis needs to be explored. The new-generation triazoles such as voriconazole, posaconazole, and ravuconazole represent advances in the evolution of the triazole antifungal class and have been developed to address the increasing incidence of fungal infections and the limitations of the currently available agents.[31,32]

Voriconazole (VFend by Pfizer Pharmaceuticals) is a second-generation synthetic derivative of fluconazole. It was developed by Pfizer Pharmaceuticals as part of a program designed to enhance the potency and spectrum of activity of fluconazole (i.e., in vitro potency of voriconazole against yeasts is 60-fold higher than that of fluconazole). Voriconazole differs from fluconazole because of the addition of a methyl group to the propyl backbone and the substitution of a triazole moiety with a fluoropyrimidine group resulting in a marked change in activity (see Fig. 11.6). Voriconazole has 96% oral bioavailability and reaches peak plasma concentrations 2 to 3 hours after oral dosing. Previous in vitro studies have shown voriconazole to have a broad spectrum of fungistatic action against *Aspergillus* species, *Blastomyces dermatitidis*, *Candida* species, *Paecilomyces lilacinus*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Penicillium* species, *Scedosporium* species, *Curvularia* species, and others.[31,32]

We designed a prospective, nonrandomized clinical study of 14 patients scheduled for elective pars plana vitrectomy surgery to investigate the aqueous and vitreous concentration achieved after oral administration of two 400 mg doses of voriconazole taken 12 hours apart before surgery. The percentages of plasma voriconazole concentration achieved in the vitreous and aqueous were 38.1% and 53.0%, respectively. Mean inhibitory vitreous and aqueous MIC_{90} levels were achieved against a wide spectrum of yeasts and molds (e.g., the vitreous concentration of voriconazole achieved with this dosing regimen exceeded the MIC_{90} for *Candida albicans* by over 13-fold).[33] To determine if voriconazole could be used safely for intravitreal injection, our group also performed a histopathologic and electroretinographic study using a rodent model. Our studies demonstrated that voriconazole did not cause retinal toxicity on either electroretinogram (ERG) or histology studies when intravitreal concentrations were 25 μg/ml or less. This represents a level of antibiotic that is 50-fold greater than commonly encountered MIC_{90} levels. When the concentration reached 50 μg/ml, focal retinal necrosis was occasionally noticed on histologic examination (see Fig. 11.7).[34] While further studies are obviously needed to delineate the appropriate level of voriconazole to use in humans, we have utilized this agent in select cases alone or with another novel intravenous antifungal (caspofungin), without evidence of apparent toxicity.[35–38]

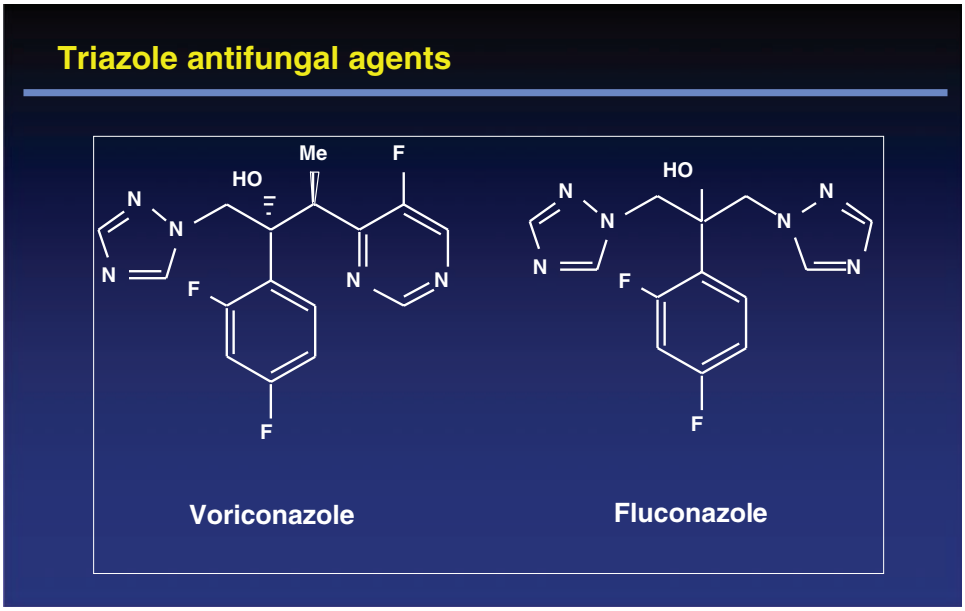

FIGURE 11.6 Graphic structures of voriconazole and fluconazole.

Orally administered voriconazole achieves therapeutic aqueous and vitreous levels in the noninflamed human eye and the activity spectrum appears to appropriately encompass the most frequently encountered fungal species involved in the various causes of exogenous and endogenous fungal endophthalmitis. In addition, oral or intravitreal voriconazole may present an alternate management technique for fungal endophthalmitis by which the risk of retinal toxicity associated with intravitreal amphotericin-B injection can be avoided.[39] Because of its broad spectrum of coverage, low MIC_{90} levels for the organisms of concern, good tolerability, and excellent bioavailability with oral administration, voriconazole may be useful to the ophthalmologist in the primary treatment of intraocular fungal infections or as an adjunct in its current management.

Intraocular Corticosteroids

The precise role that intraocular or systemic corticosteroids play in managing the various settings and etiologies of endophthalmitis remains unclear at the present time. The use of intravitreal corticosteroids was excluded from the EVS, as it was controversial at that time, and still is. The results of a survey taken in 1998 at the American Academy of Ophthalmology revealed no consensus among ophthalmologists regarding the use of corticosteroids for endophthalmitis management. There are several theoretical benefits of corticosteroid use. Corticosteroids inhibit macrophage and neutrophil migration to the area of inflammation, reduce vascular permeability, and block the release of inflammatory mediators.

Shah et al. retrospectively investigated visual outcomes between patients with acute postoperative endophthalmitis that did or did not receive intravitreal corticosteroids and found that patients who received intravitreal corticosteroids had a significantly reduced likelihood of obtaining a three-line improvement in visual acuity. While the results are most likely predicated by case selection (corticosteroids may have been employed in cases where the surgeon felt the infection was more severe), their study does not provide support for the use of corticosteroids in the postoperative setting.[40] Das et al. evaluated the efficacy of intravitreal dexamethasone in the management of exogenous bacterial endophthalmitis. They reported that intravitreal dexamethasone

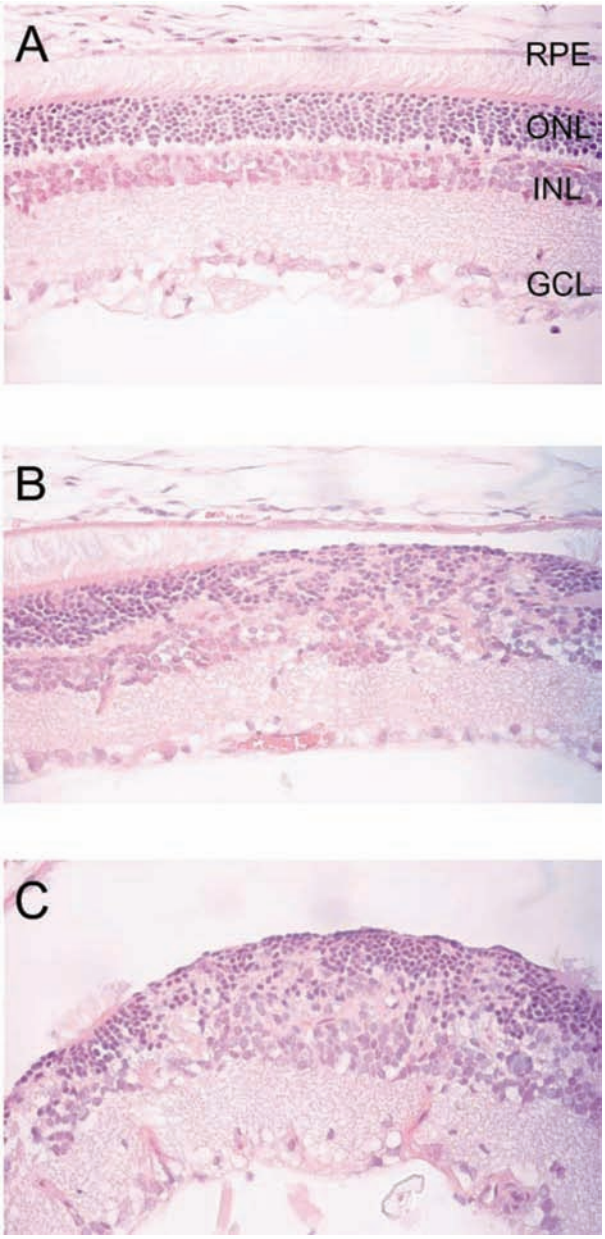

FIGURE 11.7 Intravitreal voriconazole toxicity in the rodent model. No retinal abnormalities were observed in group A (5 μg/ml, 10 μg/ml, 25 μg/ml) compared with control eyes injected with a balanced salt solution. Occasional small foci of retinal necrosis were observed in the outer retinal layers in group B (50 μg/ml). Occasional foci of more obvious photoreceptor degeneration and retinal disorganization were observed in group C (500 μg/ml). RPE, retinal pigment epithelium; ONL, outer nerve fiber layer; INL, inner nerve fiber layer; GCL, ganglion cell layer. (Reprinted from Gao H, Pennesi M, Shah K, et al. Safety of intravitreal voriconazole-histopathologic and electroretinographic study. *Trans Am Ophthalmol Soc.* 2003;101:183–189, with permission.)

aided in the early reduction of inflammation; however, its use had no independent influence on final visual outcome.[41]

At the present time the use of corticosteroids in the management of endophthalmitis remains unresolved and its use appears to be primarily based on clinical judgment and the surgeon's preference. It is not clear if this issue will ever be adequately studied in a controlled clinical trial.

Inpatient versus Outpatient Management

As the ophthalmic community develops new treatment strategies for the management of endophthalmitis, we must all be cognizant of the cost-sensitive environment in which we work. The EVS found that hospitalization and the use of intravenous antibiotics for managing postoperative endophthalmitis

alone cost tens of millions of dollars annually.[42] The EVS initially hoped that vitreous taps/biopsies would be performed outside of an operating room environment, thereby resulting in significant cost savings. As it turns out, many taps were performed in surgical operating rooms, therefore an analysis of true cost savings could not be ascertained.

Over the past several years, however, there has been a shift in the management of eye disease from the inpatient to the outpatient setting. When managing bacterial endophthalmitis, we routinely perform the tap/vitrectomy surgery on an outpatient basis, and send the patient home on oral moxifloxacin along with a topical fourth-generation fluoroquinolone. The literature does not support the use of any intravenous agent in the setting of endophthalmitis, even including antifungals such as amphotericin-B for fungal endophthalmitis, as therapeutic intravitreal levels are not achieved.[43] Therefore, hospitalization should be considered only in extenuating circumstances (i.e., noncompliance or very aggressive infection). From a socioeconomic standpoint, the shift of managing endophthalmitis from an inpatient to outpatient setting is a sensible one, which does not appear to compromise clinical outcomes.

Conclusion

In the past 20 years, numerous significant advances have undoubtedly been made in the treatment of endophthalmitis, initially culminating with the employment of intravitreal antibiotics. The EVS provided us with excellent evidence-based data regarding visual and anatomic outcomes when comparing complete pars plana vitrectomy with vitreous tap. Both groups of patients received intravitreal antibiotics. Results were shown to be equal if the visual acuity was hand motions or better, otherwise vitrectomy was the favored procedure. The ESCRS endophthalmitis study provided us guidance regarding the use of topical and intracameral antibiotics in the setting of cataract surgery; however, controversy remains regarding the choice of antibiotics and applicability of the study recommendations outside of Europe.[10,11]

There have been significant advances in the development of new-generation antibiotics also. These agents, in particular the fourth-generation fluoroquinolones, are already playing a key role in the management of ocular infection, as well as in the prophylaxis against infection. However, there are numerous unresolved issues including concerns of emerging resistance.[25–30]

Given the recent exponential growth in the number of intravitreal injections we are performing, greater attention needs to be given to optimizing the procedure to decrease rates of complications such as endophthalmitis. Simple recommendations such as use of betadine[23] and not speaking during injection procedure[24] may decrease the complication profile.

We need to rethink the applicability of the EVS data, given the availability of these "new weapons in the arsenal of ophthalmic antibiotics."[12] So while we do have evidence-based data from the EVS, with time the data has lost some of its significance, because of the new developments noted in the preceding text. Our next step is to develop new strategies for the management of intraocular infection utilizing these new fluoroquinolone agents, with a goal of limiting the impact of proven infection, or ideally eliminating the development of endophthalmitis in a cost-effective manner.

Even with the advancements over the past decade, unparalleled opportunities for the prevention and/or reduction of morbidity from intraocular infection continue to exist. While we would truly like to base all our therapeutic decisions on evidence-based data, we will still be forced to rely on data from a variety of clinical sources.

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12 Arterial Occlusive Disease

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Background

Although atherosclerotic vascular disease is primarily appreciated as the major contributor to systemic morbidity and mortality in developed nations, it is also a significant factor in ocular disease.[1,2] Furthermore, the presence of abnormalities in the ophthalmic microvasculature may reflect undiagnosed or poorly optimized systemic atherosclerotic cardiovascular disease.[3] Progressive narrowing or occlusion of the carotid arteries from atherosclerosis can cause amaurosis fugax (transient monocular vision loss) and ocular ischemic syndrome or serve as a source of emboli for branch retinal artery occlusions or central retinal artery occlusions (CRAOs).[4,5] Atherosclerotic changes in the more distal aspects of the ophthalmic vasculature such as the ophthalmic artery, the central retinal artery, and the branch retinal arteries can also cause central and branch retinal artery occlusions and has been implicated in the pathogenesis of retinal vein occlusion and nonarteritic ischemic optic neuropathy.[5–7]

The major risk factors for atherosclerotic vascular disease include increasing age, family history, diabetes mellitus, hypertension, smoking, and hypercholesterolemia.[8] Management of these risk factors is critical in the primary and secondary prevention of the ocular and nonocular complications of atherosclerotic vascular disease.[9] Patients with amaurosis fugax or retinal artery occlusions must be evaluated with carotid Doppler ultrasonography in concert with 2D echocardiography to determine if a source of the embolism can be identified.[5] More commonly, atherosclerotic disease of the internal or common carotid artery disease is the source.

In this chapter, we review three major clinical trials relevant to the management of symptomatic carotid artery disease and CRAOs as relevant to an ophthalmologist.

I. CAROTID ARTERY DISEASE—THE ROLE OF CAROTID ENDARTERECTOMY

Study Objectives

The aim of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) trial was to determine the efficacy of carotid endarterectomy (CEA) in reducing the risk of stroke among patients with a recent previous adverse cerebrovascular event and stenosis within the ipsilateral carotid artery (termed "symptomatic stenosis").[10] Despite the rising popularity of the surgery from its initial publication in 1954 through the mid-1980s, the supporting data at the time were relatively limited.[11–14]

Methodology, Design, and Outcome Measures

The trial was multicenter, parallel group, and randomized. It was conducted in a total of 106 centers within the United States and Canada. Study groups included those with a symptomatic carotid stenosis less than 50%, 50% to 69%, and 70% to 99%. Patients were randomized to receive either medical care alone or surgical endarterectomy with medical care.

To be included within the trial, patients with a carotid stenosis of 69% or less had to have suffered an ipsilateral transient ischemic attack or nondisabling stroke (Rankin score < 3) within 180 days before study entry. A total of 1,108 (CEA) and 1,118 (medical care alone) patients were randomized within this substudy.

Patients with a stenosis of 70% to 99% had to have suffered a hemispheric or retinal transient ischemic attack or a nondisabling stroke within 120 days before study entry to be included. Patients had to be less than 80 years of age. Stenoses were assessed on selective catheter angiography. Patients were required to also have a computed tomography (CT) brain, carotid Doppler ultrasound, and a chest X-ray. A total of 328 (CEA) and 331 (medical care alone) patients were randomized within this substudy. Patients were examined by neurologists at 1, 3, 6, 9, and 12 months after study entry, and then every 4 months thereafter. The study endpoint was stroke (nonfatal or fatal) ipsilateral to the side of treatment.

Summary of Major Results and Implications for Clinical Practice

The results depended on the degree of carotid stenosis. Among patients with a stenosis of less than 50%, the failure rate of treatment for the endarterectomy group was not significantly different from that for the medical treatment group (14.9% vs. 18.7% at 5 years, $p = 0.16$).

Among patients with a carotid stenosis of 50% to 69%, the 5-year rate of ipsilateral stroke was 15.7% versus 22.2% for patients treated with CEA and patients treated with medical treatment alone, respectively ($p = 0.045$). In order to prevent a single ipsilateral stroke during the 5-year period posttreatment, 15 patients would have to be treated with endarterectomy.

Among patients with a carotid stenosis of 70% to 99%, the life-table estimate of the cumulative risk of ipsilateral stroke was 36% and 9% for the medically treated and endarterectomy groups, respectively, an absolute risk reduction (±SE) of 17% ± 3.5 ($p < 0.001$). Six patients would have to be treated in order to prevent a single stroke.

Study Limitations

One of the criticisms of the NASCET trial is the method by which the percent stenosis was calculated. Authors have subsequently shown that there is a potential for variability in the ratio measurement depending on the assessor, in some cases leading to an overestimation of degree stenosis, and therefore potentially overtreatment of patients.[15] The definition of stroke has also been questioned—while the NASCET trial considered any neurological deficit lasting greater than 24 hours as a stroke, another major CEA trial, the European Carotid Surgery Trial (ECST), used 7 days as the threshold.[16] Finally, surgeon experience and operator volume have been shown to affect patient outcome following CEA (perhaps surprisingly, greater years since licensure was associated with poorer patient outcomes).[17]

Conclusions

In patients with a recent transient ischemic attack or nondisabling stroke and ipsilateral carotid artery stenosis, the benefit of endarterectomy over medical treatment alone depended upon the severity of stenosis. Patients with a severe stenosis (70% to 99%) had a significant and durable benefit from endarterectomy. Patients with a stenosis of 50% to 69% appreciated a moderate reduction in the risk of subsequent stroke, and therefore the potential benefit and indication for endarterectomy in such patients must take into account other risk factors such as surgical difficulty and patient expectations. Finally, patients with a stenosis of less than 50% did not benefit significantly from endarterectomy.

II. CAROTID ARTERY DISEASE—CAROTID ENDARTERECTOMY VERSUS CAROTID STENTING

Background

The NASCET trial, along with other landmark trials, established CEA as an effective preventive treatment for symptomatic and asymptomatic carotid artery disease

fulfilling certain criteria.[10,16,18,19] More recently, carotid artery stenting (CAS) has been used as an alternative method of restoring normal carotid blood flow via a minimally invasive, endovascular technique. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) was undertaken to directly compare CAS with traditional CEA.[20]

The Carotid Revascularization Endarterectomy versus Stenting Trial

Study Objectives

The CREST study was a large, prospective, randomized clinical trial with blinded endpoint adjudication undertaken to compare the safety and efficacy of CAS to CEA in patients with both symptomatic and asymptomatic carotid artery disease.

Methodology, Design, and Outcome Measures

The CREST trial involved 117 centers from the United States and Canada. Patients were randomized to receive either traditional CEA or CAS using the Acculink stent (Abbott Vascular, Redwood City, CA). Inclusion criteria for symptomatic patients included a history of transient ischemic attack, amaurosis fugax, or minor nondisabling stroke in the distribution of the study artery within 180 days of randomization, along with carotid artery stenosis of at least 50% by angiography, 70% by ultrasound, or 70% by CT or magnetic resonance (MR) angiography (if ultrasound was 50% to 69%). Inclusion criteria for asymptomatic patients included carotid artery stenosis of at least 60% by angiography, 70% by ultrasound, or 80% by CT or MR angiography (if ultrasound was 50% to 69%). Exclusion criteria for all patients included a history of previous disabling stroke or chronic atrial fibrillation.

The primary endpoint was a composite of any stroke, myocardial infarction (MI), or death during the periprocedural period or any postprocedural ipsilateral stroke within a 4-year time period.

Summary of Major Results and Implications for Clinical Practice

In total, 2,502 patients participated in the study, of which 53% were symptomatic and 47% were asymptomatic. There was no significant difference in the primary endpoint between CAS and CEA at 4 years (7.2% vs. 6.8%, $p = 0.51$). During the periprocedural period, there was also no significant difference in the composite primary endpoint; however, significant differences in the components of the endpoint did exist. During the periprocedural period, a higher risk of stroke was observed with CAS compared with CEA (4.1% vs. 2.3%, $p = 0.01$), while a higher risk of MI was observed with CEA compared with CAS (2.3% vs. 1.1%, $p = 0.03$). No significant difference in death rates was found during the periprocedural period between the two groups (CAS = 0.7% versus CEA = 0.3%, $p = 0.18$). The study outcomes were slightly better after CAS for patients less than 70 years and better after CEA for patients older than 70 years. Symptomatic versus asymptomatic status did not influence the outcomes.

Study Limitations

The CREST study has been criticized for grouping all the varied components of the primary endpoints together (i.e., death, stroke, and MI).[21] Also, the inclusion of an asymptomatic group potentially confounds the overall results as this group has a different natural history than the symptomatic group.[21] Finally, the CAS and CEA groups received different antiplatelet regimens periprocedurally, with the CAS group receiving double-antiplatelet therapy (aspirin in concert with clopidogrel or ticlopidine) compared with monotherapy (aspirin or clopidogrel or ticlopidine) for the CEA group. This may explain the lower MI rate observed in the CAS group.[21]

Conclusions

The results of the CREST trial suggest that clinical equipoise currently exists between CEA and CAS. This suggests that for low to average risk patients with carotid artery stenosis, either procedure can be undertaken with low overall mortality and morbidity.[22]

Further research is required to more adequately define which patients are more suitable for CEA or CAS.

III. CENTRAL RETINAL ARTERY OCCLUSION

Background

Acute CRAO is a visually devastating arterial occlusive event to the central retinal artery that results in severe ischemia to the inner retina.[23] It is not a common occurrence, accounting for 8.5 in 10,000 visits to ophthalmologists each year.[23,24] The typical presentation involves sudden, painless, and severe monocular vision loss.[25] Ophthalmic findings include poor visual acuity, typically 20/800 or worse, the presence of a relative afferent pupillary defect, whitening of the posterior pole, a "cherry-red" spot in the macula on dilated fundus examination, box-carring of the retinal vessels, and retinal artery attenuation.[26,27] Visible emboli can be seen in almost one quarter of cases.[23] Optic nerve pallor is noted in the later phases. Fluorescein angiography is valuable and shows markedly delayed filling of the retinal arterial tree.[23]

Traditional treatment options for CRAO such as anterior chamber paracentesis,[28–31] acetazolamide,[28,32] aspirin,[28,32] ocular massage and carbogen inhalation (95% oxygen, 5% carbon dioxide),[28,29,33,34] and Nd:YAG laser embolysis[35–40] have been shown to be of no utility in improving outcomes by a Cochrane meta-analysis.[28] Over the past decade, motivated by the success of using thrombolytic techniques in the management of acute MI and ischemic stroke, attention has shifted to evaluating whether thrombolysis could improve outcomes for acute CRAO.[41] Anecdotal evidence and some preliminary case reports and case series had suggested potential benefit[41–51]; however, these studies were small and had multiple design flaws, the most critical being that most of the visual gain reported could easily be attributed to learned behaviors such as eccentric viewing.[45]

The EAGLE trial (European Assessment Group for Lysis in the Eye) was designed to address this gap and rigorously evaluate the value of thrombolysis in the setting of acute CRAO.[24]

The European Assessment Group for Lysis in the Eye Trial

Study Objectives

The EAGLE trial was a randomized, controlled, and prospective multicenter superiority trial designed to compare the therapeutic efficacy of local intra-arterial fibrinolysis (LIF) using recombinant tissue plasminogen activator (tPA) to conservative standard therapy (CST) in patients with acute nonarteritic CRAO.[24]

Methodology, Design, and Outcome Measures

Nine centers across Austria and Germany were involved in this study. In total, 84 patients were enrolled over a 5-year period. The primary outcome was improvement in best-corrected visual acuity (BCVA) at 1 month; safety was evaluated as a secondary outcome. Inclusion criteria included age between 18 and 75 years, nonarteritic CRAO of 20 hours duration or less, and BCVA worse than 0.5 logMAR (Snellen equivalent of 20/63). All patients underwent a comprehensive ophthalmic examination including BCVA, visual fields, fundus photography, and fluorescein angiography. LIF was carried out by superselectively placing a microcatheter under image guidance into the ophthalmic artery. Up to 50 mg of tPA was infused and real-time measurement of visual acuity and fundoscopic examination was performed. The CST group underwent hemodilution and ocular massage and received topical beta-blockers as well as 500 mg of intravenous acetazolamide for intraocular pressure reduction.

Summary of Major Results and Implications for Clinical Practice

At 1 month, there was no significant difference between the LIF and CST groups, with both groups having visual improvement of 0.4 logMAR. There was also no statistically detectable difference in the percentage of eyes with BCVA >1.0 logMAR (Snellen equivalent of 20/200) between the two groups (15.0% vs. 16.7% for the CST and LIF groups, respectively). The study was discontinued after the first interim analysis of the data safety monitoring committee because of the LIF group's

high rate of serious adverse reactions (3 of 35 patients experienced intracranial bleeding or hemiparesis).

Study Limitations

The EAGLE trial has been criticized for certain design flaws.[52] One of the main criticisms is that the inclusion criterion for CRAO duration (up to 20 hours) was too long. Experimental research in primates, in which the central retinal artery is clamped to arrest blood flow, suggests that the retinal tissue suffers massive and irreparable damage and necrosis after approximately 4 hours of ischemia.[53,54] This would suggest that any therapy aimed at restoring blood flow after this 4-hour window would be futile. However, this experimental situation does not necessarily replicate what actually occurs in humans during acute CRAO.[55] In most cases, as fluorescein angiography often reveals, the central retinal artery is not 100% occluded and some residual blood flow is detectable. This could theoretically prolong a potential therapeutic window.

The other major criticism is that the nature of the embolism in CRAO is not amenable to thrombolysis.[52] Pathological data on enucleated eyes have shown that only 15% of retinal emboli are composed of platelet-fibrin, with the remainder being cholesterol (75%) or calcific (10%) emboli.[25] However, the latter two can potentially develop secondary platelet thrombi, suggesting that thrombolysis in CRAO does have some scientific rationale.[55–57]

Conclusions

CRAO remains a visually devastating condition with no known treatment and generally a very poor visual outcome and no proven therapy to mitigate against vision loss. It is essential to appropriately investigate patients from a cardiovascular standpoint and critical to rule out underlying giant cell arteritis as a causative factor.

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13 Retinopathy of Prematurity (ROP)

Emmanuel Chang MD, PhD and Antonio Capone MD

Introduction and Background of Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a vasoproliferative retinopathy affecting premature infants of low birth weight. With the advancing medical technology to sustain newborns of very young gestational age, there is a resurgence of ROP despite restricted oxygen saturation monitoring. It is the leading cause of preventable blindness in children.[1,2] ROP also remains a leading cause of blindness worldwide[3]: developed countries are seeing an increase in ROP as neonatologists have the ability to improve survival of the extremely young gestational age infants < 24 weeks, and developing countries are seeing an increase in survival of premature infants due to improved access to neonatal equipment.[4] This chapter will provide a basic clinical foundation and understanding of ROP and review the landmark clinical trials conducted over the last 20 years.

Pathogenesis of Retinopathy of Prematurity

ROP is multifactorial in origin, with incomplete retinal vascularization as a consequence of prematurity a prerequisite. Retinal vascular development begins prior to 16 weeks gestation and grows steadily from the optic nerve toward the ora serrata.[5] Vascular development of the immature, incompletely vascularized retina is highly influenced by systemic oxygen concentration levels and is regulated in part by vascular endothelial growth factor (VEGF). Normal vasculogenesis during early fetal development is determined by local "physiological" hypoxia as a consequence of increasing retinal thickness, which creates an increase in metabolic demand in advance of the developing intraretinal vessels. Astrocytes in this hypoxic leading edge respond by secreting VEGF that promotes vascular development to meet the increasing metabolic demand of the maturing avascular retina, resulting in normal vasculogenesis from the optic nerve to the ora serrata.[6,7]

ROP occurs as a result of an oxidative insult that inhibits normal retinal vasculogenesis of the maturing avascular retina. The prematurely born neonate is exposed to dramatically elevated oxygen levels (relative to intrauterine physiologic oxygen concentration), resulting in retinal hyperoxia, vasospasm, and shutdown of sections of the developing retinal vasculature. The ensuing retinal ischemia stimulates a reactive overproduction of VEGF, which leads to the pathologic vasculogenesis known as ROP.[7,8]

Insulin-like growth factor-1 (IGF-1) has also been implicated in controlling VEGF activation where low levels of IGF-1 prevent vascular development. Oxygen-independent IGF-1 and oxygen-dependent VEGF are complementary and synergistic vascular signaling mechanisms.[9] Genetic factors, such as defects in Norrie disease gene and Frizzled-4 gene, have also been implicated in the pathogenesis of ROP,[10,11] suggesting that some preterm babies may have a genetic predisposition to ROP.[12] This line of research suggests opportunities for therapies targeting the production of specific isoforms of VEGF or intervening at various steps of misregulated vasculogenesis.

1st edition contributions from Anna Ells, MD, FRCS (C).

In the normally developing eye, regression of the vitreohyaloidal vascular network occurs concurrently with retinal vasculogenesis. Imbalances of VEGF and other growth factors may also impair normal regression of vitreohyaloidal vasculature, impacting vitreous development and organization in the developing neonate as well.

International Classification of Retinopathy of Prematurity—(ICROP-II)

The International Classification of ROP (ICROP)[13-15] provides a widely accepted vocabulary describing the clinical features of ROP.

(a) *Location of Retinopathy:* The retina is divided into three concentric circles or zones, centered on the optic disc. The lower the zone, the more severe the disease (Fig. 13.1).
- Zone I—the posterior pole, consisting of a circle whose radius is twice the distance from the optic disc to the macula.
- Zone II—a doughnut-shaped area of retina that extends from the edge of zone I to a position tangential to the nasal ora serrata and around an area near the temporal anatomic equator.
- Zone III—the outermost residual crescent of retina anterior to zone II.

(b) *Severity of the Retinopathy:* The severity of the disease is attributed to the stage of the disease. The higher the stage, the more severe the disease.
- *Stage 1*: a demarcation line separating the normally developing retina from avascular, peripheral retina
- *Stage 2*: ridge of mesenchymal tissue with height and width in the region of the demarcation line
- *Stage 3*: the ridge develops extraretinal fibrovascular proliferation (EFP) or neovascularization (Fig. 13.2)
- *Stage 4*: partial retinal detachment (Fig. 13.4)
  - Stage 4A—detachment that does not include the macula
  - Stage 4B—detachment that does involve the macula
- *Stage 5*: complete retinal detachment

(c) *Extent of Retinopathy:* The extent of the disease is reported according to the circumferential accumulation of ROP, reported in clock hours in the appropriate zone.

Plus Disease

The presence of dilatation and tortuosity of posterior retinal vessels in at least two quadrants that may later increase in severity to include iris vascular engorgement,

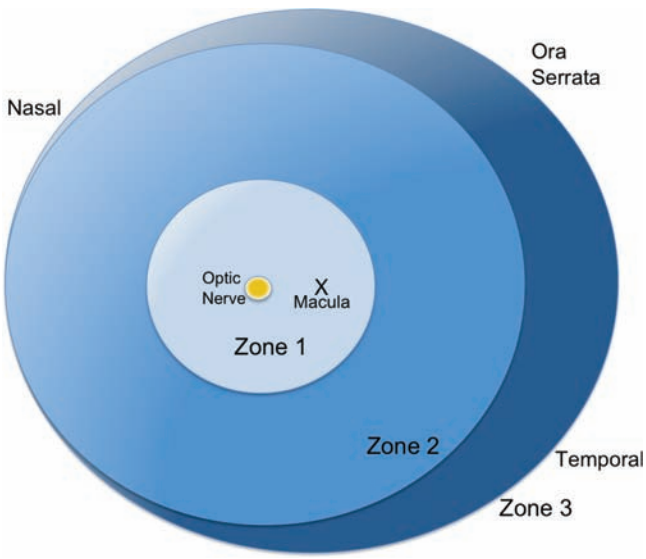


FIGURE 13.1 Diagram illustrating zones and clock hours used in the classification of retinopathy of prematurity.

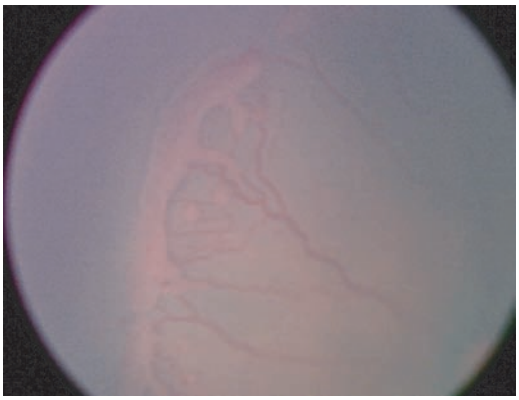


FIGURE 13.2 Photograph of right eye highlighting stage 3 extraretinal fibrovascular proliferation and several "popcorn" lesions (early fibrotic neovascular buds). Note avascular retina anterior to stage 3 retinopathy of prematurity.

poor pupil dilation in response to medication (rigid pupil), and vitreous haze are the characteristic features of "plus disease" (Fig. 13.3). Vitreous haze occurs as a consequence of blood–ocular barrier compromise and is associated with a particularly poor prognosis. Plus disease may be superimposed on any stage of ROP and is a sign that ROP is, or may become, severe.[16,17]

Advanced plus disease is obvious, but mild plus diseases can sometimes be difficult to delineate in ROP when classic EFP is not apparent. A standard photograph can be used to define the minimum amount of vascular dilatation and tortuosity required to make the diagnosis of plus disease, and this approach has been used extensively in multicentered clinical trials.

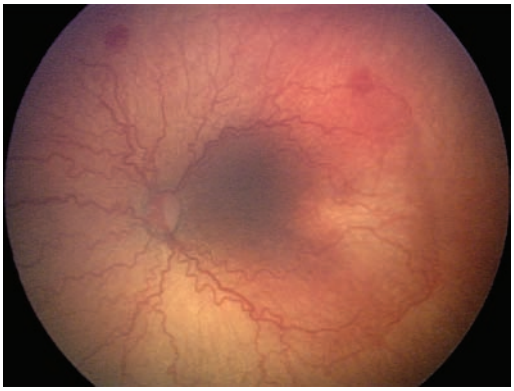


Figure 13.3 This photograph demonstrates vascular changes of the posterior pole vessels consistent with plus disease in all four quadrants. Note zone I, temporal, "flat" neovascularization and circumferential vessels, as seen in aggressive posterior retinopathy of prematurity.

The description so far refers to the acute phases of ROP. After the acute phase, regression of abnormal fibrovascular tissue can lead to late features, including cicatricial distortion of retinal architecture, with dragging of the retina usually toward the temporal retinal periphery and collapse of the temporal vessel arcade angle (Fig. 13.4).[18]

Revision of the International Classification of Retinopathy of Prematurity (2005)—ICROP-II[15]

The 1984–1987 classification has recently been revisited and published for the first time, in its entirety. As a result of research and experiences gained over the last 20 years, the following amendments have been made:

a) *Clarification of zone I.* If the disc is seen at the edge of the retinal image when examining the retina with a 25 or 28 D lens, the approximate limit of zone I will be visualized at the opposite edge of the condensing lens.

b) *Addition of pre-plus to the classification.* Pre-plus is defined as increased dilation and/or tortuosity of retinal arteries and/or veins in at least two quadrants, which is not severe enough to meet the criteria of plus disease (Fig. 13.5). These dilated and/or tortuous vessels are often present peripherally, initially near the ridge and progress posteriorly with increasing VEGF activity. Therefore, it is important to evaluate the vasculature near the ridge since simply evaluating the vasculature near the optic disc may miss early pre-plus clinical findings. Over time, the vessel abnormalities of pre-plus may progress to frank plus disease or revert to normal.

c) *Addition of "aggressive, posterior ROP" (AP-ROP).* This is a once uncommon severe form of ROP, which presents earlier and

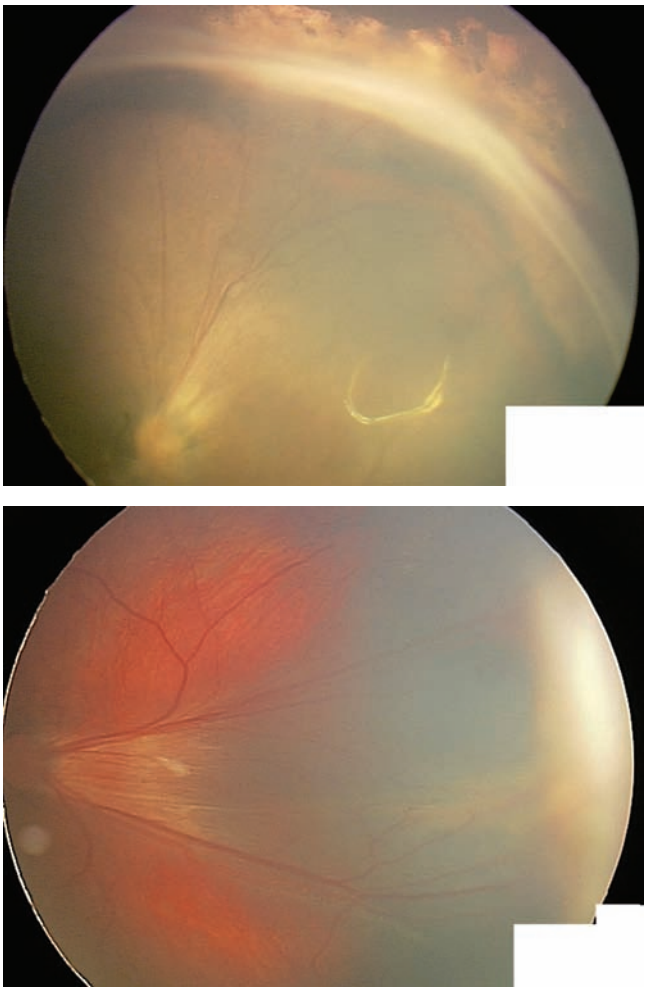


Figure 13.4 Wide-angle photograph of cicatricial retinopathy of prematurity. Note dragging of retinal vessels and significant collapse or narrowing of the temporal arcade angle. Also note peripheral elevated fibrotic membrane, remnant of a stage 4B detachment, forming a macular fold.

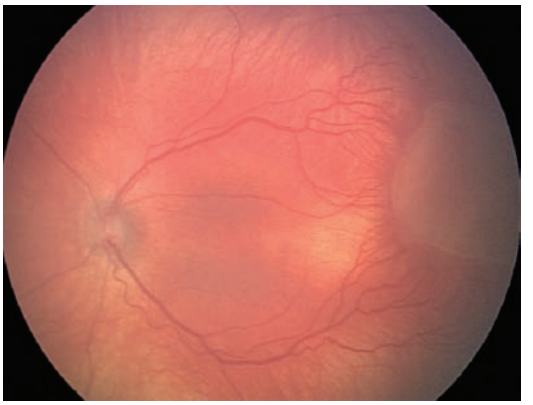


FIGURE 13.5 Photograph demonstrating pre-plus vascular changes in the temporal quadrants, forming a "notch-type" configuration of stage 3 disease.

progresses rapidly to stage 4 and 5 if left untreated (Fig. 13.6). AP-ROP has the following characteristics:

a. Posterior location—Usually zone I
b. Plus disease without prominent ridge proliferation or classic stage 3
c. Low-lying, tangled web of vessel (sometimes called "flat neovascularization")
d. Typically extends circumferentially

Major Clinical Trials in Retinopathy of Prematurity

1. The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (***CRYO-ROP***)—1990

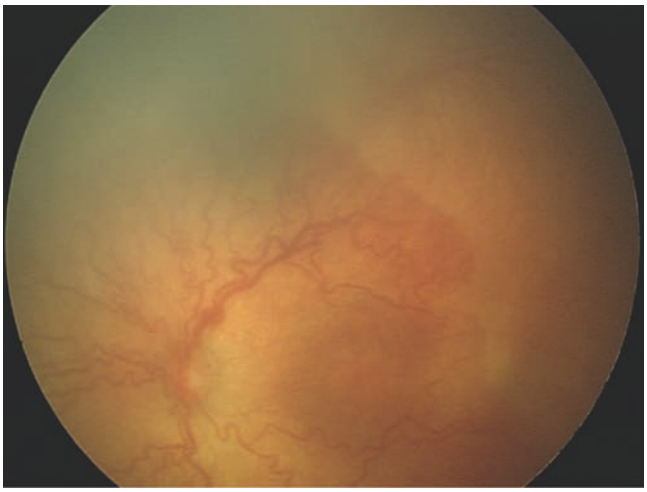


FIGURE 13.6 Photograph demonstrating aggressive posterior retinopathy of prematurity (posterior, flat neovascularization, associated with plus disease in all four quadrants).

2. Supplemental Treatment of Oxygen Protocol for Retinopathy of Prematurity—2000
3. The Early Treatment for Retinopathy of Prematurity Study—2003

The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity

A multicenter randomized trial by the Cryotherapy for ROP Cooperative Group, which published its first outcome report in 1990.

Study Question

1. Does retinal ablation using cryotherapy of the peripheral avascular retina reduce the risk of significant visual loss (stage 4 or above; macular retinal fold; vision less than 20/200) in the treated eye?
2. Using natural history data from nontreated eyes, what are the factors associated with development of severe ROP and unfavorable outcomes?

Inclusion Criteria

1. Birth weight less than 1,251 g
2. Survived at least 28 days

Exclusion Criteria

1. The presence of lethal congenital abnormalities
2. Major ocular abnormalities
3. Progression beyond threshold disease in either eye, prior to randomization
4. Transfer of infant to a nonstudy hospital or follow-up not feasible

Definition of Threshold Retinopathy of Prematurity

Five continuous or eight noncontinuous clock hours of stage 3 ROP, in the presence of plus disease. This definition was based on natural history ROP data, indicating that there was a "threshold" of amount of severe disease, which predictably resulted in significant cicatricial ROP and subsequent poor visual outcome.

Study Design

This is a multicenter, randomized interventional study with a longitudinal natural history cohort. During serial biweekly or weekly ROP examinations, if both eyes developed "threshold ROP," one eye was randomized to receive treatment of the peripheral avascular retina for 360° using cryotherapy or no treatment. If only one eye reached threshold ROP, then only that eye was randomized to cryotherapy or no treatment. Cryotherapy was performed within 72 hours of determination of threshold disease, to limit the risk of progression of disease to stage 4.

A detailed fundus examination was performed independently by two investigators at 3 and 12 months after cryotherapy and

stereophotographs of the posterior pole and the anterior segment of the eye were then sent to a Fundus Photograph Reading Center where photographs were graded as "unfavorable outcome" or "favorable outcome."

1. *Unfavorable Outcome*: An unfavorable **structural** outcome referred to a retinal fold involving the macula or a retrolental tissue. An unfavorable **visual** outcome referred to Snellen visual acuity less than 20/200.
2. *Favorable Outcome:* A favorable **structural** outcome referred to no retinal fold through the macula, with an attached retina. A favorable **visual** outcome referred to Snellen visual acuity of 20/200 or better.

Summary of Major Findings (Table 13.1)

1. The average number of clock hours of stage 3 at determination of "threshold" was 9.6 in both treated and nontreated eyes.
2. Infants who reach "threshold ROP" should be treated because the risk of blindness is predicted to approach 50% at this level of disease severity. A total of 50.6% of the control eyes were categorized as being blind or having low vision, whereas only 31.9% of the treated eyes showed acuity results in the blind or low vision category at the 1-year outcome.
3. Peripheral retinal ablation with cryotherapy reduced the incidence of retinal detachment by 50% and reduced the incidence of "unfavorable" visual outcome from 56.3% to 35.0% in the treated eyes.
4. Long-term follow-up of these children confirms the continued benefits of treatment, but despite the best available treatment at that time, over 50% of children had a visual acuity of <20/200 in the treated eye at 10 years.[19] The proportion of eyes with visual acuity 20/200 or better was 25.9% in the control group and 48.9% in the treated group at the 15-year examination.

Implications for Clinical Practice

The question of whether or not cryotherapy ablating the avascular retina in the presence of a significant amount of EFP (threshold ROP) would decrease cicatricial ROP and the resultant loss of vision or blindness led first to the unification of the ROP classification and then publication of the ICROP. The formation of the Cryotherapy for ROP Cooperative Group soon followed to study the question of treatment using cryotherapy for this potentially blinding disease. This clinical trial was not the first study addressing treatment of ROP but it was the first multicenter randomized clinical trial in the treatment of ROP.[23,24]

With the advent of argon and diode lasers in treating other retinal diseases, and the publication of smaller studies demonstrating that ablation of the peripheral avascular retina reduced the likelihood of visual loss and blindness, photocoagulation of the avascular retina for threshold ROP quickly replaced cryotherapy in many centers throughout North America and the world.[25-30] Transpupillary diode and argon retinal laser photocoagulation has subsequently been shown in small clinical studies to reduce

TABLE 13.1 Summary of the CRYO-ROP Outcomes Published to Date

CRYO-ROP outcomes	1 y[20] treated/control	5.5 y[21] treated/control	10 y[19] treated/control	15 y[22] treated/control
Unfavorable Structural Outcome	25.1/44.7%	26.9/45.4%	27.2/47.9%	30.0/51.9%
Total retinal detachments	18.3/33.0%	22.1/38.6%	21.6/41.4%	No data
Number of blind eyes	51/80%	56/85%	70/105%	69/102%
Unfavorable VA Outcome	Recognition VA not measured at 1 y	47.1/61.7%	44.4/62.1%	44.7/64.3%

CRYO-ROP, The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity; VA, visual acuity.

the amount of myopia and improve visual outcomes from less pigment disruption in the macula, when compared with cryotherapy.[31,32]

An enormous amount of information about the natural history of ROP was documented as the secondary objective of the CRYO-ROP study in the 1-, 5-, 10-, and 15-year outcome reports. The salient points with clinical applications are summarized as follows:

1. *Age of Onset of ROP:* ROP develops over a relatively narrow postmenstrual age (PMA) range and is related more to the stage of development of the infant, by PMA, than neonatal events.[33,34]
2. *Zone of involvement:* The propensity for severity is governed to a large extent by the state of retinal vascularization at birth, so that zone is perhaps the most important predictor of outcome.[17,35] Thus, incomplete vascularization in zone I carries a 54% risk of reaching threshold, but this falls to only 8% when vessels have reached zone II.
3. *Progression of Disease:* The more premature the neonate, the more posterior the zone or location of the retinopathy and the greater the potential for progression of the disease. Thus, zone I disease is very likely to progress to stage 3 needing treatment, but ROP confined entirely to zone III rarely requires treatment. As with the onset, the rate of progression is also governed predominantly by developmental age (i.e., PMA) rather than by postnatal age, or neonatal events.[33] The median PMA at which the various stages develop is as follows: stage 1, 34 weeks; stage 2, 35 weeks; stage 3, 36 weeks, and for threshold ROP, 37 weeks PMA (Fig. 13.7). In the CRYO-ROP study, babies were randomized for treatment within 72 hours of diagnosis of threshold ROP, which was at a mean age of 37.7 weeks PMA (range 32-50 weeks).[20] This was confirmed by comparing the rate of progress in CRYO-ROP and LIGHT-ROP trials.[36] It is important to note the extremes of this range. Subhani et al.[37] reported threshold ROP at 31 weeks PMA, but almost all infants will develop severe ROP by 46.3 weeks PMA. The no-treatment, natural history arm of the CRYO-ROP trial showed that once threshold develops, there is progression to an unfavorable outcome in approximately 50% of eyes.
4. *Regression of ROP:* Most infants with stage 1 or 2 ROP will have spontaneous regression of the disease.[33,38] For infants with birth weight of <1,251 g, stage 1 ROP was the highest stage reached in 25.2%, stage 2 ROP in 21.7%, and threshold in 6.0%.[33]

Major Unanswered Questions or Limitations of the Cryotherapy for Retinopathy of Prematurity Study

1. Unfavorable outcome of visual acuity for the CRYO-ROP study was visual acuity

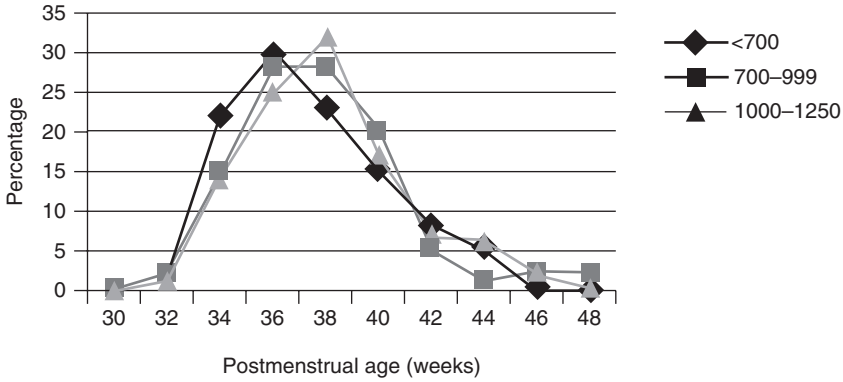


FIGURE 13.7 Graph showing the onset of threshold retinopathy of prematurity by gestational age in the CRYO-ROP trial. (Republished from Palmer E, Flynn J, Hardy R, et al. Incidence and early course of retinopathy of prematurity. *Ophthalmology.* 1991;98(11):1628–1638, with permission.) CRYO-ROP, The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity.

less than 20/200 or structural outcome of macular fold, retrolental tissue, or retinal detachment. Our management strategies in the new millennium aim for a favorable outcome of better than 20/40 visual acuity, preserved macular architecture, and minimal cicatricial peripheral retinal changes.[39,40]

2. Cryotherapy is no longer the primary modality of treatment for severe ROP.
3. "Threshold ROP" was the upper limit of severe disease beyond which blindness from retinal detachment and cicatricial ROP would occur. This was determined from a retrospective study and then used in the CRYO-ROP study.[41] According to the Early Treatment Trial for ROP (ET-ROP), it is not necessarily the amount of stage 3 disease that should determine the timing of treatment.[42]

Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity

Purpose of Study

To determine the efficacy and safety of supplemental therapeutic oxygen for infants with prethreshold ROP to reduce the probability of progression to threshold ROP and subsequent need for laser treatment.[43]

Study Question

Does supplemental inspired oxygen therapy for premature infants at high risk for threshold disease prevent the progression of disease? Are there any negative impacts from treating infants with higher oxygen levels?

Inclusion Criteria

Premature infants who reached prethreshold ROP in at least one eye and had a median pulse oximetry less than 94% saturation (SaO_2) while breathing room air; no lethal anomalies or congenital eye anomalies.

Study Definitions

1. *Threshold ROP*: Zone I ROP, any stage, with plus disease in at least two quadrants; stage 3 without plus disease. Zone II, plus disease, and stage 3 in five continuous or eight noncontinuous clock hours.
2. *Prethreshold ROP:* Zone I ROP of any stage, less than threshold. Zone II, stage 3 ROP, less than threshold, or zone II, stage 2 ROP with plus disease.

Study Design

Multicenter, randomized, controlled clinical trial, comparing the effects of two oxygenation strategies on the progression of severe ROP. Infants with prethreshold disease (same definition as above) were randomized to receive either supplemental or therapeutic inspired oxygen via nasal prongs titrated to an oxygen saturation of 96% to 99%, measured by pulse oximetry or conventional amounts of inspired oxygen to maintain target oxygen saturation levels of 89% to 94%.

Summary of Major Findings

1. There was a reduction in the rate of conversion from prethreshold ROP to threshold ROP from 48.5% for the conventional oxygen group down to 40.9% for the supplemental oxygen group. This was **not** a statistically significant result ($P = 0.032$).
2. There was a benefit for the subgroup of infants with prethreshold disease without plus disease. The conversion rate to threshold decreased from 46% in the conventional group to 32% in the supplemental oxygen group ($P = 0.004$).
3. Threshold disease took longer to develop in the supplemental oxygen group, suggesting an effect on the tempo of the disease.
4. Chronic lung disease was **worse** in those infants randomized to supplemental oxygen (8.5% to 13.2%), with an increased incidence of pneumonia, requiring longer hospital stays.
5. No adverse effect on ROP in the supplemental group was detected in the study.

Implication for Clinical Practice

1. The risks and benefits of supplemental oxygen for prethreshold ROP must be analyzed by the treating physician for each infant. Infants without severe pulmonary disease with prethreshold ROP, without plus disease, may benefit from liberal use of inspired oxygen, without any additional risks to the infant.

2. If an infant requires supplemental oxygen for cardiac reasons, the increased levels can be given with confidence that this will not have an adverse affect on the ROP.

Limitations of the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity Study

1. At most centers, two-thirds of the prethreshold infants were excluded from the study for various reasons. Infants were excluded if they had a pulse oximeter reading greater than 94% at any time before enrollment. This potentially establishes a study group with a greater severity of prethreshold ROP (and lower birth weights and gestational ages) than the overall population of premature infants that reach prethreshold.[44]
2. The frequency of examinations in the supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP) study was every 2 weeks prior to the development of prethreshold ROP. If weekly examinations had been performed, prethreshold ROP may have been detected at an earlier phase. Later detection of prethreshold ROP in the study may have had an impact on the outcomes.
3. The majority of STOP-ROP infants in the supplemental oxygen group were maintained at a median pulse oximetry level of 96% or 97% (80% of infants). Only 1% of infants in the therapeutic group had a medium pulse oximetry of 99%.

A study by Chow et al. in 2003 examined the incidence of ROP before and after the institution of tighter guidelines for oxygen administration in premature infants with birth weight <1,250 g.[45] The new guidelines aimed to reduce hyperoxic and hypoxic fluctuations with a target oxygen saturation of 85 to 93%. The incidence of stage 3 to 5 ROP dropped from 12.5% to 2.5% after adoption of the new protocol, supporting the role of oxygen fluctuations in stimulating ROP. Studies by Wright et al. in 2006[46] and Tokuhiro et al. in 2009[47] examined the incidence of ROP after adoption of reduced oxygen protocols, and both found reductions in threshold ROP with the newer reduced oxygen saturation targets. These studies taken together support the theory that lower oxygen saturation targets more closely mimic the *in utero* environment and thereby limit the hyperoxic stimulus in the initial stage of ROP. Similarly, Sears et al. evaluated the incidence of ROP for reduced oxygen saturation prior to 34 weeks PMA and elevated oxygen saturation after 34 weeks PMA and found the incidence of ROP decreased from 35 to 13%.[48] These stricter oxygen saturation guidelines have been more difficult to implement in developing countries due to the higher level intensive care unit surveillance and nursing required.

Early Treatment for Retinopathy of Prematurity Study

Purpose of Study

To determine whether earlier treatment with retinal laser ablation in high-risk prethreshold ROP leads to improved visual function and improved retinal structure outcomes compared with treatment at conventional threshold ROP.[42]

Study Questions

Does earlier treatment of ROP, with characteristics of severe disease, improve structural and visual outcomes compared with conventional timing of treatment?

Inclusion Criteria

1. Infants with birth weights <1,251 g
2. Development of prethreshold ROP

Definitions

1. Prethreshold ROP: Zone I, any stage ROP, less than threshold; zone II, stage 2, with plus disease or stage 3 without plus disease; zone II, stage 3 with plus disease, but less than threshold.
2. Threshold ROP: Zone I or zone II, with five continuous or eight noncontinuous clock hours (30° sectors) of stage 3 ROP, in the presence of plus disease.
3. Risk Management model for ROP (RM-ROP) Treatment: Theoretical model based

on infant risk factors used to assign risk of blindness without treatment. Risk factors observed about the infant and the retina are correlated with structural outcome. The model consists of five mathematical equations converted into a risk analysis computer program, based on data from the CRYO-ROP study.[49,50]

4. Favorable visual outcome at a corrected age of 9 months was defined as vision better than 1.85 cycles per degree, using Teller Acuity testing. An unfavorable visual outcome was defined as vision worse than 1.85 cycles per degree, light perception or no light perception.
5. An unfavorable structural outcome at 6 and 9 months corrected age was defined as (1) posterior retinal fold involving macula, (2) retinal detachment involving macula, (3) retrolental mass or tissue obscuring the view of the posterior pole.

Study Design

RM-ROP was used to determine the theoretical risk of progression to an unfavorable outcome in the absence of treatment. This model is based on CRYO-ROP natural history data. RM-ROP "low-risk" prethreshold was defined as having a less than 15% risk of progression to unfavorable outcome if not treated and "high-risk" prethreshold was defined as having a greater than 15% risk of progression to unfavorable outcome if not treated. Prethreshold eyes that were determined to be RM-ROP "high risk" were therefore randomized to early treatment or conventional timing of treatment, and RM-ROP "low-risk" eyes were continued to be screened for conventional timing of treatment (waiting until traditional threshold ROP occurred). Eight hundred and twenty-eight infants who had enrolled in the study reached prethreshold disease in one or both eyes and therefore enrolled and analyzed using the RM-ROP-II model. Three hundred and twenty-nine infants were determined to be "low-risk" prethreshold and were not randomized, but continued to be screened. Four hundred and ninety-nine infants were determined to be "high-risk" prethreshold and thus were randomized to early laser treatment or conventional treatment. Unfavorable outcome at 3 months was defined anatomically, as either a macular fold or a posterior retinal detachment.

Summary of Major Findings

1. At 9 months of PMA of follow-up, early treatment using Type I criteria reduced unfavorable visual outcomes from 19.5% to 14.5% (primary outcome) and reduced unfavorable structural outcome from 15.6% to 9.1% (secondary outcome), both statistically significant.
2. Using the RM-ROP-II algorithm, 136 eyes with "high-risk" prethreshold ROP would have had favorable outcomes without treatment, but would have been treated. In addition, 140/372 of "high-risk" eyes randomized to conventional treatment did not go on to threshold. To address the concerns of "overtreatment," the study data were analyzed to identify "clinical" subgroups at high risk for progression to severe disease with unfavorable outcome that benefited from early treatment and another group that benefited from conventional treatment timing. These subgroups were termed Type I (early treatment) and Type II (conventional ROP treatment timing) ROP. Using these clinical subtypes, instead of the RM-ROP-II model, there would be a 35% reduction of eyes treated, while ensuring favorable outcomes.

Type I (Early treatment) Clinical Characteristics:

a. Zone I, any ROP with plus disease
b. Zone I, stage 3 with and without plus disease
c. Zone II, stage 2 or 3 with plus disease

Type II (Conventional treatment) Clinical Characteristics:

a. Zone I, stage 1 or 2 without plus disease
b. Zone II, stage 3 without plus disease

Implications for Clinical Practice

1. If one waits for CRYO-ROP threshold ROP definition, 6% of infants would require treatment; if one were to add RM-ROP-II algorithm to the prethreshold

definition, 9% of infants would require treatment and using ET-ROP Type I and II criteria (ICROP based), 8% of infants would likely require treatment.
2. Treat infants within 72 hours of observation of ET-ROP Type I clinical characteristics to maximize favorable anatomical outcomes.
3. Observe frequently for progression of ET-ROP Type II ROP. Surveillance or screening may be required as often as two times per week, in the presence of prethreshold criteria that do not meet Type I ET-ROP criteria for early treatment (Fig. 13.8).[32]
4. Caveat: Use clinical judgment for extent of stage 3, birth weight, and gestational age of infant.

Major Unanswered Questions or Limitations of the ET-ROP Study

1. ET-ROP treatment decision is driven by the presence of plus disease; however, plus disease may be a relatively "soft" clinical sign.
   a. Clinical diagnosis of plus disease may vary from observer to observer and the inter-rater reliability has not been well studied.
   b. A standard photograph was used in the study to determine the presence of plus disease. This is not an objective measure and does not ensure accuracy or reproducibility.
   c. We are not able to objectively determine or quantify plus disease, as yet, although recommendation of timing of intervention depends heavily on this clinical characteristic of severe disease.
   d. No photographic documentation of plus disease was performed in the study, although determination of prethreshold and threshold disease was confirmed by two study investigators.
2. ET-ROP Type I and II criteria do not take into account the amount of stage 3 present; yet, the last 15 years of much clinical study and management decisions have been based on quantification of stage 3 disease. The ET-ROP study did not analyze the extent of stage 3 disease (Fig. 13.9), as it related to timing of intervention or clinical outcomes.

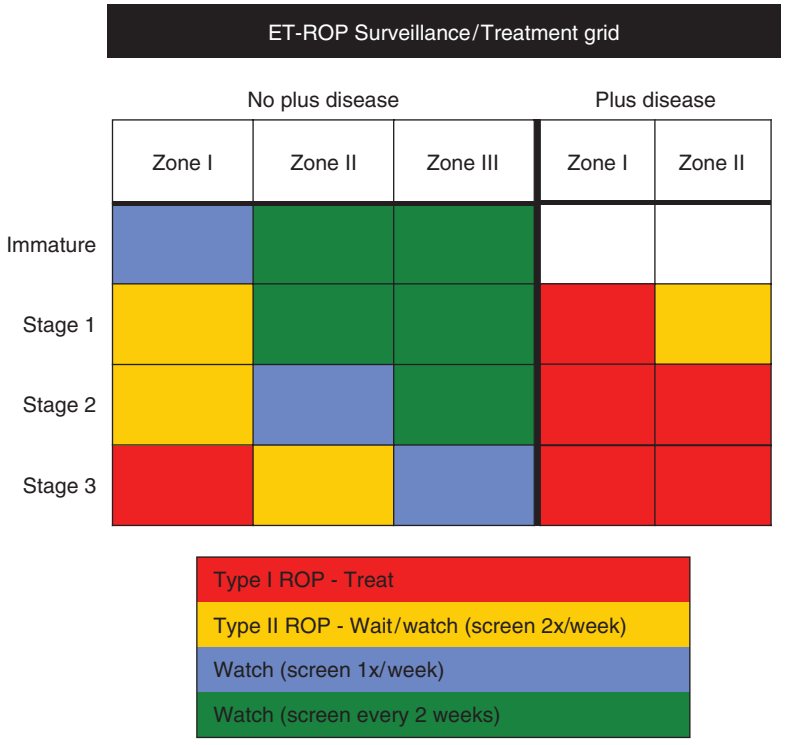
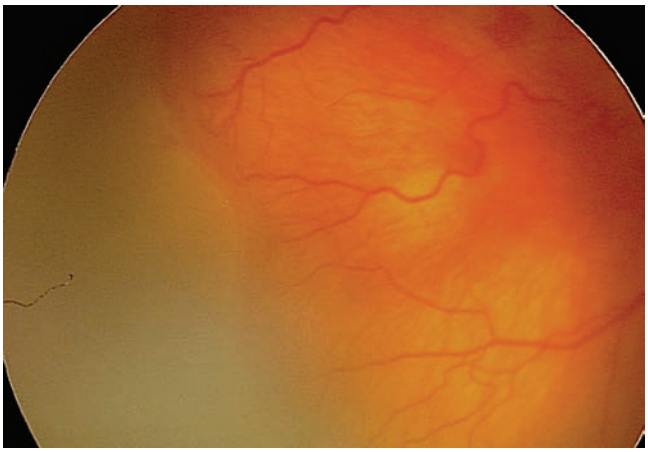


FIGURE 13.8 ET-ROP recommended surveillance and treatment grid. ET-ROP, Early Treatment Trial for Retinopathy of Prematurity.



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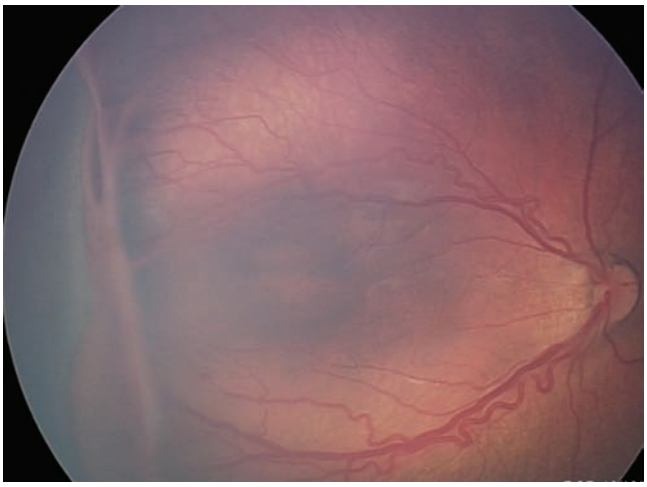

B

FIGURE 13.9 Examples of various stage 3 neovascularization in retinopathy of prematurity **(A)**. Late stage 3 neovascularization with early tractional changes **(B)**.

3. A favorable visual outcome in both the CRYO-ROP and ET-ROP studies is defined as vision better than 20/200 or lack of macular fold. Based on other reports, a more reasonable favorable outcome for eyes treated for severe ROP should be 20/50 or better with preservation of macular architecture.[51-53]
4. Timing of intervention may not be the only critical management factor in preventing visual loss from severe ROP. Data from longer follow-up periods may demonstrate factors other than timing of intervention, which may prevent visual loss.

Summary of Other Clinical Trials in Retinopathy of Prematurity That Are Noteworthy

1. *Lack of Efficacy of Light Reduction in Preventing Retinopathy of Prematurity* (LIGHT-ROP; 1998)[54] demonstrated that light reduction within the first 24 hours of birth until 31 weeks of PMA had no significant affect on the development of ROP or the conversion of prethreshold ROP to threshold ROP.
2. *Vitamin E Meta-Analysis of Six Controlled Clinical Trials*[55] summarized data analysis from infants randomized to receive vitamin E supplementation or not. No statistical significance in the development of ROP was found between these two groups. There may potentially be increased harmful systemic effects and even mortality from vitamin E supplementation.
3. *Evidence-Based Screening Criteria for Retinopathy of Prematurity—Natural History Data from the CRYO-ROP and LIGHT-ROP Studies*[36] This is a report of compiled data from these two prospective clinical trials in

order to determine the approximate date for the initial ROP screening examination. The study recommended the first examination should be at 31 weeks PMA or 4 weeks of chronological age, whichever is later.

4. *Can Changes in Clinical Practice Decrease the Incidence of Severe Retinopathy of Prematurity in Very Low Birth Weight Infants:*[45] This is a prospective study that reported a dramatic decrease (4.5% to 0%) in premature infants requiring laser photocoagulation for severe disease, after implementing early oxygen curtailment and enforcement of strict oxygen guidelines by the neonatal nursing staff. The findings from this report have led to the recent design of a multicenter randomized trial of early weaning of inspired oxygen in extreme premature infants.
5. *Characteristics of Infants with Severe Retinopathy of Prematurity in Countries with Low, Moderate, and High Levels of Development: Implications for Screening Programs.*[56] This observational study reports that infants from low human development countries (LHDC) and middle human development countries (MHDC) with severe ROP may have a different demographic profile from those of high human development countries (HHDC). Infants with severe ROP from LHDC and MHDC are of greater gestational ages and of higher birth weights. ROP screening guidelines need to be specific for the local population.

Important Note in Interpreting Clinical Trials

Epidemiologic research published in the last decade has highlighted the demographic differences in profile of infants at risk for severe disease requiring treatment.[56,57] Infants in HHDC treated for ROP are of lower gestational age and birth weight as compared with MHDC. LHDC, until recently, have had no blindness from ROP due to low survival rates of premature infants. Currently, with increasing technology and neonatal strategies in both MHDC and LHDC, combined with decreasing infant mortality rates, ROP is emerging as the leading cause of preventable childhood blindness. The results and recommendations of the clinical trials that have been reviewed in this chapter apply to HHDC and may have different implications in other parts of the world.

Anti-Vascular Endothelial Growth Factor Therapies

Many studies in mice and rats have confirmed a two-stage dysregulation of VEGF that drives pathogenesis of ROP. As detailed earlier, premature exposure to the comparatively hyperoxic extrauterine environment causes decreased VEGF expression within the retina, which results in incomplete vascularization and vascular obliteration. The hypoxic retina then subsequently upregulates VEGF levels, which drives aberrant neovascularization. In animal models, administration of VEGF or anti-VEGF molecules during either stage significantly accelerates or mitigates progression of the disease, respectively.[58,59]

Several clinical case series have reported the use of anti-VEGF therapy for ROP, specifically intravitreal bevacizumab. Nazari et al. injected bevacizumab in 12 eyes of six patients who demonstrated progressive disease after laser treatment, with regression in all treated eyes by a mean of 11 days.[60] Chung et al. combined laser ablation with intravitreal bevacizumab in both eyes of one patient, with prompt and sustained regression of ROP.[61] Mintz-Hittner and Kuffel reported the use of bevacizumab in 22 eyes of 11 patients with stage 3 disease in zone I or posterior zone II. All eyes showed regression without retinal detachment at 13 to 85 weeks of follow-up.[62] Kusaka et al.[63] and others, however, have described tractional retinal detachment shortly following bevacizumab injection.[64,65]

A large collaborative series from Mexico, Portugal, and New York City reported outcomes of 53 eyes of 27 patients injected with bevacizumab.[66] Eyes were divided into three groups: progression to subtotal retinal detachment despite peripheral ablation (Group 1), threshold ROP with poor visualization preventing peripheral ablation (Group 2), and high-risk threshold or prethreshold ROP without prior treatment (Group 3). The authors reported that all eyes responded favorably with respect to neovascularization, but five eyes with advanced ROP worsened anatomically. No serious systemic adverse events were appreciated. Longer term follow-up of 18 of

these patients demonstrated uncomplicated regression in all eyes by 38 weeks after injection, with the exception of two eyes in Group 1 requiring vitrectomy.[67] The vitrectomized eyes remained stable with attached retinas at 38 weeks of follow-up.

The largest study to date on the use of bevacizumab in ROP is the ***Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) Study***[68]

Purpose of the Study

Evaluate the outcomes comparing intravitreal bevacizumab monotherapy to conventional laser among infants with stage 3+ ROP with zone I or II disease.

Inclusion Criteria

1. Infants with birth weight < 1,500 g and gestational age of 30 weeks or less
2. Infants with stage 3+ ROP in zone I or zone II

Exclusion Criteria

1. Stage 4 or 5 ROP in either eye

Study Design

This is a multicenter, randomized, prospective interventional study comparing intravitreal bevacizumab with conventional laser in ROP. During serial biweekly or weekly ROP examinations, if stage 3+ in zone I or II was identified in either eye, the infant (not the eye) was randomized to either an intravitreal bevacizumab injection or conventional laser group. Half of the patients received bevacizumab while the other half received conventional laser therapy. Patients (not eyes) were randomly assigned to either laser or intravitreal injection since the drug can have contralateral eye effects due to systemic penetration. The amount injected was 0.625 mg in 0.025 ml of bevacizumab. Treatment failure was defined as recurrence of neovascularization in one or both eyes by 54 weeks PMA.

Summary of Major Findings

1. At 54 weeks, 32 of the 146 eyes treated by conventional laser therapy had recurrence of ROP compared with 6 of the 140 eyes treated by intravitreal bevacizumab.
2. Five infants died in the bevacizumab group compared with two in the conventional laser group. The study was not statistically powered to evaluate mortality.
3. In this study, the rate of recurrence observed for zone I disease was 42% in the conventional laser group compared with 6% in the bevacizumab group. Rate of recurrence for zone II disease was comparable between the two groups.

Limitations of the BEAT-ROP Study

1. The disproportionate number of Hispanic infants introduces possible population bias.[69]
2. The number of study centers with a single investigator is unusually high for a multicenter study, increasing the possibility of single-investigator biases.
3. The criteria of recurrence were limited to prior to 54 weeks, although much later recurrences have been noted in the bevacizumab group.
4. The study was not appropriately powered to evaluate comorbidities and long-term side effects of using bevacizumab—the higher mortality among bevacizumab-treated infants in this study is of particular concern.
5. The clinical appearance and time course of regression of ROP differ in eyes treated with VEGF suppression as compared with those managed with peripheral retinal ablation. Length of typical follow-up, timing of retreatment, and management of persistently avascular peripheral retina all need to be evaluated in bevacizumab-treated eyes.
6. The primary endpoint was changed midway through the study.

Implications for Clinical Practice

While there is an appeal and hope that anti-VEGF therapy can be the "golden bullet" to treat ROP, careful analysis must be given to appropriate patient selection, treating each infant on a case-by-case basis and to understand what compromises are made with newer treatments. From the CRYO-ROP and ET-ROP studies, it is known that ROP recurrence following peripheral

retinal ablation generally occurs prior to 55 weeks, and postnatal monitoring guidelines currently for ROP are up to that age at which complete retinal vascularization occurs. There have been established well-documented guidelines on the outcome, natural history, and follow-up of ROP from CRYO-ROP and LIGHT-ROP studies,[70] which remain unknown in bevacizumab-treated eyes. It is important to note that the interval from treatment to recurrence in the bevacizumab-treated eyes was approximately 18 weeks, with the longest interval at almost 28 weeks, significantly longer than what was seen in CRYO-ROP and ET-ROP studies. Conventional laser recurrence occurred approximately at 6 to 7 weeks, with the longest interval at 13 weeks. The delayed recurrence interval of retinal neovascularization following intravitreal bevacizumab therapy is significantly longer than that after conventional laser peripheral retinal ablation, necessitating longer and closer monitoring in premature infants. It is also important to be aware that the timing of intravitreal bevacizumab administration may also affect the ROP outcome. While BEAT-ROP excluded eyes with stage 4 to 5 ROP, late administration may result in accelerated contraction of membranes leading to a tractional ROP retinal detachment, which has been seen.[64] Also, other authors have reported new stage 5 ROP detachments occurring as late as 72 weeks after bevacizumab treatment due to inadequate continued follow-up.[71] Lastly, no studies have yet evaluated the stability of the retinal vasculature that develops beyond the initial ridge in bevacizumab-treated eyes. Clinical examination and fluorescein angiography demonstrate that while the retina vascularizes beyond the initial ridge, the vascular architecture is not completely normal and the long-term stability has yet to be established.

Another key question remains regarding systemic circulating bevacizumab levels after intravitreal injection and its impact on other organ development. Sato et el. measured the serum concentration of bevacizumab and VEGF in 11 ROP infants treated with bevacizumab who received 0.25 or 0.5 mg of bevacizumab to either one or both eyes with active ROP. Infants who received a total dose <0.5 mg of bevacizumab did not appear to have an associated reduction on serum VEGF levels at 1 week; however, infants receiving a total dose of ≥ 0.5 mg of bevacizumab demonstrated a corresponding associated serum VEGF level decrease the first 2 weeks after injection.[72] These serum plasma VEGF levels are lower than what has been found to be normal in premature infants both with and without ROP.[73]

There is likely to be an important role for anti-VEGF therapy in ROP management in the future; however, judicious use is necessary since long-term morbidity of bevacizumab remains unclear for an intravitreal drug with systemic penetration in a population that still has multiple organs undergoing development that are highly sensitive to vascular regulatory processes (i.e., brain and lungs) in addition to the eyes. Infants with ROP often have other comorbidities such as underdeveloped lungs that require adequate VEGF levels for alveolar development and lung maturation.[74] While clinical reports of definitive causal morbidity associated with intravitreal bevacizumab in the treatment of ROP are lacking, it is important to be cognizant of the many developmental years that remain ahead of these neonates treated with bevacizumab wherein continued medical care may be needed.

Overview of the Clinical Approach to Retinopathy of Prematurity

As mentioned at the beginning of this chapter, ROP is one of the leading causes of *preventable* blindness. Infants with low birth weight and early gestational age are at highest risk for developing ROP. Many newborns that develop ROP have the disease progress at fairly predictable intervals, with initial manifestations at 32 weeks post-PMA and reaching threshold for treatment generally around 37 weeks PMA. However, there is a subset that also progresses more rapidly.[17,70]

Frequent monitoring and appropriate early intervention can arrest the disease process and prevent significant tractional detachments during the cicatricial phase. It is

important to realize that ROP detachments can have both an exudative and a tractional component. The exudative component arises from leaky vasculature and the intraretinal shunting present in the neovascularly active ridge.[75] The tractional component arises during the regression of abnormal vasculature in the retina and vitreous that contracts. This tractional component may unmask itself postablative treatment or after 40 weeks PMA when transforming growth factor beta levels increase and suppress VEGF.[76,77]

ROP is treated by applying near confluent laser spots from the ora serrata to the vascularized retina; however, complete treatment may not always be possible due to limitations of the surgeon's view secondary to media opacities. Iris neovascularization and persistent tunica vasculosa can limit pupillary dilation. It is important, however, to obtain as complete a treatment as possible. In addition, new areas of avascular retina may appear secondary to regression of prior neovascularization, or vascularization beyond the initial ridge may stall leaving more anterior avascular areas that may need additional laser treatment. Anti-VEGF therapy has been demonstrated to have potential benefit in the management of severe ROP in these instances, especially in eyes with aggressive posterior ROP with poor pupillary dilation or vitreous hemorrhage that prevent adequate laser treatment that may provide a temporizing measure until appropriate laser treatment is applied.

While it is an exciting period in the management of ROP as better clinical and basic science understanding of the disease is attained, clinicians must consider new treatment modalities against the backdrop of established ROP treatment guidelines. Blindness is a highly—though not universally—preventable consequence of ROP with appropriate close monitoring and early intervention. As our understanding of the various vascular regulatory pathways in organ development improves in neonates, we will have a finer ability to maximize the health and normal development of premature infants and improve the quality of life of these infants and their families.

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14 Amblyopia

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A number of multicenter randomized controlled trials (RCTs) and prospective observational studies have been conducted by groups in North America and Europe addressing questions in the treatment of amblyopia. The Pediatric Eye Disease Investigator Group (PEDIG) in the United States[1] consists of approximately 200 pediatric ophthalmologists and pediatric optometrists across North America, in both academic and community-based private practice settings, who conduct large simple trials or simple data collection studies, each study mimicking clinical practice with the exception of randomization and standardized masked assessment of outcome measures. This chapter summarizes the major findings of completed PEDIG amblyopia studies[2–17] and also describes several studies conducted by other investigator groups in Europe.[18–24]

To date, RCTs in amblyopia have exclusively addressed questions in the management of unilateral amblyopia caused by anisometropia, strabismus, or a combination of anisometropia and strabismus. No RCTs have been conducted in deprivation amblyopia, and therefore, this chapter will not discuss the management of deprivation amblyopia or bilateral amblyopia.

Visual Acuity Testing in Amblyopia Studies

The standardization and masking of visual acuity (VA) measurement are critical for clinical trials in amblyopia. The use of age-appropriate clinical tests that incorporate a logMAR scale is important for the analysis and presentation of results. For children aged <7 years, PEDIG uses the amblyopia treatment study (ATS) VA protocol,[25] incorporating HOTV optotypes with surround bars. The test has been automated with a computer-based electronic visual acuity (EVA) tester.[26] Many children under 3 years are untestable with HOTV optotypes,[25] so PEDIG studies of younger children with amblyopia have focused on 3- to <7-year-olds. For children aged 7 years or more, PEDIG uses an EVA version of the early treatment of diabetic retinopathy study (ETDRS) test (the e-ETDRS test),[27] presenting single optotypes with surround bars and yielding a letter score comparable to standard ETDRS testing. In the European studies, Clarke et al.,[19] Stewart et al.,[20–24] and Awan et al.[18] also used logMAR-based VA tests for outcome assessment.

Atropine versus Patching in Moderate Amblyopia

Background and Study Questions

Historically, advocates of atropine administered to the fellow eye in the treatment of amblyopia have suggested that enhanced compliance and better binocular outcomes are advantages of atropine, while advocates of patching the fellow eye have suggested that patching produces a more complete and more rapid response. In order to address this controversy, the first RCT conducted by PEDIG compared patching of the fellow eye prescribed for at least 6 hours per day to atropine 1% one drop each morning to the fellow eye.[2,9]

Patients Included in the Study

Children were <7 years old at the time of enrollment and had to be able to complete optotype VA testing (HOTV matching), effectively limiting the study to 3- to <7-year-olds. They had moderate amblyopia defined as 20/40 to 20/100 in the amblyopic eye, fellow eye acuity of at least 20/40, and at least 3 logMAR lines of interocular difference to ensure that they had bona fide amblyopia. In addition, the presence or history of an amblyogenic (or more properly amblyopiogenic) factor that met criteria for strabismus, anisometropia, or both was required for enrollment. Patients could have had no more than 2 months of amblyopia therapy in the past 2 years and optimum spectacle correction (if needed) was required for at least 4 weeks.[2]

Intervention and Outcome Measures

Randomization and follow-up schedule are shown in Figure 14.1. If the amblyopic eye had not improved by 3 lines or to at least 20/32 after 16 weeks of randomized treatment, the treatment was increased by either changing the spectacle lens over the fellow eye to plano in the atropine group or increasing the patching to 12 or more hours per day in the patching group.[2]

The primary outcome was best-corrected amblyopic eye VA measured 6 months from enrollment and randomization.[2] After 6 months of treatment according to randomization, investigators were allowed to treat each patient at their discretion. A long-term follow-up examination was then conducted at 2 years from enrollment, at age 10 years, and further follow-up is being conducted at age 15 years.

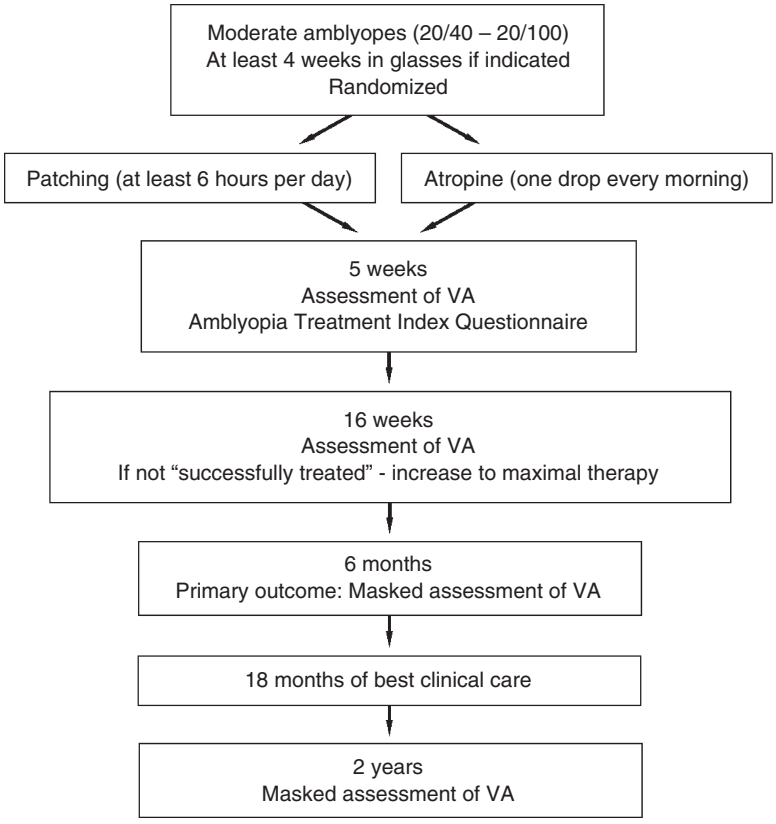

FIGURE 14.1 Randomization and follow-up schedule for children with moderate amblyopia assigned to atropine versus patching in a randomized clinical trial conducted by the Pediatric Eye Disease Investigator Group.

Major Findings

At the 6-month primary outcome, both groups showed similar improvement in the amblyopic eye VA (a mean improvement of 3.16 lines in the patching group and 2.84 lines in the atropine group).[2] The difference in VA between treatment groups was small—equivalent to approximately 1.5 letters—and not clinically meaningful (mean difference 0.034 logMAR units; 95% confidence interval [CI], 0.005 to 0.064). Improvement was initially faster in the patching group, with a mean improvement from baseline to 5 weeks of 2.22 lines in the patching group and 1.37 lines in the atropine group. Defining the 6-month outcome dichotomously as success or failure, with success defined as "20/32 or better in the amblyopic eye and/or improved from baseline by three or more lines," success was achieved in 79% of the patching group and 74% of the atropine group, which was not statistically different. The relative treatment effect did not vary according to age, depth of amblyopia, or cause of amblyopia.[2]

Atropine had a slightly higher degree of acceptability when rated on a parental questionnaire[28,29] administered at the 5-week visit, before knowledge of any VA improvement.

Between 6 months and 2 years following randomization,[9] treatment was at the discretion of the investigator, but only about a quarter of the children underwent treatment using the other modality. At the 2-year outcome, the mean improvement in amblyopic eye VA was again similar in the patching and atropine groups (3.7 lines in the patching group and 3.6 lines in the atropine group). The difference in mean VA between the groups was very small (0.01 logMAR units; 95% CI, –0.02 and 0.04). In both groups, the mean amblyopic eye acuity at 2 years was approximately 20/32, 1.8 lines poorer than the mean fellow eye acuity, which was approximately 20/20. It is noteworthy that only about half of the patients in each group reached 20/25 or better in the amblyopic eye. There was no difference in stereoacuity between patients in the patching and atropine groups when assessed at the 2-year outcome.

At the 10-year-old examination,[30] the mean amblyopic eye acuity, measured in 169 patients, was 0.17 logMAR (approximately 20/32) and 46% of amblyopic eyes were 20/25 or better. Mean amblyopic and fellow eye visual acuities at age 10 years were similar in the original treatment groups ($p = 0.56$ and 0.80, respectively). Examinations at age 15 years are ongoing and will be completed in the late summer 2013.

Implications for Clinical Practice

Both patching and daily atropine drops administered to the fellow eye are excellent initial treatments for moderate anisometropic and strabismic amblyopia. It is reasonable to involve the parents and the child in deciding which treatment to start. If that treatment modality is unsuccessful, the child could be put on the alternative therapy.

Unanswered Questions

The optimum dose of patching and dose of atropine were not addressed in this study. The doses used in this study were selected by consensus of the investigator group prior to initiating the RCT, and the patching dose was prescribed at the discretion of the investigator (starting with at least 6 hours per day in this study). Questions regarding optimum dose would begin to be addressed by studies described later in this chapter.

If a patient had not responded at 16 weeks to atropine therapy, the hypermetropic glasses correction over the fellow eye was reduced to a plano lens. This would have the effect of further blurring the VA of the cyclopleged fellow eye. Whether the use of a plano lens in addition to atropine results in increased effectiveness of treatment is being studied in a PEDIG RCT and will be described later in this chapter.

Analysis of fixation data and near VA data in patients randomized to atropine surprisingly revealed that fixation switch to the amblyopic eye was not necessary for VA improvement, and that patients who had better near VA in the fellow eye while under atropine cycloplegia could also show improvement in the amblyopic eye.[31] For practical reasons, this assessment was limited by performing these tests at the 5-week visit. The issues of fixation switch and near VA predicting success with

atropine were also explored in the PEDIG RCT of atropine regimes, described later in the chapter.

At the outcomes 2 years from randomization[9] and at 10 years of age,[30] only about half the children improved to 20/25 or better. This indicates that amblyopia is difficult to "cure." Future studies need to address the best treatment strategy for residual amblyopia and one such study is described later in this chapter. It is probable that a proportion of children with amblyopia have organic deficits that cannot be completely reversed by current treatment.

The role of optical treatment of amblyopia (termed "refractive adaptation" by some)[22,24,32] with spectacles alone was not addressed in this trial. The choice of "at least 4 weeks in glasses, if needed" was made as a compromise between those who wanted to start patching or atropine immediately and those who wanted to wait for maximal improvement. Subsequent work of Moseley, Stewart, Fielder et al.[22,24,32] has provided evidence that a great deal of improvement can be obtained with glasses alone in both strabismic and anisometropic amblyopia, in some cases eliminating the need for patching or atropine. Two studies of optical treatment of amblyopia are described.

Optical Treatment of Anisometropic Amblyopia

Background and Study Questions

In purely anisometropic amblyopia, it seems reasonable that correcting the refractive error alone might be enough to treat amblyopia, by providing a focused image to the retina of the amblyopic eye.

Patients Included in the Study

A total of 84 children 3 to <7 years old with previously untreated anisometropic amblyopia were enrolled with visual acuities ranging from 20/40 to 20/250.[12]

Intervention and Outcome Measures

In this nonrandomized prospective observational study,[12] optimal refractive correction was provided and VA was measured with the new spectacle correction at baseline, confirming the presence of amblyopia and then measured at 5-week intervals until VA stabilized or amblyopia resolved. The main outcome measure was the maximum improvement in best-corrected VA in the amblyopic eye and proportion of patients whose amblyopia resolved.

Major Findings

Amblyopia improved with optical correction by 2 or more lines in 77% of the patients and resolved in 27%.[12] Improvement took up to 30 weeks before stabilization criteria were met. Even after stabilization, additional improvement occurred with spectacles alone in 21 of 34 patients followed in a control group of a subsequent randomized trial, resolving in 6 patients. Treatment outcome was not related to age, but was associated with better baseline VA and lesser amounts of anisometropia.[12]

Implications for Clinical Practice

Refractive correction alone improves VA in most cases and results in resolution of amblyopia in about one-third of 3- to <7-year-old children with previously untreated anisometropic amblyopia. While most cases of resolution occur in those with moderate (20/40 to 20/100) levels of amblyopia, the nearly 3-line average improvement in VA resulting from initial treatment with spectacles alone may lessen the burden of subsequent therapy.[12]

Unanswered Questions

It is difficult to be certain that a case of presumed anisometropic amblyopia is purely anisometropic or whether there is a strabismic component. Some investigators suggest that most cases of anisometropic amblyopia have a small angle misalignment, and this is supported by recent evidence on lack of bifoveality in many cases of anisometropic amblyopia.[33] In fact, it has been very recently suggested that the "microesotropia flick" seen in some cases of anisometropic amblyopia may represent fixation instability.[34] Since there may be a contribution of strabismic amblyopia to cases of presumed anisometropic amblyopia, it raises the question of whether optical treatment has a role in strabismic and combined

strabismic–anisometropic amblyopia. This question is address next.

Optical Treatment of Strabismic Amblyopia

Background and Study Questions

In the previous study, we also enrolled 12 children with strabismic amblyopia for optical treatment alone,[12] as a run-in phase for a subsequent RCT. Surprisingly, we observed improvement in VA almost to the same degree as the children with purely anisometropic amblyopia.[35] Amblyopia improved with optical correction by 2 or more lines in 9 of 12 (75%) of the patients and resolved in 3 (25%). We hypothesized that there might be two mechanisms explaining the improvement: 1) correction of blur that would place a focused image on the retina of the amblyopic eye, which might be beneficial despite apparent lack of fixation and 2) improvement of alignment, which might place the image on the fovea of the amblyopic eye. We addressed these questions in the following subsequent study.[36]

Patients Included in the Study

A total of 146 children 3 to <7 years old with previously untreated strabismic amblyopia (N = 52) or combined-mechanism amblyopia (N = 94) were enrolled in this prospective observational study.[36]

Intervention and Outcome Measures

Optical treatment was provided as spectacles (prescription based on a cycloplegic refraction, the full cylinder correction, and generally the full plus correction according to protocol) that were worn for the first time at the baseline visit.[36] VA with spectacles was measured using the ATS HOTV VA protocol at baseline and every 9 weeks thereafter until no further improvement in VA. Ocular alignment was assessed at each visit. The main outcome measure was best-corrected VA 18 weeks after baseline.[36]

Major Findings

Overall, amblyopic eye VA improved a mean of 2.6 lines (95% CI, 2.3 to 3.0), with 75% of children improving ≥2 lines and 54% improving ≥3 lines.[36] Resolution of amblyopia occurred in 32% (95% CI, 24% to 41%) of the children. The treatment effect was greater for strabismic amblyopia than for combined-mechanism amblyopia (3.2 vs. 2.3 lines, adjusted p = 0.003). VA improved regardless of whether eye alignment improved.[36]

Implications for Clinical Practice

Optical treatment alone of strabismic and combined-mechanism amblyopia results in clinically meaningful improvement in amblyopic eye VA for most 3- to <7-year-old children, resolving in at least one quarter of the children without the need for additional treatment.[36] It is therefore reasonable to prescribe spectacles alone for children with strabismic and combined anisometropic–strabismic amblyopia, in addition to those with presumed anisometropic amblyopia.

Unanswered Questions

The mechanism for improvement of VA with optical correction alone for strabismic and combined anisometropic–strabismic amblyopia is not entirely clear. Since similar improvement occurred in eyes that remained strabismic with hypermetropic correction, we speculate that putting a focused image on the retina of the amblyopic eye contributes to the improvement, whether or not we can detect "fixation" with that eye on a clinical exam.

Additional Treatment Beyond Spectacles versus No Additional Treatment

Background and Study Questions

PEDIG conducted an RCT of "continued spectacles alone" versus "adding 2 hours of daily patching," in children whose VA had stabilized on optical (spectacle) treatment.[11]

Patients Included in the Study

One hundred and eighty children 3 to <7 years old with best-corrected amblyopic eye VA of 20/40 to 20/400 associated with strabismus, anisometropia, or both who had worn optimal refractive correction (if needed) for at least 16 weeks or for two consecutive visits without improvement[11] were included in this study.

Intervention and Outcome Measures

Children were randomized either to 2 hours of daily patching with 1 hour of near visual activities or to continued spectacles alone (if needed). Patients were continued on the randomized treatment (or no treatment) until no further improvement was noted. The main outcome measure was best-corrected VA in the amblyopic eye after 5 weeks.[11]

Major Findings

Improvement in VA of the amblyopic eye from baseline to 5 weeks averaged 1.1 lines in the patching group and 0.5 lines in the control group ($p = 0.006$), and improvement from baseline to best measured VA with continued treatment beyond 5 weeks averaged 2.2 lines in the patching group and 1.3 lines in the control group ($p < 0.001$).[11]

Implications for Clinical Practice

This has been one of the few RCTs in amblyopia with an untreated control group, and the study showed that, following a period of optical treatment of amblyopia and after VA had stabilized, 2 hours of daily patching combined with 1 hour of near visual activities improves moderate to severe amblyopia in children 3 to <7 years old.

Unanswered Questions

Surprisingly, there was continued improvement in VA in the control group where we thought that maximum VA had already been reached following optical treatment of amblyopia. This suggests that the criteria for "stability" used in this study (no improvement in VA over 2 visits 5 weeks apart, or treatment for at least 16 weeks) and in clinical care were inadequate. Nevertheless, this does not detract from the primary finding of a benefit from 2 hours of daily patching, because this study was an RCT.

Prescribed Full-Time versus Prescribed Part-Time Patching in Severe Amblyopia

Background and Study Questions

When patching is chosen to treat amblyopia, there has been much controversy among pediatric ophthalmologists regarding the dose of patching to prescribe. Some practitioners have prescribed as little as 1 hour a day, whereas others have prescribed as much as 24 hours a day. In severe amblyopia (20/100 to 20/400), regimes at the more intense end of the spectrum have typically been prescribed. Nevertheless, there has been ongoing debate regarding the necessity of full-time patching. Therefore, an RCT was conducted to compare prescribed full-time patching (all or all but 1 waking hour a day) with prescribed 6 hours of daily patching.[4]

Patients Included in the Study

One hundred and seventy five children 3 to <7 years old with severe amblyopia (best corrected VA 20/100 to 20/400) secondary to strabismus, anisometropia, or both were enrolled.[4] The VA in the fellow eye was at least 20/40 or better. Patients could have had no patching treatment within 6 months and no other amblyopia treatment of any type other than spectacles within 1 month. Any significant refractive error had to be corrected for at least 4 weeks before enrollment.[4]

Intervention and Outcome Measures

Randomization and follow-up schedule are shown in Figure 14.2. Due to debate regarding the need for near visual activities during patching, both groups were also prescribed at least 1 hour of near visual activities during patching. This study was not designed to test the maximum VA improvement, but rather to assess the initial response in the first 17 weeks.[4]

Major Findings

At the 17-week primary outcome exam, VA in the amblyopic eye improved by a similar extent in both groups.[4] The improvement in the amblyopic eye acuity from baseline to 17 weeks averaged 4.8 lines in the 6-hour group and 4.7 lines in the full-time group, with $p = 0.45$. The study concluded that 6 hours of prescribed daily patching produces an improvement in VA that is of similar magnitude to the improvement by prescribing full-time patching in treating

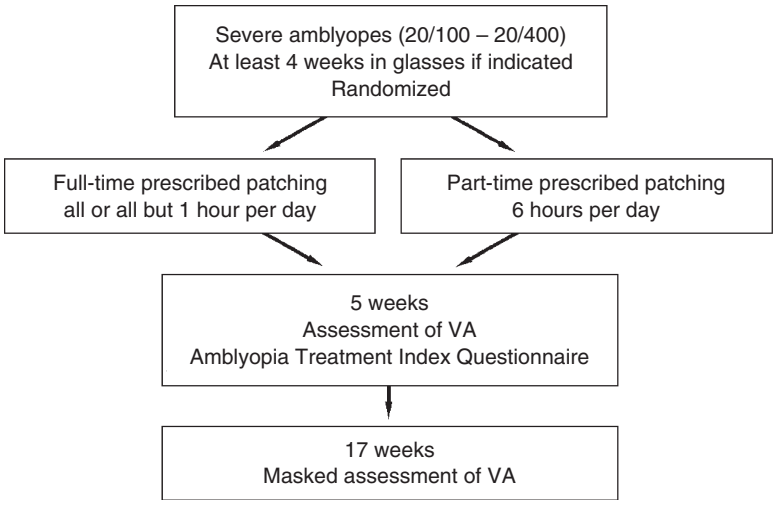

FIGURE 14.2 Randomization and follow-up schedule for children with severe amblyopia prescribed part-time patching versus full-time patching in a randomized clinical trial conducted by the Pediatric Eye Disease Investigator Group.

severe amblyopia in children 3 to <7 years of age. There was no difference in the rate of improvement.[4]

Parental acceptance of both treatments was good, on the basis of the Amblyopia Treatment Index questionnaire.[28,29] The mean questionnaire scores and subscale scores (adverse effects, treatment compliance, and social stigma) were similar between part-time and full-time patching.[4]

Implications for Clinical Practice

Since prescribing fewer hours per day of daily patching reduces the treatment burden for both the parents and the child, it would be reasonable to initially prescribe 6 hours of the daily patching in severe amblyopia caused by anisometropia and strabismus. The study did not support prescribing full-time patching as an initial treatment for amblyopia. In children who do not respond, or incompletely respond, to lower dose patching, it is entirely reasonable to increase or switch treatment.[37,38]

Unanswered Questions

This RCT did not address actual patch wearing times. and it was acknowledged[4] that some of the children who were prescribed full-time patching might have worn the patch far less than full-time. Nevertheless, the RCT was designed as a real-world study of effectiveness and it is noteworthy that prescribing 6 hours of patching resulted in marked improvement in VA in children with severe amblyopia. Stewart et al.[23] have conducted an RCT comparing 12 hours per day to 6 hours per day of patching, indicating that the actual patching time, measured using an occlusion dose monitor, was similar between groups (4.2 ± 1.7 hours vs. 6.2 ± 3.9 hours, $p = 0.06$).[39] These results indicate that the lack of superiority of more intense regimes might be due to reduced compliance with intense patching. Alternatively, there may be a ceiling effect on the rate of improvement of the amblyopic eye, which fewer hours can achieve, so that increased patching hours do not result in faster improvement.[4] These issues are worthy of further study.

The possibility of enhancing compliance is being addressed by Loudon et al.[40] in another RCT comparing patching with compliance aids to standard patching.

This PEDIG RCT[4] did not address whether the final VA of these children, after long-term treatment, might be different between treatment groups, but on applying these results to clinical practice, it would seem reasonable to start treatment with 6 hours a

day, since the initial response to treatment appears similar between prescribed part-time and prescribed full-time patching. It is possible that some children may require a more intense treatment later in the course, and further studies will need to address the issue of managing residual amblyopia.

Although the study prescribed 1 hour of "near visual activities" while being patched, the role of such near visual acuities remains controversial; a more recent RCT[14] found that there was no clinically important benefit of near activities over distance activities when combined with 2 hours of daily patching.

It is also noteworthy that in that subsequent RCT of near activities versus distance activities combined with 2 hours of daily patching,[14] children with *severe* amblyopia 20/125 to 20/400 showed a similar magnitude of mean improvement to those treated in the trial of full-time versus 6 hours/day, and six children had resolution of their severe amblyopia (within 1 line of the fellow eye) with only 2 hours of daily patching, suggesting that it is not unreasonable to start with 2 hours of daily patching even in severe amblyopia.

The question of how to wean, taper, or reduce treatment, when maximum response has been achieved, was the subject of a prospective observation study conducted by PEDIG.[7] In children who had been patched for 6 to 8 hours a day, there was a fourfold increased risk of recurrence when the treatment was not tapered or weaned, as compared to those who had been weaned to 2 hours a day of treatment before cessation. In addition, those children who had been weaned from 6 or 8 hours of treatment per day to 2 hours of treatment per day had a low recurrence rate (14%), similar to those who had been on 2 hours a day from the start of treatment. Although these analyses were adjusted for initial VA, VA prior to cessation, tropia status, and stereoacuity prior to cessation, the study was not an RCT, and therefore these preliminary findings should be interpreted with caution. An RCT in the future might test the hypothesis that weaning or tapering of treatment is associated with a decreased recurrence rate.

Prescribed 6 Hours a Day versus Prescribed 2 Hours a Day Patching for Moderate Amblyopia

Background and Study Questions

The rationale for this RCT of patching regimens in moderate amblyopia was similar to that described for comparing patching regimens in severe amblyopia. The optimum intensity of patching, that is, number of hours per day, has not been rigorously studied previously.

Patients Included in the Study

One hundred and eighty-nine children between 3 and 7 years of age with moderate amblyopia (20/40 to 20/80) due to strabismus and anisometropia or both were enrolled.[3] The VA in the fellow eye had to be at least 20/40 or better, with an intraocular acuity difference of 3 logMAR lines or more. No patching treatment within the last 6 months and no other treatment except spectacles within the prior month were allowed. Any significant refractive error had to be corrected for at least 4 weeks before enrollment.[3]

Intervention and Outcome Measures

Patients were randomized to either 2 hours per day of prescribed patching of the fellow eye or 6 hours per day of prescribed patching. The follow-up schedule is shown in Figure 14.3. Due to the controversy of whether near activities during patching enhances the effect of patching, 1 hour per day of near activities during occlusion was also prescribed in each group.[3]

Major Findings

At the 17-week outcome visit, there was similar improvement in VA in both groups.[3] The improvement in VA of the amblyopic eye from baseline to 17 weeks was a mean of 2.4 lines in each group. This study was not designed to determine the maximum level of VA achievable, and indeed only 62% of patients in each group achieved at least 20/32 or improvement of 3 or more lines from baseline.[3]

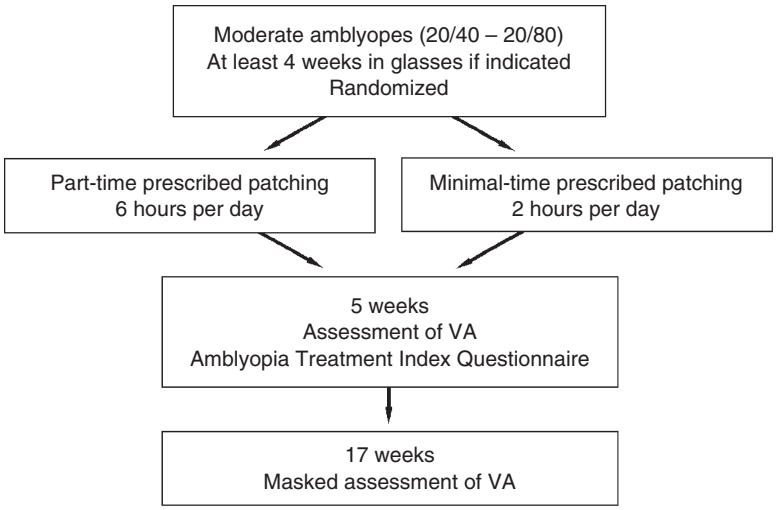

FIGURE 14.3 Randomization and follow-up schedule for children with moderate amblyopia prescribed 6 hours per day of patching versus 2 hours per day of patching in a randomized clinical trial conducted by the Pediatric Eye Disease Investigator Group.

On the basis of the Amblyopia Treatment Index questionnaire,[28,29] parental acceptance was similar between groups, but the "social stigma" subscale score was worse in the 6-hour group than in the 2-hour group.[3]

Implications for Clinical Practice

In moderate amblyopia (20/40 to 20/80), due to strabismus, anisometropia, or both, it is reasonable to start patching by prescribing 2 hours a day. This decreased burden of patching may be more acceptable to both the child and the parent. In children who do not respond, or incompletely respond, to lower dose patching, it is entirely reasonable to increase or switch treatment to attempt further improvement in the residual amblyopia. PEDIG recently reported a small RCT[17] finding that on average an intensive "final push" of combined treatment with patching and atropine did not produce a better VA outcome after 10 weeks compared with weaning treatment for children who have stopped improving with 6 hours prescribed daily patching or daily atropine. Nevertheless, for an individual child, who does not respond, or incompletely responds, to lower dose patching, we still feel it is reasonable to increase or switch or add treatment.[37,38] Further study of this issue is ongoing.

Unanswered Questions

The possible role of optical treatment alone, before starting patching or atropine, has been discussed in the preceding text and has also been studied by Moseley, Stewart, and Fielder et al.[20-24,32] As described earlier, no benefit of near activities during patching was found in a PEDIG RCT of 2 hours of daily patching with distance activities versus near activities.[14]

It is also possible that <2 hours patching per day is effective in treating amblyopia. Recent data from Stewart et al.[21] suggest that only 1 hour per day of patching is effective in some children with amblyopia. There also appears to be a great deal of individual variability of response to treatment with a given dose of patching.[21,24] These issues will be the subject of future studies.

Daily versus Weekend Atropine for Moderate Amblyopia

Background and Study Questions

In the same way that, until recently, there have been few rigorous studies addressing patching regimes for amblyopia, there are even fewer studies addressing different dosing regimens of atropine. Once or twice a week atropine to the fellow eye has been reported

to be successful in some children with amblyopia,[41] and therefore, an RCT was conducted to compare weekend atropine (2 days a week) to daily atropine.[6]

Patients Included in the Study

One hundred and sixty-eight children aged 3 to <7 years with moderate amblyopia (20/40 to 20/80), associated with strabismus, anisometropia, or both, were enrolled. VA in the fellow eye was 20/40 or better with an intraocular acuity difference of at least 3 logMAR lines. Children with myopia of −6.00 diopters (D) in the amblyopic eye or more than −0.50 D of myopia in the fellow eye or with Down syndrome were excluded. It was felt that some degree of uncorrected hypermetropic refractive error at near in the fellow eye would be needed for atropine to be effective, although this had not been rigorously studied.[6]

Intervention and Outcome Measures

Patients were randomized to 1% atropine drops to the fellow eye either daily or on the weekend (Saturday and Sunday).[6] The randomization and follow-up schedule are summarized in Figure 14.4.

Major Findings

Both groups improved by an average of 2.3 lines from baseline to 17 weeks.[6] The VA of the amblyopic eye at study completion, in follow-up extended until the child stopped improving, was at least 20/25, or better than or equal to the fellow eye in 47% of the daily group and 53% of the weekend group. The VA of the fellow eye at the end of long-term follow-up was reduced by 2 lines in one patient in each group at final follow-up. Stereoacuity was similar in both groups.[6]

The impact of the treatment on the child and the family was similar between groups when assessed by the Amblyopia Treatment Index questionnaire,[28,29] in all but the compliance subscale, which was slightly worse in the weekend group. It is possible that the children who were receiving daily atropine became accustomed to the routine, whereas the children who received atropine only on the weekend were less compliant.[6]

The improvement in the amblyopic eye was similar in subgroups based on gender, age, cause of amblyopia, iris color, prior amblyopia treatment, and refractive error of the fellow eye.[6]

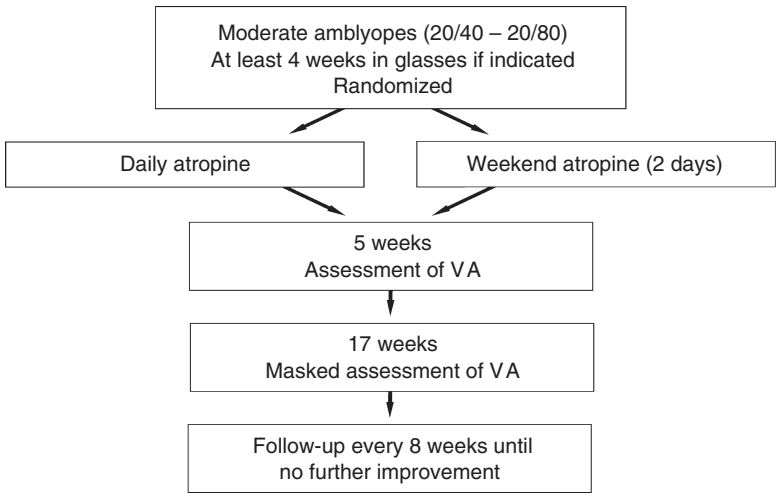

FIGURE 14.4 Randomization and follow-up schedule for children with moderate amblyopia prescribed daily versus weekend atropine in a randomized clinical trial conducted by the Pediatric Eye Disease Investigator Group.

Implications for Clinical Practice

Since the first PEDIG RCT[2] provided evidence that both patching and atropine are effective in treating moderate amblyopia, the choice of initial treatment may be left to the parent and the child. If atropine is chosen, a reasonable approach would be to start with a twice-weekly dose of the 1% drop.

Unanswered Questions

It is possible that even less frequent administration of atropine might be effective in treating moderate amblyopia, and this should be studied further. It is also possible that atropine might be effective in treating more severe amblyopia, since in both this study and the previous atropine study,[2] improvement in the amblyopic eye was seen in children whose near VA of the fellow eye with cycloplegia from atropine was not reduced below the level of the amblyopic eye. We speculate that, in these conditions, the amblyopic eye might be used in conditions other than those evaluated with near VA testing. It is also possible that atropine selectively degrades higher spatial frequencies, which might be critical in the treatment of amblyopia, and that measurement of VA alone does not detect such an effect of atropine.

A recent PEDIG study comparing atropine with and without a plano lens is described next.

Atropine with or Without a Plano Lens for Moderate Amblyopia

Background and Study Questions

For patients whose fellow eyes are optically corrected for distance, atropine results in blur of the fellow eye at near only, but some practitioners augment the effect of atropine by leaving hypermetropic refractive error uncorrected or undercorrected, increasing blur for both distance and near. PEDIG conducted an RCT to study whether such an approach gave an advantage to atropine in the initial treatment of amblyopia, after optical treatment.[15]

Patients Included in the Study

A total of 180 children with amblyopia aged 3 to <7 years were enrolled. Best-corrected VA in the amblyopic eye was between 20/40 and 20/100 inclusive, fellow eye best-corrected VA of 20/40 or better, interocular acuity difference of ≥3 logMAR lines, the presence of or history of an amblyopiogenic factor meeting study-specified criteria for strabismus and/or anisometropia, hypermetropia ≥+1.50 D spherical equivalent in the fellow eye, and the wearing of optimal spectacle correction for a minimum of 16 weeks or until stability of VA was documented (no improvement in amblyopic eye VA at two consecutive visits at least 4 weeks apart).[15]

Intervention and Outcome Measures

Children were randomized to weekend atropine augmented by a plano lens or weekend atropine alone. The primary outcome was a masked assessment of best-corrected amblyopic eye VA using the ATS HOTV VA testing protocol at 18 weeks.[15]

Major Findings

At 18 weeks, amblyopic eye improvement averaged 2.8 lines in the atropine plus plano lens group and 2.4 lines in the atropine-alone group (mean difference between groups adjusted for baseline acuity 0.3 lines; 95% CI, −0.2 to 0.8). Amblyopic eye acuity was 20/25 or better in 24 (29%) patients in the atropine-only group and 35 (40%) patients in the atropine plus plano lens group (p = 0.03). More patients in the atropine plus plano lens group had reduced fellow eye acuity at 18 weeks; however, there were no cases of persistent reverse amblyopia.[15]

Implications for Clinical Practice

As initial treatment for moderate amblyopia, the augmentation of weekend atropine with a plano lens does not substantially improve amblyopic eye acuity when compared with atropine alone.[15]

Unanswered Questions

Despite our finding no substantial benefit of adding a plano lens at the start of atropine treatment, it seems reasonable to add a plano

lens to atropine treatment for children who do not respond, or incompletely respond to atropine, and this is the topic of an ongoing PEDIG RCT. Nevertheless, care should be taken to carefully follow children who are treated by adding a plano lens to atropine, since these children appear to be at most risk for reverse amblyopia.

Regarding atropine for severe amblyopia, in two PEDIG RCTs,[13,15] we included children with severe amblyopia (20/125 to 20/400); 60 children 3 to 6 years of age (mean age 4.4 years) were randomized to weekend atropine plus a plano lens with weekend atropine[15] with full spectacle correction for the fellow eye and 40 children 7 to 12 years of age (mean age 9.3 years) were randomized to weekend atropine or 2 hours of daily patching.[13] The VA outcome was assessed at 17 or 18 weeks. In the younger cohort,[15] VA improved by an average of 4.5 lines in the atropine plus correction group (95% CI, 3.2 to 5.8 lines) and 5.1 lines in the atropine plus plano lens group (95% CI 3.7 to 6.4 lines). In the older cohort,[13] VA improved by an average of 1.5 lines in the atropine group (95% CI, 0.5 to 2.5 lines) and 1.8 lines in the patching group (95% CI, 1.1 to 2.6 lines). We therefore conclude that atropine can improve VA in children 3 to 12 years of age with *severe* amblyopia, but improvement may be greater in younger children.

Bangerter Filters

Background and Study Questions

In some parts of the world, Bangerter filters or foils, placed on the spectacle lens of the fellow eye, have been used to treat amblyopia. These transparent filters, available since the 1960s, were designed as a method to modulate the degree of deprivation from occlusion, by producing diffuse image defocus that degrades fellow eye VA. This treatment modality has not previously been directly compared to patching.[16]

Patients Included in the Study

One hundred and eighty six children, 3 to <10 years old, with moderate amblyopia (20/40 to 20/80).[16]

Intervention and Outcome Measures

Children were randomly assigned to receive either 2 hours of daily patching or to use a Bangerter filter full-time on the spectacle lens in front of the fellow eye. Study visits were scheduled at 6, 12, 18, and 24 weeks. The main outcome measure was best-corrected VA in the amblyopic eye at 24 weeks.[16]

Major Findings

At 24 weeks, amblyopic eye improvement averaged 1.9 lines in the Bangerter group and 2.3 lines in the patching group (difference in mean visual acuities between groups adjusted for baseline acuity = 0.38 lines).[16] The upper limit of a one-sided 95% CI was 0.76 lines, which slightly exceeded a prespecified noninferiority limit of <0.75 lines. Similar percentages of subjects in each group improved ≥3 lines (Bangerter group 38% vs. patching group 35%, $p = 0.61$) or had 20/25 or better amblyopic eye acuity (36% vs. 31%, respectively, $p = 0.86$). There was a lower treatment burden in the Bangerter group as measured with the Amblyopia Treatment Index. With Bangerter filters, neither a fixation switch to the amblyopic eye nor induced blurring in the fellow eye to worse than that of the amblyopic eye was required for VA improvement.[16]

Implications for Clinical Practice

Bangerter filter treatment is a reasonable option to consider for initial treatment of moderate amblyopia, following optical treatment, because the average difference in VA improvement between Bangerter filters and patching was less than 2 letters, and there was lower burden of treatment on the child and family.

Unanswered Questions

It is unclear why amblyopic eye VA improves in cases when neither a fixation switch to the amblyopic eye occurs or when induced blurring in the fellow eye is not worse than that of the amblyopic eye.

Optical Treatment versus Optical Treatment Plus Patching and Atropine in 7- to 17-Year-Olds

Background and Study Questions

Some eye care professionals have believed that the sensitive period for the treatment of amblyopia ends at the age of 6 or 7 years and therefore have not offered treatment to older children. Other providers treat patients aged 9 years or even older and there are case reports and small cases series reporting successful treatment of amblyopia in still older children. In a pilot study[7] of children 10 to 17 years old with amblyopia treated with part-time patching, VA improved by 2 or more lines in 27% of patients. Therefore, a formal RCT was designed to test the hypothesis that patching (with or without atropine) would be superior to optical correction alone.[8]

Patients Included in the Study

Five hundred and seven patients aged 7 to 17 years with unilateral amblyopia secondary to strabismus, anisometropia, or both were enrolled (404 children aged 7 to 12 years and 103 aged 13 to 17 years).[8] No amblyopia treatment other than spectacles in the prior month and no more than 1 month of amblyopia treatment in the last 6 months was allowed. Best-corrected VA was 20/40 to 20/400, with fellow eye acuity of 20/25 or better. No more than 6.0 D of myopia was allowed to exclude patients with possible organic retinal disease. For patients younger than 13 years, an additional eligibility criterion was no more than 0.5 D of myopia in the fellow eye, since this group could be randomized to atropine in addition to patching.[8]

Intervention and Outcome Measures

Patients were randomized to treatment with either optical correction alone or optical correction augmented with patching of the fellow eye 2 to 6 hours a day, with 1 hour of near visual activities (see Fig. 14.5). This study was conducted before the previously described observational studies of optical treatment of amblyopia. A Game Boy (Nintendo, Redmond, Washington) was provided to be used for the near visual activities. Younger patients in the augmented treatment group (age 7 to 12 years) were also prescribed one drop of 1% atropine daily. In these children, glasses were provided for near work if they were unable to read grade-appropriate print. Patients aged 13 to 17 years were not prescribed atropine, due to the increased demands of their activities. The use of simultaneous atropine and patching in the younger children was based on the rationale that a first RCT of treatment in children over 7 years should be designed to maximize the probability of finding a treatment effect, beyond glasses, if one did in fact exist.[8]

The primary outcome was defined as the proportion of patients in each group classified as a responder. The patient was classified as a responder if the amblyopic eye acuity was 10 or more letters (2 lines) better than the baseline acuity. VA testing was performed at 6, 12, 18, and 24 weeks. The responder status was confirmed by a masked examiner. By the 24-week visit, if the amblyopic eye had not improved by 10 or more letters, the patient was classified as a nonresponder. The patient could also be classified as a nonresponder at an earlier visit if there was no improvement from the prior visit or only minimal improvement from baseline, defined at the 6-week visit as a zero-letter improvement, <3-letter improvement from the baseline at the 12-week visit, and <5-letter improvement from the baseline at the 18-week visit. Patients who did not complete the randomized trial and patients in the optical correction group who received additional amblyopia treatment were considered to be nonresponders in the primary analysis.[8]

Due to concerns about inducing diplopia in these older children with patching, the patients (and parents) were asked at each visit if they ever saw two of the same thing and if so, the frequency. For both the patient and the parent, any diplopia was recorded as "Less than once a week," "once a week," "once a day," "up to 10 times a day," "more than 10 times a day," and "all the time."

Responders in both groups continued with follow-up, with visits every 6 weeks until no

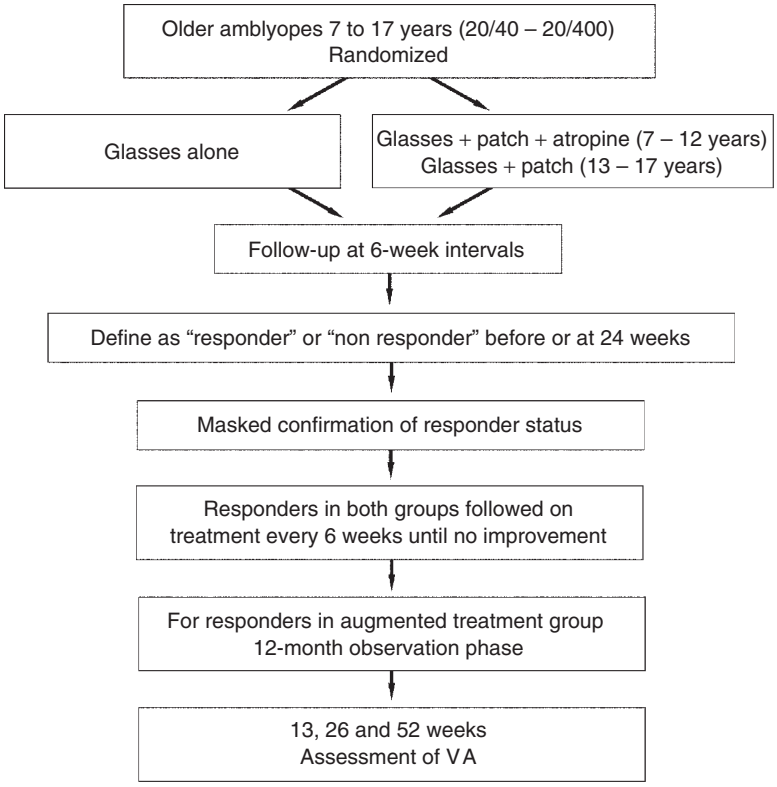

FIGURE 14.5 Randomization and follow-up schedule for 7 to 17 year olds with amblyopia prescribed optical treatment versus optical treatment plus patching and atropine in a randomized clinical trial conducted by the Pediatric Eye Disease Investigator Group.

further improvement was observed. After no further improvement, responders to augmented treatment stopped treatment and entered a 12-month observation phase to determine whether any improvement was long lasting. This phase is ongoing at this time.

Major Findings

In the 7- to 12-year-olds, the responder criterion was met by 106 of the 201 patients (53%) in the augmented treatment group and by 50 of the 203 patients (25%) in the optical correction group ($p < 0.001$).[8] The unadjusted odds ratio for improvement was 3.41 for the augmented treatment group compared to the spectacles-only group (95% CI, 2.24 to 5.21, $p < 0.001$). A benefit of augmented treatment was seen for those children with moderate amblyopia (20/40 to 20/80) and severe amblyopia (20/100 to 20/400), for all three causes of amblyopia (anisometropic, strabismic, and combined) and for children with or without a history of prior treatment.[8]

In the older group, 13 to 17 years, the responder criteria were met by 14 (25%) of the 55 patients in the treatment group and by 11 (23%) of the 48 patients in the optical correction group ($p = 0.47$). The unadjusted odds ratio for improvement was 1.15 (95% CI, 0.46 to 2.84, $p = 0.38$). Nevertheless, among patients who had not been previously treated for amblyopia, those in the augmented treatment group did show a greater improvement than those in the optical correction group, 47% versus 20%, adjusted $p = 0.03$.[8]

No patient developed constant diplopia during the randomized trial phase.

Implications for Clinical Practice

In patients with amblyopia secondary to anisometropia and/or strabismus aged 7 to 12 years, augmenting optical correction with

patching, near activities, and atropine should be offered. The 25% responder rate in the pure optical correction group was surprising and therefore it might be reasonable to start spectacle correction first to determine maximum acuity improvement prior to starting patching. This might be described as refractive adaptation[22,32] or optical treatment of amblyopia, as described earlier in studies for children <7 years of age.

The fact that 23% of the 13- to 17-year-olds responded to optical correction alone suggests that the sensitive period for treatment of amblyopia does not end before the teenage years. It is possible that the lack of difference between the augmented treatment and optical correction alone was due to poor compliance with patching in this age group. It is also possible that efforts to improve compliance might produce better results. The individual response to treatment in the 13- to 17-year-olds was variable, with examples of individuals who had marked improvement in VA. Therefore, offering patching to teenagers after a period of optical correction is reasonable.

Subjects who received augmented treatment and whose amblyopic eye acuity improved 10 or more letters (>2 lines) continued treatment until acuity stopped improving.[42] Eighty patients then discontinued all treatment except for spectacles and had acuity measured 3 months, 6 months, and 1 year later. At the time of treatment discontinuation, VA had improved on treatment by an average of 17 ± 8 letters (3.4 ± 1.6 letters). During the year following cessation of treatment, five patients experienced a worsening of acuity, defined as a decrease of 10 or more letters (1-year cumulative probability = 7%; 95% CI, 3% to 17%). Among the 67 patients who completed 1 year of follow-up, the mean 1-year change in VA was a decrease of 1.3 letters (95% CI, −2.4 to 0.0 letters), and 82% of patients maintained an increase in acuity of 10 or more letters compared with acuity prior to starting treatment. We concluded that VA improvement occurring during amblyopia treatment initiated between 7 and 17 years of age is sustained in most children for at least 1 year after discontinuing treatment other than spectacles.[42]

Unanswered Questions

A subsequent follow-up PEDIG RCT[13] found that monotherapy with atropine or patching leads to similar degrees of improvement in 7- to <13-year-old children with moderate amblyopia.

In a recent meta-analysis of four PEDIG RCTs,[43] subjects 7 to <13 years were significantly less responsive to treatment compared with younger age groups (3 to <5 years, 5 to <7 years) for moderate and severe amblyopia ($p < 0.04$ for all four comparisons). There was no difference in treatment response between subjects aged 3 to <5 years and 5 to <7 years for moderate amblyopia ($p = 0.67$), but there was a suggestion of greater responsiveness of subjects aged 3 to <5 years compared with those aged 5 to <7 years for severe amblyopia ($p = 0.09$). We concluded that amblyopia is more responsive to treatment among children younger than age 7 years. Although the average treatment response was smaller in 7- to <13-year-olds, some individuals show a marked response to treatment.

Patching Dose Regimes Using Occlusion Dose Monitors to Record Compliance

Background and Study Questions

As described earlier, previous RCTs of patching regimes have not addressed actual patch-wearing times. Awan et al.[18] used occlusion dose monitors to record the actual wearing time during an RCT comparing 0, 3, and 6 hours of daily patching for moderate strabismic and mixed anisometropic–strabismic amblyopia. The occlusion dose monitors were flat discs placed on the patch, logging temperature differences between the front and back of the disc at 5-minute intervals.

Patients Included in the Study

Sixty newly diagnosed children, 37 with strabismic amblyopia and 23 with combined strabismic and anisometropic amblyopia, were enrolled. Children wore glasses (if needed) for 6 weeks before the study started. VA ranged from 20/40 to 20/160. The mean age was approximately 4.5 years.

Intervention and Outcome Measures

Children were randomized to one of three groups, no patching, 3 hours of daily patching, and 6 hours of daily patching (see Fig. 14.6). The primary outcome measure for this study was actual patch-wearing time. VA was also measured at a 12-week outcome exam.

Major Findings

The mean daily patching durations were 1 hour 43 minutes in the 3-hour group and 2 hours 33 minutes in the 6-hour group. The compliance represented as a proportion of patching hours prescribed was also similar (58% vs. 41%).

The mean improvement in VA over the 12-week study was similar between all three groups (0.24 logMAR with no patching, 0.29 logMAR with 3 hours per day, 0.34 logMAR with 6 hours per day). Although there was a positive correlation between hours of patching completed and the proportion of VA deficit corrected, there was marked individual variability. A post hoc analysis revealed that confirmed patching of 3 to 6 hours per day was significantly better than no patching.

Implications for Clinical Practice

In this small study, there is controversial evidence that "on average" no patching is as good as prescribing 3 or 6 hours per day. Nevertheless, these children did not have a prolonged period of only optical treatment of amblyopia (refractive adaptation)[22] until no further improvement was observed, so the true effect of patching will have been somewhat masked by the simultaneous optical treatment. In addition, poor compliance in a proportion of children assigned to patching likely masks the potential real effect of patching. The post hoc analysis suggests a real effect of patching, so treatment of amblyopia with patching should not be abandoned.

Improving compliance is clearly important in maximizing the chance of a successful outcome. Educating the families and the child on the importance of treatment and consequences of not treating in a timely manner may be a first step in improving compliance.[44,45] Other compliance aids are the topic of ongoing studies.[40,46]

Unanswered Questions

The individual variability in response to a particular dose of patching is a noteworthy finding of this study[18] and the study of Stewart et al.[24] who also used occlusion dose monitors of a different design. Further studies are needed to establish why some children are resistant to treatment, whereas others seem to respond quickly and completely.

As discussed earlier, further work is needed on techniques to improve compliance with patching. In a prospective RCT, Loudon et al.[40]

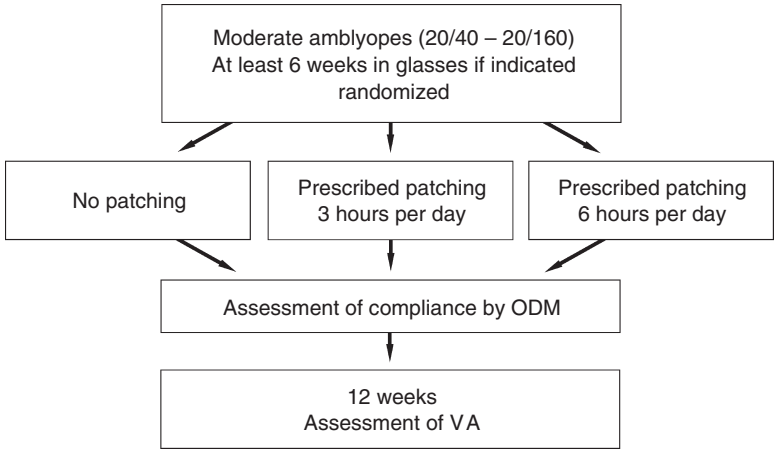

FIGURE 14.6 Randomization and follow-up schedule of patients prescribed patching for 6, 3, and 0 hours per day using occlusion dose monitors to measure compliance.

reported increased compliance when the children received an educational cartoon story and a calendar with reward stickers, and the parents received an one-page information sheet. Of note was the decreased proportion of children who completed no patching. It is unknown whether such educational programs or behavioral interventions will favorably impact the proportion of children who respond to patching.

Unilateral Visual Impairment Detected at Preschool Vision Screening

Background and Study Questions

In the late 1990s, public health policy makers were questioning whether screening for amblyopia in the United Kingdom should be abandoned.[47] They argued that the benefits of patching had not been demonstrated in an RCT, that patching placed a severe psychological burden on the child and the family, and that it was unclear whether unilateral amblyopia actually created any true disability. In that context, Clarke et al.[19] designed an RCT with a completely untreated control group. They studied a population of children who had failed VA screening and were referred for possible amblyopia.

Patients Included in the Study

One hundred and seventy-seven children with a mean age of 4 years and with unilateral moderately decreased VA (20/30 to 20/120), with 20/20 VA in the fellow eye, were enrolled.

Intervention and Outcome Measures

Children were randomized to no treatment, treatment with glasses alone, or treatment with glasses plus patching if indicated (see Fig. 14.7). The primary outcome was corrected VA at 54 weeks. Children in the no-treatment or glasses-only groups were then offered patching if needed, and best corrected VA was measured in all groups 6 months later, at 18 months from study enrollment.

Major Findings

Children who were treated with glasses alone or glasses plus patching had a better mean

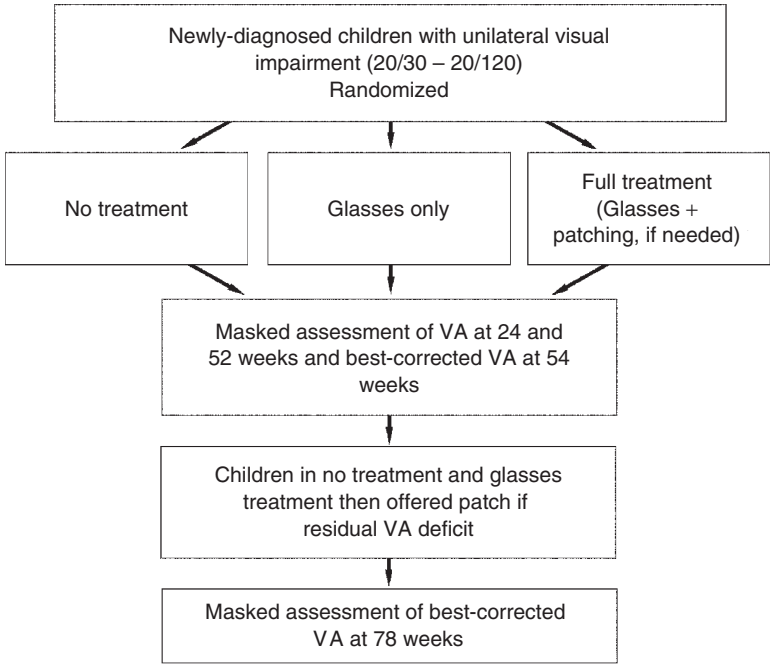

FIGURE 14.7 Randomization and follow-up schedule of patients assigned to no treatment versus glasses-only versus glasses plus patching in unilateral visual impairment.

best corrected VA at 54 weeks than those who received no treatment (mean difference of about 1 logMAR line). In a planned subgroup analysis, children with more severe VA deficit (20/60 to 20/120) showed additional improvement with patching (of approximately another logMAR line) over and above that with glasses alone. Children with a mild uncorrected VA deficit (20/30 to 20/40) had no significant improvement over no treatment, with glasses alone or glasses plus patching.

After subsequent full treatment (patching if needed) for 6 months, the no-treatment group and glasses-only group improved to have corrected visual acuities indistinguishable from the originally fully treated group (glasses plus patching).

Implications for Clinical Practice

From a public health perspective, the results of Clarke's study are very important. Treating unilateral VA deficit with glasses and patching (if indicated) results in improvement of best corrected VA. Much of the VA deficit in this study may have been due to amblyopia, though an unknown proportion would have been purely refractive error. Children should continue to be screened for VA deficits and referred for treatment. Despite the dilution of the amblyopic cohort in this study, this RCT provided excellent evidence that patching works.

The improvement of children whose treatment was delayed for a year indicates that the sensitive period for treating amblyopia is not over by the age of 4 years. This lack of age effect is consistent with the findings of the several PEDIG studies,[2,3,8] in the 3- to 7-year age range, and has also been confirmed by others.[18,21]

Unanswered Questions

The failure of children with mild unilateral VA deficit in Clarke's study to improve with glasses and patching compared to no treatment raises the issue of pass/fail acuity criteria that should be used for screening. This topic is beyond the scope of this chapter, but it should be noted that "normal" VA for a 3- to 5-year-old is not 20/20 and that there is some test–retest variability in VA testing. These factors should be taken into consideration when setting referral criteria.

In order that public health officials can make rationale decisions in allocating health care resources (e.g., preschool vision screening), the true lifetime disability of amblyopia needs to be better defined. Although there are data on the effect of losing the better eye later in life,[48,49] there are little data on the effect of amblyopia on the day-to-day life of individuals who have residual or untreated amblyopia that lasts for the remaining decades of their lives.

Conclusions

The evidence for the rational treatment of amblyopia is rapidly evolving. At the time of writing this chapter, there is excellent evidence for initially prescribing the best refractive correction for children with anisometropic, strabismic, and combined anisometropic–strabismic amblyopia and monitoring VA until it stabilizes. This may take several months and a proportion of patients will achieve equal VA with glasses alone. For residual anisometropic and strabismic amblyopia, the choice of patching or atropine or a Bangerter filter should involve the parent and the child. The dose of prescribed patching or atropine may initially be quite modest, such as 2 hours of patching a day or twice-weekly atropine. Treatment should be offered to children at least until the age of 12 years and even to teenagers. Until we have evidence to the contrary, it is entirely reasonable to increase or switch treatment in children who do not respond, or incompletely respond, to lower intensity treatment.[37,38]

Ongoing studies will define the role of oral levodopa as a potential adjunct to patching and will better define the role of increasing patching and augmenting atropine with a plano lens, if VA improvement plateaus. Future studies are needed to investigate whether weaning treatment is needed at the end of a course of amblyopia therapy, how compliance can be enhanced, and why a few children appear to have resistant amblyopia despite complying with intense treatment.

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15 Uveal Melanoma: Approaches to Management

Ernest Rand Simpson MD, FRCSC

Background

Choroidal melanoma is the most common primary human intraocular malignancy. The estimated incidence throughout North America is 6 to 7 cases per million per year. Mortality from melanoma typically results from metastatic spread to the liver. Metastases are often delayed in presentation by many years. Historically, the primary therapy for choroidal melanoma was enucleation. The failure of enucleation to prevent metastatic disease has led to the exploration of adjunct therapies. In addition, therapeutic alternatives to enucleation emerged because of a desire to develop globe- and potentially vision-sparing procedures. Evaluation of therapy for choroidal melanoma has proven difficult due to the relative rarity of the malignancy and the long time horizon for metastatic spread.

Collaborative Ocular Melanoma Study

Nearly 20 years ago, the Collaborative Ocular Melanoma Study (COMS) was launched to address the survival benefit of competing treatment options that, at the time, included enucleation and radiotherapy. The study addressed three clinical questions:

1. Does subtherapeutic external beam radiation prior to enucleation of large choroidal melanomas reduce metastases and mortality?
2. Is there a survival benefit to enucleation compared to radioactive I^{125} plaque application in patients with medium-sized choroidal melanoma?
3. What is the natural history of small choroidal melanomas?

For reasons of consistency in clinical comparison, size characteristics of choroidal melanoma were defined as small (1.0 to 3.0 mm in apical height and at least 5.0 mm in basal diameter), medium (2.5 to 10 mm in height and 16 mm or less in largest basal diameter), and large (greater than 10 mm in height or greater than 16 mm in largest basal diameter and at least 2 mm or greater in height).

Methodology for Collaborative Ocular Melanoma Study Trials

A process of certification to establish clinical center uniformity required repeated certification of each investigator, clinical coordinator, plaquing surgeon, enucleating surgeon, examining ophthalmologist, radiation oncologist, radiation physicist, echographer, photographer, ophthalmic pathologist, and visual acuity examiner.

Patient eligibility and enrollment were determined by a rigid protocol that included

1. A complete ophthalmic and systemic evaluation.
2. Color photographs and fluorescein angiography to document tumor size and characteristics.
3. Standardized echography, including A and B scan evaluation.
4. Eligibility was confirmed and randomization provided by the Central Study Coordinating Center after full ophthalmologic, radiation, and medical oncology review.

Collaborative Ocular Melanoma Study Protocol Compliance

Overall protocol compliance in the COMS requiring radiation therapy for large tumors was >98% and nearly 95% for medium tumors. Data were collected on standardized forms and submitted within a specific time frame to the COMS central coordinating center and to specific resource centers.

Collaborative Ocular Melanoma Study Small Choroidal Melanoma Observational Study

This component of the study was an observation series of otherwise healthy adults with small choroidal melanomas. The primary endpoints were 5-year mortality and tumor growth. The overall 5-year mortality was low. Five-year all-cause mortality was 6.0% (95% confidence interval [CI], 2.7% to 9.3%) and 8-year all-cause mortality was 14.9% (95% CI, 9.6% to 20.2%.[1]

Of the small choroidal melanomas initially observed, 21% demonstrated growth by 2 years and 31% by 5 years.[2] Factors associated with time to growth were greater initial tumor thickness and diameter, presence of orange pigment, absence of drusen, and absence of retinal pigment epithelial alteration adjacent to the tumor. These observations have also been noted in other large case series of small choroidal melanomas and atypical choroidal nevi. In a separate study, Shields et al. found increased tumor thickness (greater than 1 mm), proximity to the optic nerve, visual symptoms, presence of orange pigment, and presence of subretinal fluid to be predictive of future growth (Fig. 15.1).[3]

Collaborative Ocular Melanoma Study Medium Choroidal Melanoma Trial

The medium tumor trial compared enucleation to radioactive I^{125} plaque application. Patients included in the study met the following criteria (Fig. 15.2):

1. Apical height between 2.5 and 10 mm and basal diameter of 16 mm or less
2. Visual acuity of at least 20/200 in fellow eye
3. No neovascular glaucoma
4. No iris involvement with tumor
5. No angle involvement with tumor
6. Clear ocular media
7. Tumor must not be contiguous with optic disk
8. Tumor within 2 mm of optic disk must fit within a 90 degree angle with the apex at the center of the optic disk
9. The tumor must be "plaqueable" in the opinion of the ophthalmologist

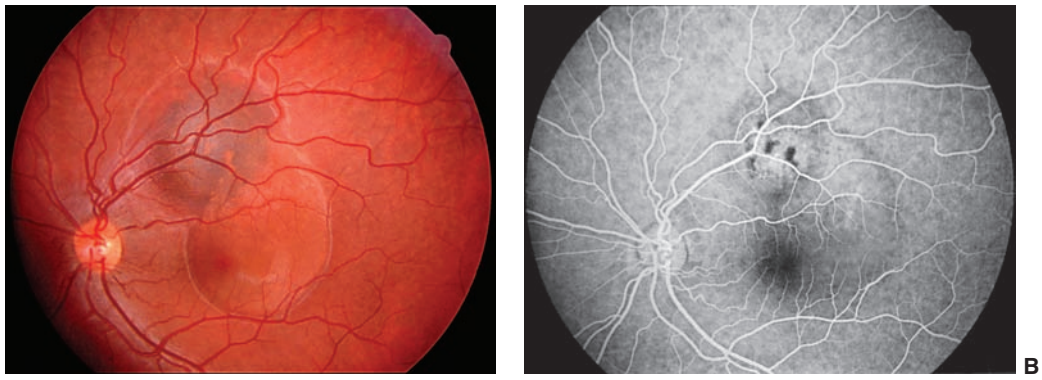

FIGURE 15.1 Small melanocytic choroidal mass with associated serous subretinal fluid. **(A)** Clinical appearance showing surface lipofuscin and macular involvement with serous fluid. **(B)** Fluorescein angiogram demonstrating abnormal hyperfluorescence at the level of the choroid with blocked fluorescence due to lipofuscin over the mass. Note reduced fluorescence underlying the serous detachment extending into the foveal region.

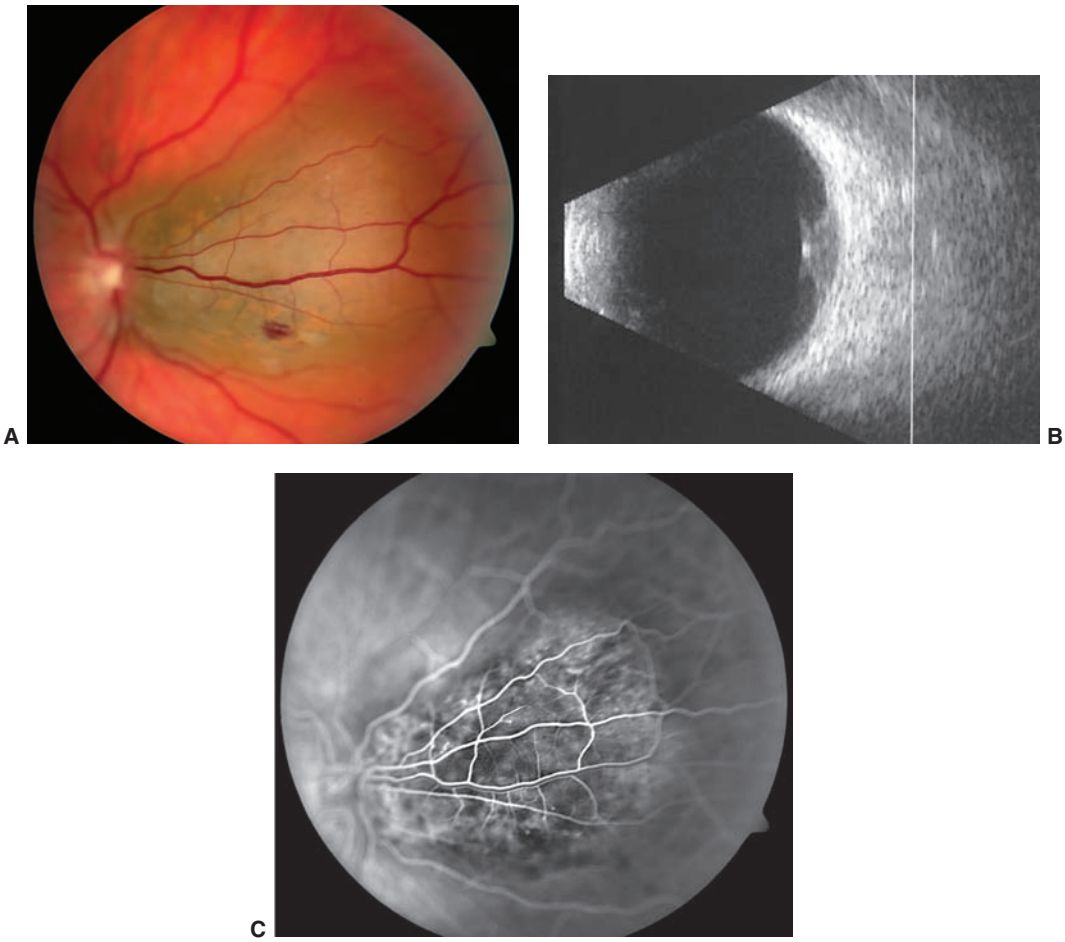

FIGURE 15.2 Juxtapapillary choroidal melanoma excluded from enrollment in the COMS due to proximity to the optic nerve. **(A)** Clinical appearance showing the tumor involving 180 degrees of the nerve. **(B)** Ultrasonogram in B mode demonstrating low reflective dome-shaped mass with overlying serous fluid. **(C)** Fluorescein angiogram of juxtapapillary mass showing mottled hyperfluorescence at the level of the choroid.

Patients evaluated in the COMS were excluded for the following indications (Fig. 15.3):

1. Use of immunosuppressive therapy
2. Previous treatment for choroidal melanoma
3. Previous intervention in the eye that was tumor related
4. Previous fine needle biopsy of suspected tumor
5. Extrascleral extension of >2 mm
6. Diffuse, "ring," or multiple melanoma
7. Other known primary tumors except cervical carcinoma in situ or nonmelanotic skin cancers
8. Any disease compromising survival
9. Involvement of 50% or more of the ciliary body with tumor
10. Tumor contiguous with optic nerve
11. Contraindications to surgery or radiation therapy
12. Contraindication to anesthesia if enucleation required

A total of 22% of patients evaluated for the study were deemed to be ineligible for enrollment. The most common reasons for exclusion were proximity of the tumor to the optic disk (40%), one or more primary cancers (20%), and melanoma that was primarily in the ciliary body (11%).

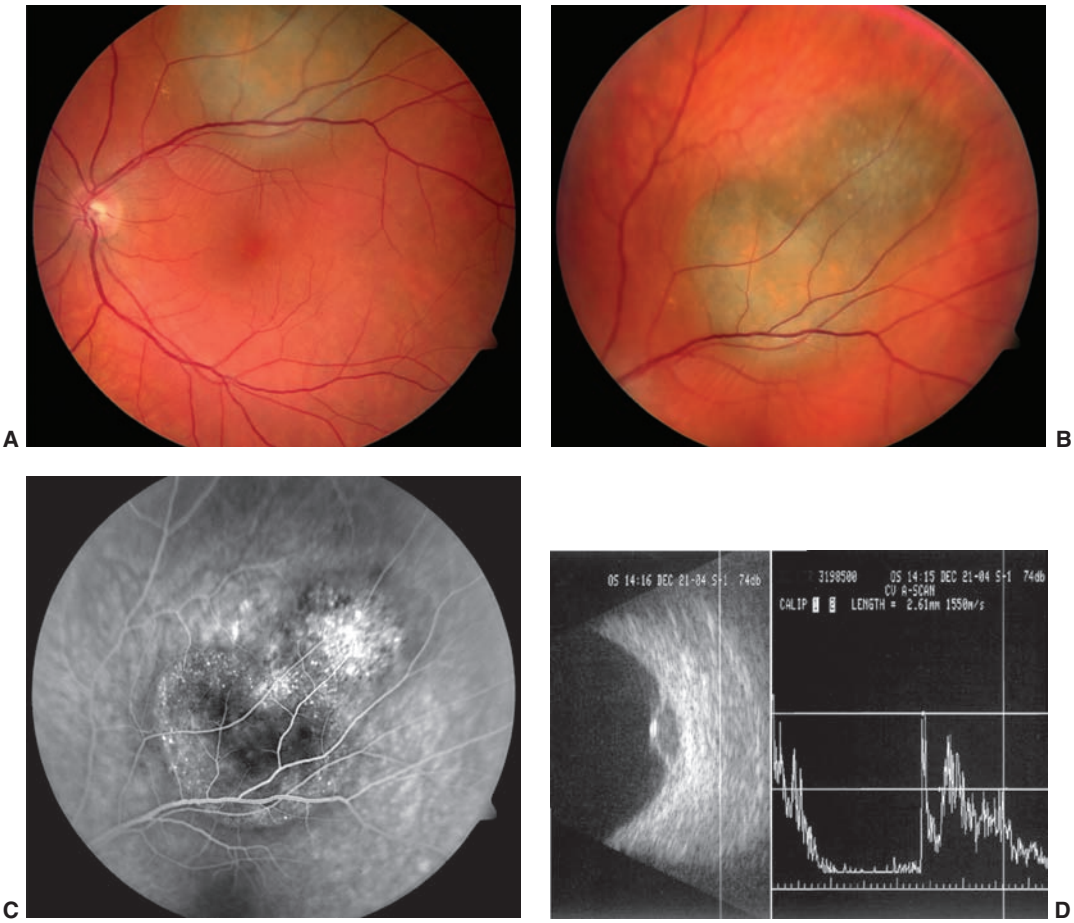

FIGURE 15.3 Medium choroidal melanoma with orange pigment, beginning to affect macular function. **(A)** Clinical appearance of choroidal mass with overlying lipofuscin beginning to exert traction on paramacular retina. **(B)** Margins of tumor are ill-defined with an irregular contour. **(C)** Fluorescein angiogram showing more specific contour of the mass, abnormal hyperfluorescence with partial blocking effect from orange pigment, and dot-like fluorescence indicating Bruch's membrane alteration. **(D)** Ultrasonogram in B mode showing dome-shaped low reflective mass with an A-mode height measurement of 2.61 mm.

Brachytherapy

Plaque radiotherapy remains in widespread use throughout the world as the most common method of delivering therapeutic doses of radiation to intraocular tumors, including choroidal melanoma. High-energy sources such as cobalt have been replaced by lower energy radioisotopes including iridium-192, ruthenium-106, palladium-103, and iodine-125. There are a number of reasons why iodine-125 was the radioisotope chosen for the COMS. Eleven millimeters of lead is needed to block 50% of emitted photons from a plaque employing cobalt, whereas only 1 mm of gold can arrest all radioactive emission from an iodine-125 containing plaque. Although some investigators utilize different radioisotopes for various tumor shapes and volumes, the most commonly employed radioactive isotope is iodine-125. With a half-life of 60 days, this isotope is relatively safe for both the patient and the operating surgeon and can be incorporated into the plaque structure on site with a high degree of accuracy and reproducibility. Iodine-125 can provide sufficient dose rates to tumors without exposing the sclera to excessive radiation.

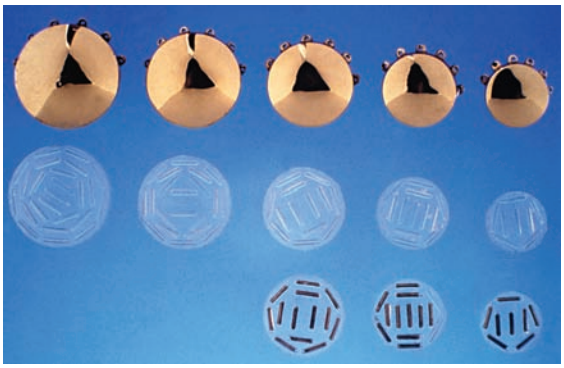

FIGURE 15.4 Structure of iodine-125 radioactive plaques employed in brachytherapy for choroidal melanoma. Seeds, silastic inserts, and gold backing disassembled. Plaque sizes range from 12 to 20 mm in diameter.

Plaque dosimetry for individual tumors is provided by the ocular oncologist and radiation oncologist in conjunction with the radiophysicist, and according to precise clinical measurements obtained through ophthalmoscopy, ocular imaging, and echography, plaques are constructed to cover the tumor base with a 2.0 mm margin greater than the largest tumor base dimension (Fig. 15.4). At the time of surgery, plaque placement is facilitated by either transillumination of the tumor margins or standard indirect ophthalmoscopic localization techniques with or without ultrasound assistance. The plaque is then secured to the sclera and the final position verified by either intraoperative echography or an indirect ophthalmoscopic-fiberoptic system (Fig. 15.5).

Brachytherapy is usually applied to medium category tumors with the aim of treating the tumor apex with ~8,500 cGy, with dose delivery over 3 to 7 days (Fig. 15.6). Brachytherapy in the COMS employed iodine-125 plaques.

Complications of plaque therapy include treatment failure due to tumor recurrence, radiation vasculopathy, cataract formation, vitreous hemorrhage, optic neuropathy, and diplopia resulting from ocular muscle manipulation during plaque placement and removal.

Collaborative Ocular Melanoma Study Medium Tumor Results

Of the 1,317 patients enrolled in the study of medium-sized choroidal melanomas, 660 were assigned to enucleation and 657 to iodine-125 brachytherapy. The primary outcome was mortality at 5 and 10 years (Table 15.1). Eighty-one percent of patients had been followed for 5 years and 32% for 10 years at the end of the 11.5-year accrual period. The unadjusted estimated 5-year survival rates were 81% and 82%, respectively, with no clinical or statistical difference in survival rates overall (Table 15.2). Five-year rates of death with histopathologically proven melanoma metastasis were 11% and 9% following enucleation and brachytherapy, respectively (Table 15.3).[4] The power of the study was sufficient to indicate that neither treatment was likely to increase or decrease mortality rates by as much as 25% relative to the other.

While there was no significant survival advantage conferred by removal of the eye, the visual results of patients receiving treatment with radioactive I^{125} plaque did show significant visual impairment due to radiation-related complications, particularly radiation retinopathy. At 3 years, 50% of patients had a loss of 6 or more lines of visual acuity and 43% had a visual acuity less than 20/200.[5] The risk factors for visual loss at 3 years included

- Apical tumor height >5.0 mm
- Distance to foveal avascular zone < 2.0 mm
- History of diabetes
- Presence of tumor-associated retinal attachment
- Tumor not dome shaped

By 5 years following brachytherapy for choroidal melanoma, treatment failure resulting in enucleation occurred in 12.5% of patients. Treatment failure was the most common reason for enucleation within 3 years, and beyond 3 years, ocular pain was most common. The

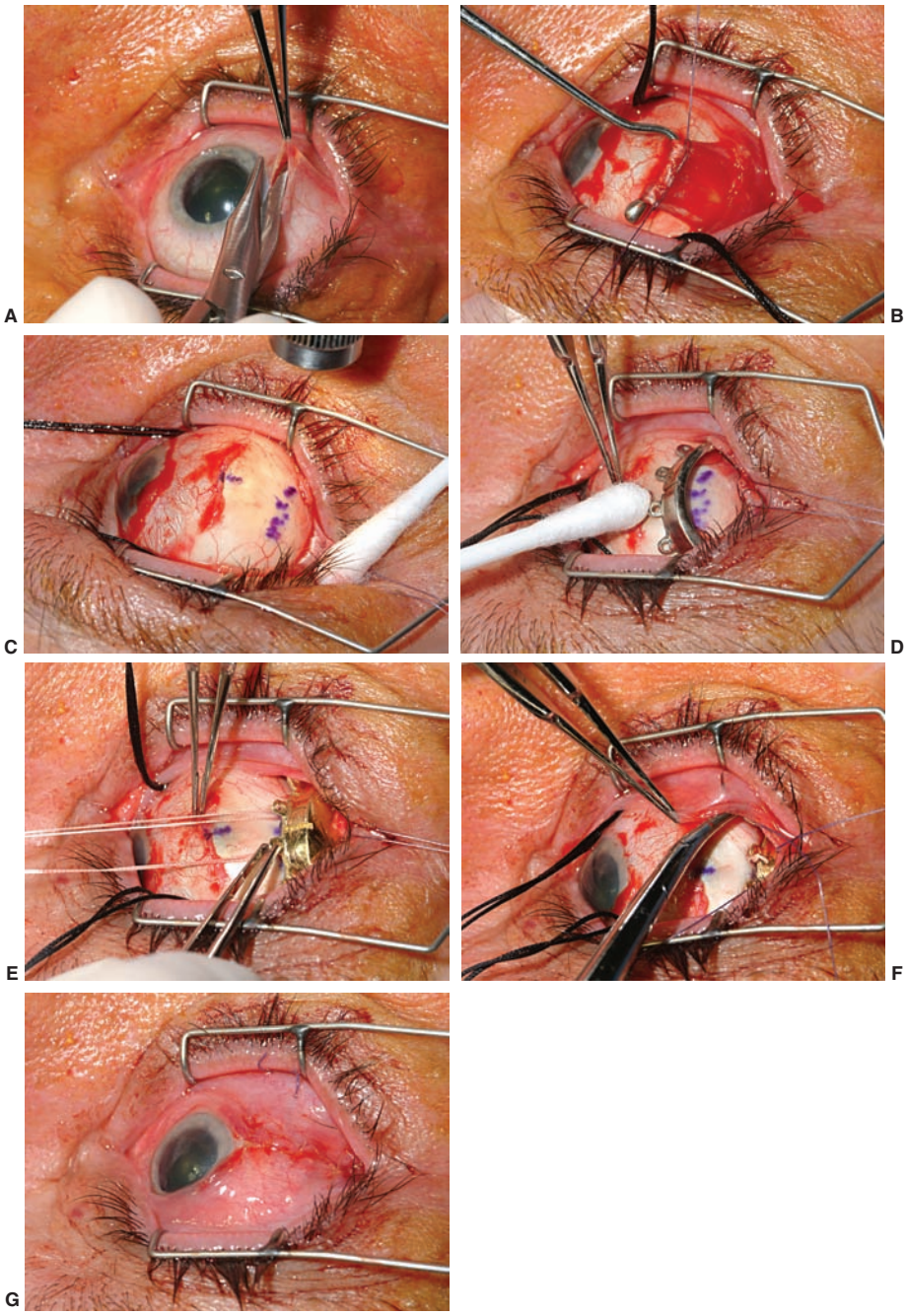

FIGURE 15.5 Surgical placement of an I-125 radioactive plaque in the treatment of a choroidal melanoma in the right eye. **(A)** The conjunctiva is peritomized laterally to permit access to the tumor situated posteriorly lying in the 9:00 meridian. **(B)** The lateral rectus muscle is placed on colored Vicryl suture and removed from its insertion. **(C)** The anterior border of the tumor is identified by transillumination, indirect ophthalmoscopy, or intraoperative ultrasound and marked on the scleral surface. **(D)** A plaque without radioactivity identical to the proposed I-125-containing plaque is placed to cover the marked sclera and suture points are noted. **(E)** The "dummy" plaque is removed and replaced with the radioactive plaque which is secured with Mersilene suture. **(F)** The lateral rectus muscle is temporarily tied into the inferior fornix to be later resutured to the original insertion at the time of plaque removal and **(G)** the conjunctiva is closed.

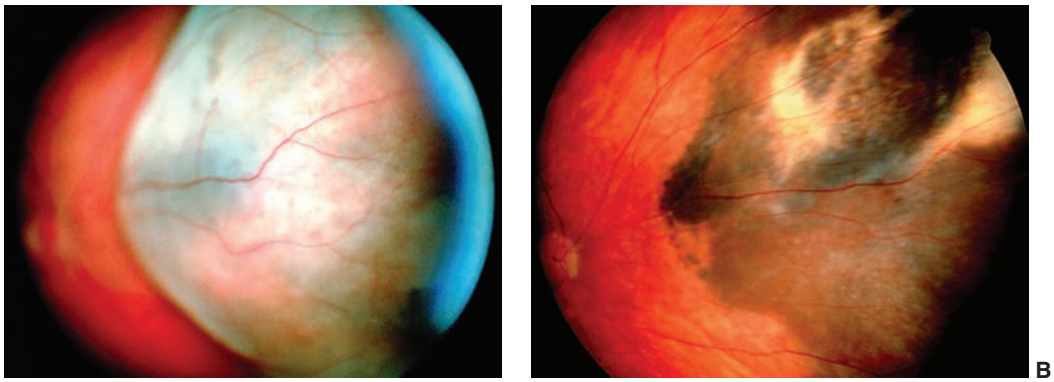

FIGURE 15.6 Medium choroidal melanoma treated by iodine-125 plaque radiotherapy. **(A)** Before treatment with I-125 plaque radiotherapy. **(B)** The same tumor 2 years following treatment. Note the treatment has reduced the tumor to a flat pigmented remnant over this time interval.

TABLE 15.1 All-Cause Mortality Data for Collaborative Ocular Melanoma Study (COMS) Medium Tumors (COMS Report #18)

Interval (years)	"Life Table" Rates, % (95% CI)	
	Enucleation	Iodine-125
3	9 (7–11)	9 (7–12)
5	19 (16–23)	18 (15–21)
8	32 (28–36)	28 (24–32)
10	37 (33–42)	34 (30–39)

TABLE 15.2 Five-Year Mortality By Treatment And Age For Collaborative Ocular Melanoma Study Medium Tumor Patients

Age (years)	Enucleation (%)	Iodine-125 (%)	Log rank *p*-value
<60	11	8	0.20
60–69	22	25	0.95
>69	29	28	0.57

TABLE 15.3 Death with Confirmed Melanoma Metastasis for Collaborative Ocular Melanoma Study Medium Tumor Patients

Interval (years)	Life Table Rates, % (95% CI)	
	Enucleation (*n* = 660)	Iodine-125 (*n* = 657)
3	3.6 (2.4–5.3)	2.5 (1.5–4.0)
5	10.6 (8.3–13.4)	8.8 (6.7–11.4)
8	15.9 (12.8–19.5)	13.5 (10.7–17.0)

risk factors for treatment failure included older age at enrollment, larger tumors, and increasing proximity of the tumor to the fovea. Treatment failure was associated weakly with poorer survival. Almost all surviving patients retained good visual acuity in the fellow eyes throughout 5 years following treatment for choroidal melanoma.[6]

Collaborative Ocular Melanoma Study Large Choroidal Melanoma Trial

Enucleation of eyes containing choroidal melanoma does not necessarily prevent metastatic disease from presenting years later. The observations of Zimmerman et al.[7] and McLean et al.[8] raised the question of whether globe manipulation during enucleation disseminated viable tumor cells to produce metastases. This premise is often referred to as "The Zimmerman hypothesis." Adjunctive treatments have been proposed for large choroidal melanoma to reduce the possibility of tumor dissemination during enucleation. These have included pre- and post-enucleation irradiation of the globe and orbit as well as cryotherapy, chemotherapy, immunotherapy, and combinations thereof. The COMS was the first prospective randomized management strategy to assess preoperative radiation preceding enucleation. The primary outcome measure was mortality at 5 and 10 years.

The Large COMS Tumor Trial compared preoperative external beam radiation (2,000 cGy) followed by enucleation to enucleation alone for large tumors. Inclusion criteria included the following (Fig. 15.7):

1. Apical height >10 mm (or >8 mm whenever the proximal border of the tumor was too close to the optic nerve to qualify for the trial of enucleation vs. iodine-125 brachytherapy) or
2. Basal diameter > 16 mm and apical height at least 2 mm.

Five-year and 10-year survival of patients with large choroidal melanoma randomized to either 2,000 cGy of preoperative external beam radiation followed by enucleation or enucleation alone was shown to be neither clinically nor statistically different between treatment arms regardless of whether all-cause or disease-specific death was considered. At 5 years, the all-cause mortality and disease-specific death rates were 43% and 38%, respectively. Ten-year all-cause mortality was 61% for patients in both treatment arms. The 10-year rate of disease-specific death was 45% in the pre-enucleation radiation arm and 40% in the enucleation-only arm (Table 15.4). Older age and larger basal tumor diameters were the most significant predictors of both all-cause and disease-specific mortality.[9]

Histopathologic Findings in Collaborative Ocular Melanoma Study

The COMS yielded additional important clinical information. In particular, it confirmed the improved diagnostic accuracy for choroidal melanoma. Since first reported over 35 years ago, the misdiagnosis rate for choroidal melanoma fell from 20% to 1.4% over an 11-year period. In 1990, the COMS reviewed 413 specimens. Of these, 411 were correctly diagnosed as melanoma. One hemangioma and one melanocytoma were misdiagnosed. This established a misdiagnosis rate of 0.48%, the lowest rate ever reported.[10] An analysis based on 1,527 cases of enucleated eyes with uveal melanoma demonstrated a diagnostic accuracy for COMS centers of 99.7%.

The COMS also provided a large series of globes for evaluation to further characterize the pathology of choroidal melanoma. Histology showed the tumor cell type distribution to be spindle cell tumors in 9% of cases, mixed tumors in 86% of cases, and epithelioid in 5% of cases. Extensive local invasion of tumor was reported with rupture of Bruch's membrane (87.7%), invasion of the retina (25.2%), vortex vein invasion (8.9%), and invasion into emissary canals (55.0%). Scleral invasion was noted in 55.7% of eyes, with extension outside the sclera in 8.2%. This pathologic review reported 81.1% of eyes with involvement of the sclera by tumor in one form or another; these observations would suggest caution in accepting eye-wall resection as a treatment option for choroidal melanoma.[11]

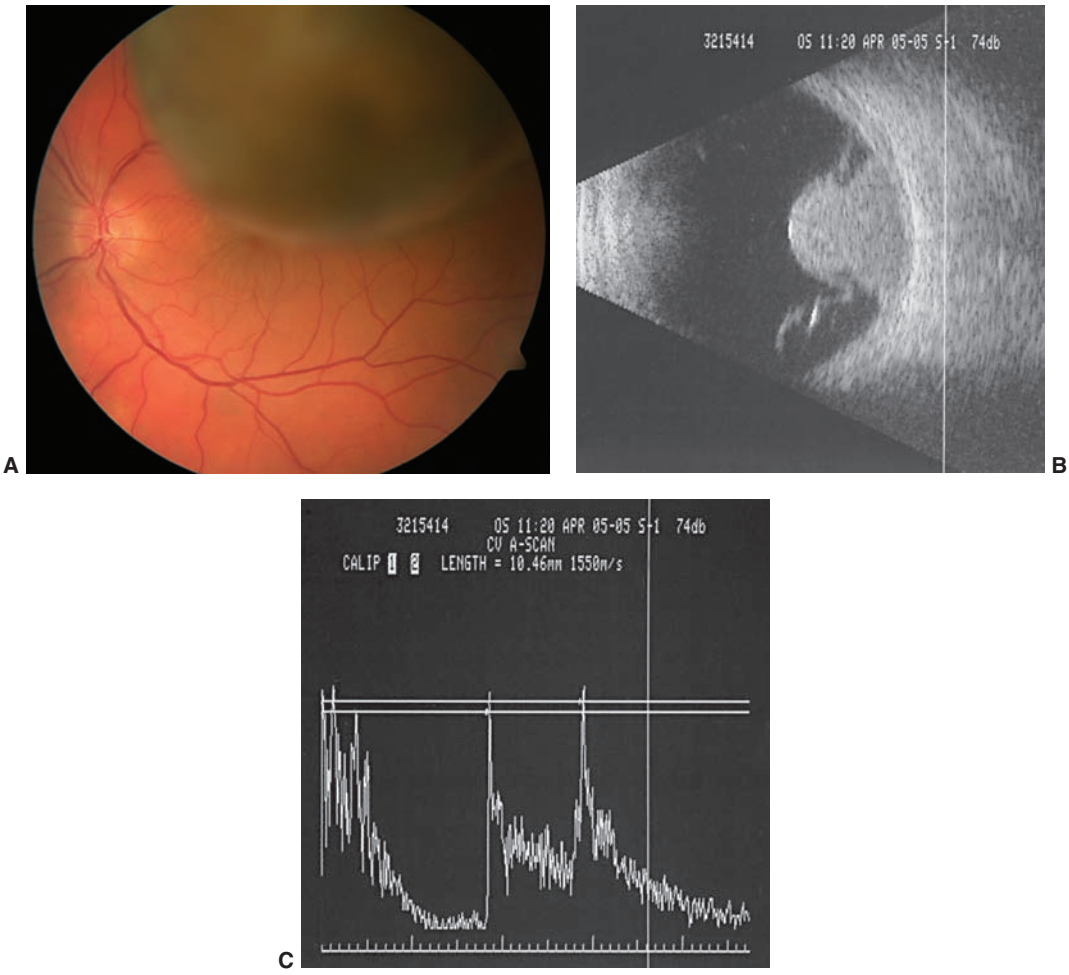

FIGURE 15.7 Large choroidal melanoma. **(A)** Clinical appearance of a pigmented mass occupying the posterior pole with an associated serous retinal detachment. **(B)** Ultrasonogram in B mode demonstrating a collar-button-shaped solid choroidal mass with associated serous retinal detachment. **(C)** A mode of the same tumor showing a vertical height of 10.46 mm.

Beyond Collaborative Ocular Melanoma Study

Despite the successes of the COMS, many questions regarding the management of ocular melanoma remain. New therapies designed to avoid enucleation, preserve vision, and reduce metastatic deaths have emerged. Combination treatments incorporating radiation and laser have been suggested to reduce the secondary retinal complications of radiation. Specially

TABLE 15.4 **Collaborative Ocular Melanoma Study (Coms) Large Tumor Trial Melanoma-Specific Mortality (Coms Reports # 10 And 24)**

Interval (years)	Enucleation Alone (%)	Enucleation with Preoperative Radiation (%)
5	28	26
10	40	45

designed plaques have allowed brachytherapy to tumors not considered treatable in the COMS protocol. The relative rarity of the tumor makes it difficult to evaluate all new therapeutic approaches, with large clinical trials making clinicians reliant on evaluation of multiple case series for treatment decisions.

Observation

Although the natural history of choroidal melanoma remains unclear with regard to its potential for malignancy, some small melanocytic tumors nevertheless appear clinically inactive and remain stable throughout long periods of observation (Fig. 15.8). Shields et al. documented growth in 18% of 1,329 small melanocytic lesions and the COMS reported 31% growth in 204 patients with small choroidal lesions presumed to be melanomas over 5 years. Observation may therefore be appropriate for some slow growing lesions especially in visually critical situations, elderly or ill patients, or cases in which the consequences of intervention might outweigh any perceived treatment benefit.

Transpupillary Thermotherapy

Infrared diode laser energy has been employed in the management of some small choroidal melanomas both as a primary treatment modality and as secondary adjuvant therapy in patients receiving brachytherapy. Tumor death occurs through cellular necrosis as opposed to coagulative necrosis, a consequence of thermal laser energy, and has the theoretical advantage of providing tumor control with minimal collateral damage to normal tissue. The limited penetration of 810 nm light to a depth of approximately 4.0 mm permits treatment of relatively flat primary tumors and small recurrences. Secondary adjuvant therapy has been proposed as a method to achieve complete tumor control while limiting the radiation dose at the tumor apex and the possibility of radiation retinopathy (Fig. 15.9).

The evidence for transpupillary thermotherapy (TTT) to date is confined to a number of case series with variable duration of follow-up. Oosterhuis et al. published the first study of TTT as a treatment for choroidal melanoma in 1995.[12] Shields et al. reported reduced tumor thickness (27% in heavily pigmented tumors and 15% in amelanotic tumors) over 1.7 months.[13]

Several questions have been raised regarding the efficacy and long-term safety of TTT. Specifically, questions exist about the ability of TTT as a primary therapy to achieve tumor control given its limited penetration depth and the high incidence of cellular scleral invasion observed in medium-sized tumors. In addition, its role in amelanotic and variably pigmented tumors has been questioned. In one series, Stoffelns showed that despite apparent tumor regression, the

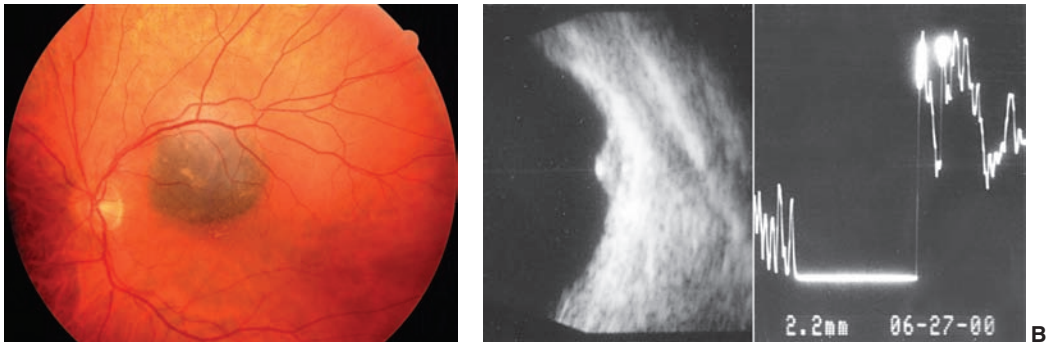

FIGURE 15.8 Small untreated choroidal melanoma observed over 2 years without change in clinical appearance. **(A)** Clinical appearance. **(B)** Ultrasonogram demonstrating dome-shaped choroidal mass measuring 2.2 mm in vertical height.

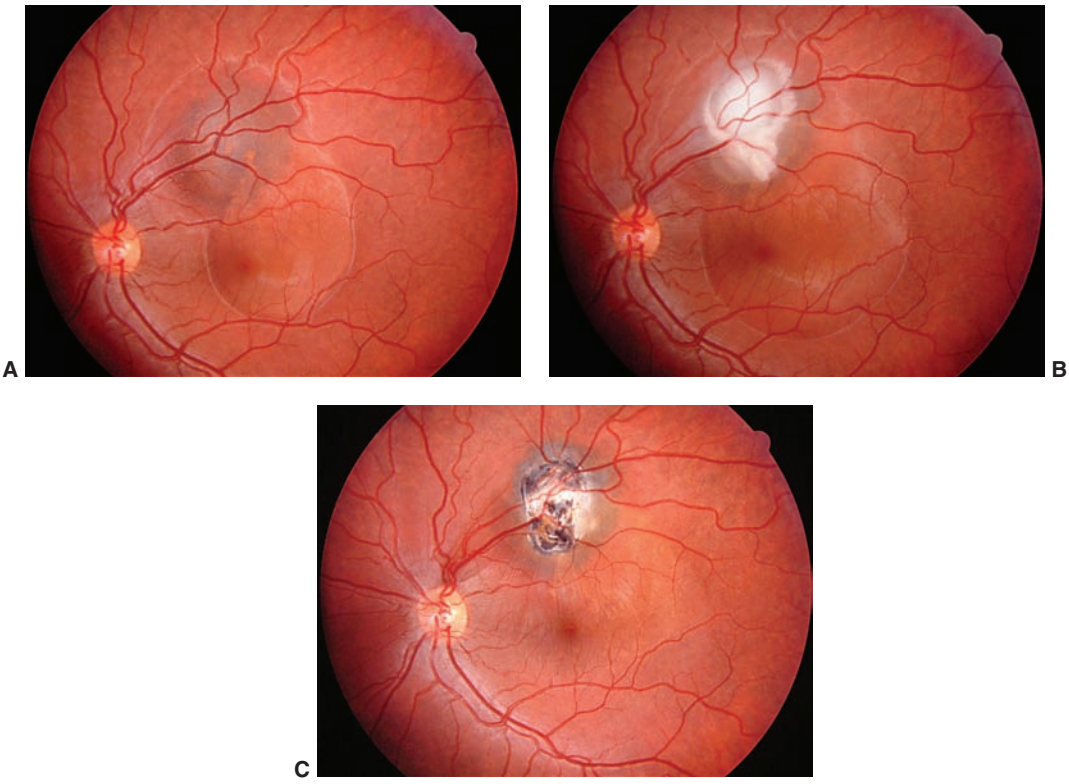

FIGURE 15.9 Transpupillary thermotherapy (TTT) treatment of a small choroidal melanoma (seen in Fig. 15.1). **(A)** Clinical appearance of small melanoma with high-risk characteristics and associated serous detachment extending into the macula. **(B)** Initial response immediately following TTT. **(C)** One month following initial treatment with TTT. Note the absence of serous fluid with return of macular function.

choriocapillaris was incompletely destroyed in 90% of cases.[14] Harbour and coworkers reported retinal complications in 76% and treatment failure in 29% with primary TTT. Treatment failure occurred primarily at tumor margins.[15]

Brachytherapy for Peripapillary Melanoma

Plaques can be configured with indentations to treat juxtapapillary tumors with some success; however, the mechanical effect alone of this peripapillary plaque placement can restrict the circulation to the optic nerve, inducing significant early visual loss.

Charged Particle Radiotherapy

An alternative radiotherapeutic approach to treating choroidal melanoma employs charged particles in the form of protons or helium ions. This form of radiotherapy requires the surgical placement of tantalum markers, sutured to the sclera, for tumor localization, followed by the delivery of charged particle radiation in a highly focused system to the tumor. During treatment sessions, which last several minutes, 10 to 16 Gy fractions are delivered to the desired total dose. Positively charged particles pass through tissue in a highly collimated beam path, ionizing surrounding atoms to a given ionization density known as the Bragg peak. Collateral tissue damage is thereby minimized and tumor irradiation is more uniform, with the lateral irradiation dose dropping from 100% to 10% in <2.5 mm of the radiation field. A treatment margin of 2 to 3 mm is usually employed to

account for a safety factor, an allowance for patient movement, and a factor to account for lateral spread of radiation. Although tumor control rates compare favorably with those reported for brachytherapy, the use of charged particles results in a higher rate of neovascular glaucoma, cataract formation, keratoconjunctivitis, and lash loss.

A similar spectrum of tumors are treated with charged particle radiotherapy as with brachytherapy but because a significant amount of energy is delivered to the anterior aspect of the eye during treatment with charged particles, anterior complications are more prevalent than with radiation delivered posteriorly through the sclera. Gragoudas et al. reported that following proton beam radiation, radiation maculopathy occurred in ~75% of eyes with tumors within 1 disk diameter of the fovea and in 40% of eyes with tumors >1 disk diameter of the fovea.[16]

Other Teletherapy Approaches

More recently, other methods of radiotherapy employing either gamma knife or stereotactic hypofractionated radiation therapy have been evaluated in the treatment of choroidal melanoma. Gamma knife techniques have been associated with a higher incidence of neovascular glaucoma and there remains uncertainty in optimal dose delivery. Linac-based stereotactic radiotherapy has provided satisfactory control of juxtapapillary choroidal melanomas when plaque radiotherapy was not considered appropriate and has the advantage of supplying radiation (usually 70 Gy in five fractions) without the need for surgical intervention (Fig. 15.10).[17]

Lamellar and Full-Thickness Eye-Wall Resection

Originally intended to manage iridociliary tumors to minimize radiation consequences following radiotherapy, this technically challenging surgery is accomplished now with less frequency, owing to observed complications over time. In 1986, Foulds and Damato recommended resection for tumors 10 to 15 mm in diameter.[18] In lamellar sclerouvectomy, the tumor base is defined and a free margin around the tumor is outlined. After a scleral flap is fashioned, the deep scleral lamella is incised down to choroid. The tumor is dissected from the retina, delivered with the scleral wall, and the scleral flap is replaced. A full-thickness resection includes removal of all layers of the eye wall beneath the tumor, including the retina. A corneoscleral graft repairs the defect and a vitrectomy is

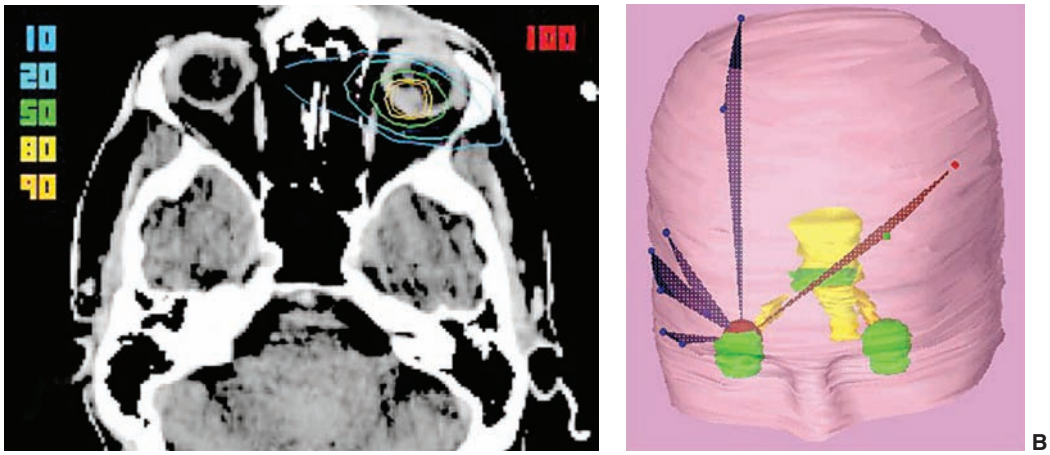

FIGURE 15.10 Linac-based stereotactic radiotherapy. **(A)** Computerized tomogram showing the isodose distribution in the treatment plan for a choroidal melanoma. **(B)** Three-dimensional graphic demonstrating a noncoplanar arc plan for stereotactic hypofractionated radiation therapy to achieve a total dose of 70 Gy. This form of radiotherapy is administered as 5 fractions on alternate days.

accomplished. Despite the most fastidious surgical technique, often employing hypotensive anesthesia, complications including vitreous and choroidal hemorrhage, retinal detachment, cataract formation, and residual tumor are frequently observed. The most compelling argument against eye-wall resection for treating ciliochoroidal melanoma, however, is the COMS enucleation experience, which reported local invasion of the sclera in 81.1% of eyes, suggesting the significant potential for viable melanoma cells to remain within the eye following treatment.

One matched case–control study compared transscleral resection to iodine brachytherapy for choroidal melanomas 6 mm or greater in thickness in 49 pairs of patients. The authors found similar rates of survival but their results favored transscleral resection for the preservation of 20/200 vision while avoiding some of the major complications of iodine brachytherapy, but the risk of local recurrence is increased with transscleral resection as compared to iodine brachytherapy.[19]

Internal Resection

Internal or endoresection of choroidal melanomas is a globe-saving technique first performed by Gholam Peyman in 1984 and described in 1986.[20] The technique involves the creation of an arcuate retinotomy or retinal flap during vitrectomy with, following diathermy and laser photocoagulation, resection of all visible tumor down to bare sclera under hypotensive anesthesia. The retina is then reposited during an air–fluid exchange and laser applied to the edges of the retinotomy and liberally to the resection bed in an effort to destroy any remaining viable melanoma cells. A scleral buckle is placed and the eye filled with silicone oil.[21] In one series of 32 patients followed for a mean of 40.1 months, 3 developed distant metastases and succumbed to their disease, only one of which was associated with a local recurrence, and 10 eyes (31.2%) had visual acuities ≥20/200.[21] This modality seems best suited to highly elevated posterior tumors, although the COMS findings of relatively common local invasion into the retina and sclera would suggest caution in the use of this technique.

Enucleation

For large tumors with extensive ocular involvement with intractable glaucoma, which are unresponsive to radiotherapy or demonstrate significant extrascleral extension or orbital invasion, enucleation is appropriate and remains the standard management option for some choroidal melanomas (Fig. 15.11).[22] The COMS evaluated the use of adjunctive preoperative external beam radiation prior to enucleation for patients with large choroidal melanoma and determined that there was no survival benefit following administration of 20 Gy prior to surgery. Nevertheless, surgical techniques to minimize globe manipulation seem valid. Wrapped implants and scleral shell/implant connections can result in highly effective cosmetic results.

Ciliary Body Melanoma

Ocular melanoma accounts for less than 0.5% of all human malignant neoplasms, and uveal melanoma is 1/10 as common as mucocutaneous melanoma. Melanomas of the ciliary body account for about 10% of all uveal melanomas. Since the human eye is devoid of lymphatics, the tumor spreads hematogenously or by local invasion.

Certain characteristics of the ciliary body in the human eye complicate the evaluation of this intraocular structure during routine ocular assessments. Since the ciliary body is situated posterior to the iris base, the anterior location of the ciliary body melanomas permit substantial growth to proceed hidden from both the patient and the clinician.[23]

Clinical Evaluation. Although a growing ciliary body melanoma can remain undetected by patient and clinician for years, certain features suggest their presence. Large tumors can be associated with dilated episcleral vasculature, bulging of the iris, sector cataract, lens deformation, and focal episcleral pigmentation. Such tumors can invade the anterior chamber or progress posteriorly to involve the peripheral choroid (ciliochoroidal). Transillumination may provide assistance in localization but the presence of retinal detachment and ciliary band shadows can confuse interpretation.

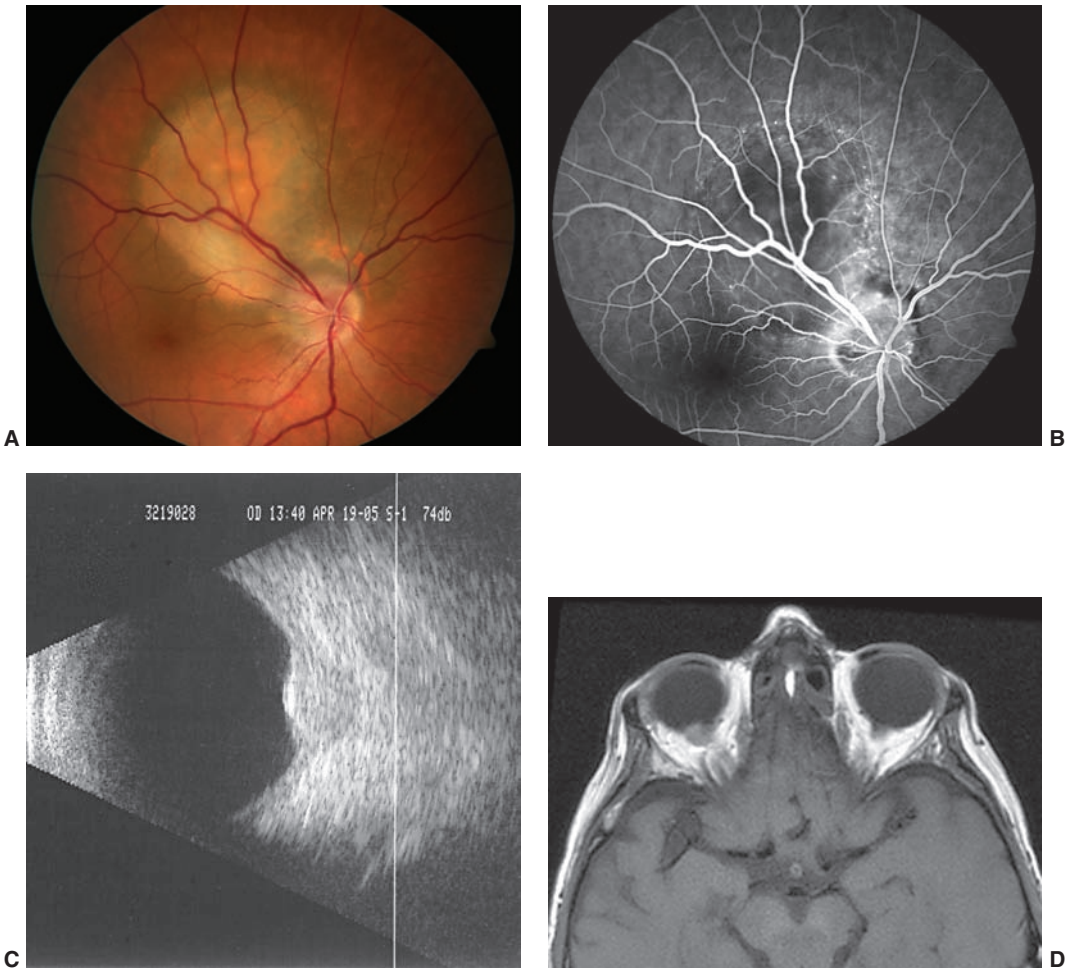

FIGURE 15.11 Juxtapapillary choroidal melanoma with extrascleral extension. **(A)** Clinical appearance of a juxtapapillary choroidal melanoma with retained foveal vision. **(B)** Fluorescein angiogram of the same tumor showing mottled fluorescence at the level of the choroid. **(C)** Ultrasonogram in B mode revealing a solid mass involving the choroid and extending through sclera posteriorly. **(D)** Magnetic resonance imaging, T1 weighted, demonstrating the tumor occupying the choroid with extension through the sclera. This patient required enucleation with an extensive tenonectomy.

Medium-sized ciliary body tumors can be defined by B-scan (stand-off) echography and are frequently dome shaped with low internal reflectivity. Tumor characteristics, including anterior and posterior margins, are more easily defined with ultrasound biomicroscopy (UBM), which can provide valuable information when considering biopsy, resection, or radiotherapeutic intervention (Fig. 15.12).[24] Small ciliary body melanomas are usually discovered incidentally following peripheral retinal examination for other disease. Tumors under 3.0 mm in thickness change very little over time and can be followed carefully with UBM (Fig. 15.13). The clock hour extent of these tumors should be noted with care to avoid overlooking early diffuse or ring tumor configuration, which, although rare, presents a more grave management issue and ultimate prognosis. The "ring" variety of ciliary body melanoma occurs with a frequency of about 3 cases per 1,000 uveal melanomas and is commonly overlooked if not considered as the underlying cause for unilateral glaucoma,

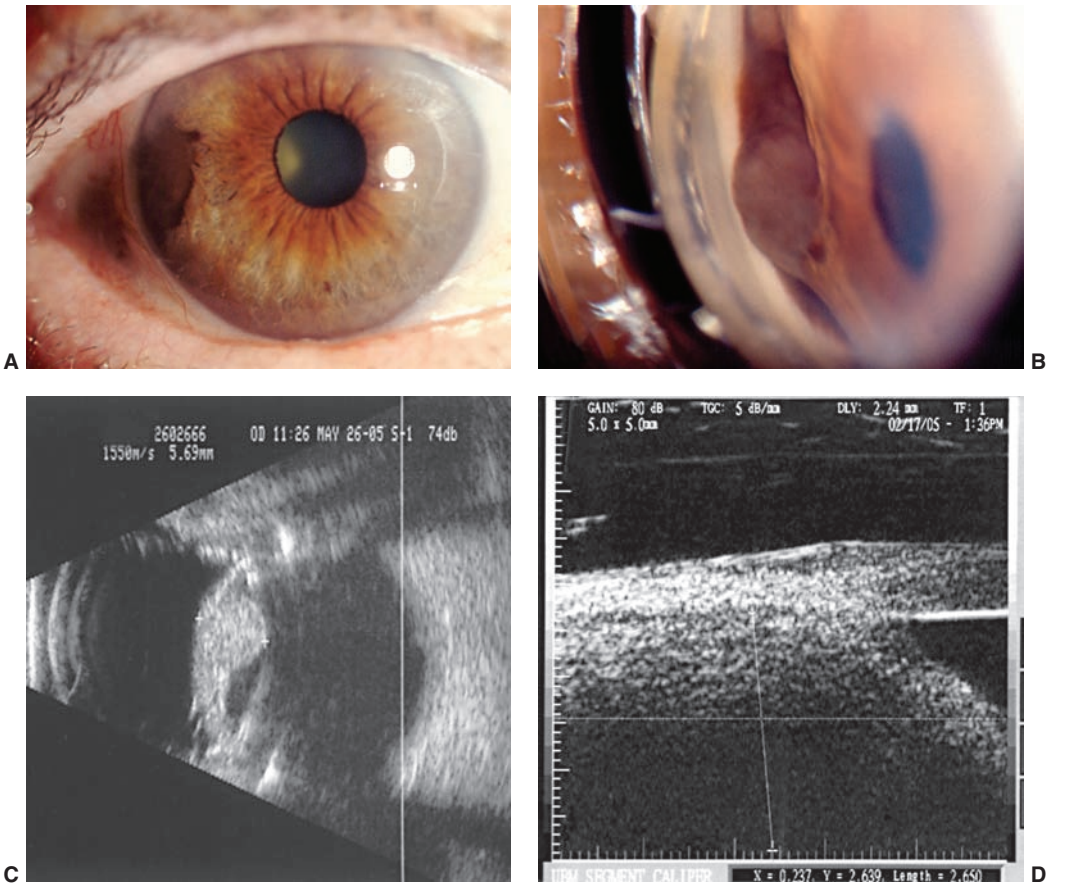

FIGURE 15.12 Ciliary body melanoma with extension into the anterior chamber. **(A)** Clinical appearance of anterior extension of ciliary body melanoma into the iris base. **(B)** Appearance of tumor involvement of angle structures. **(C)** Ultrasonogram in B mode (stand-off) to show main body of tumor occupying the ciliary body. **(D)** Ultrasound biomicroscopy showing anterior aspect of ciliary body melanoma involving the chamber angle.

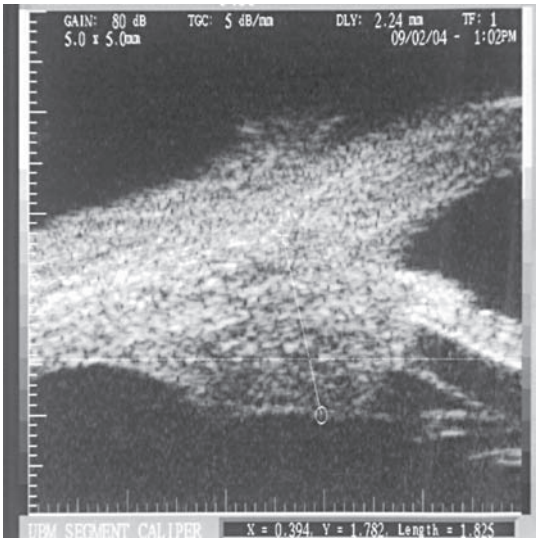

FIGURE 15.13 Small ciliary body melanoma. **(A)** Ultrasound biomicroscopy through the ciliary body showing a small melanoma or nevus occupying the ciliary body and involving the iris base.

refractory to treatment. Owing to the generally large size of ring melanomas at the time of diagnosis, the prognosis is poor and management is limited to enucleation.

Management of Ciliary Body Melanoma. Tumor size, extent of intraocular involvement, systemic health, and patient preference must be considered when managing patients with ciliary body melanoma. Fine needle aspiration biopsy has been helpful in difficult diagnostic situations,[25] but care in the interpretation of findings is essential. Although the majority of small tumors of the ciliary body demonstrate little or no growth over time, if growth should occur or if other ocular structures should become compromised, treatment is usually considered. Brachytherapy has been shown to achieve effective tumor control for medium-sized tumors with relatively well-preserved vision. Cataract formation, radiation vasculopathy, vitreous hemorrhage, and chronic keratitis are notable complications. Charged particle radiotherapy employing protons has demonstrated a similar treatment benefit in managing ciliary body melanoma, although neovascular glaucoma and lash loss are somewhat more prevalent as complicating factors. Large tumors of the ciliary body, including ring melanomas, usually require enucleation and, in some cases, exenteration if significant extrascleral or intraorbital invasion has developed.

Although local ciliary body tumor resection is achievable with small- and medium-sized tumors and has the advantage of providing histopathology, complications, including cataract formation, vitreous hemorrhage, retinal detachment, and visual distortion, can be hazardous. More compelling, however, is the concern that the resection margins may be incompletely excised despite the most fastidious surgical technique. The application of a radioactive plaque over the resection site may add an element of security in some cases, but a significant survival benefit has yet to be demonstrated following this adjunctive measure.

Iris Melanoma

Considered the most common primary iris malignancy, malignant melanoma involving the iris nevertheless comprises only 5% to 10% of all uveal melanomas. The disease is usually noted in later life, shows no sex predilection, and, if confined to the iris, is associated with a low disease-specific mortality, in the range of 4% to 8%. Metastasis is rare.

Iris melanomas have a variable pattern of presentation including solitary nodular, plaque-like, and diffuse varieties with different degrees of pigmentation and vascularity. Most iris pigment proliferations do not require intervention, but if accurate follow-up discloses a changing pattern of growth, increasing iris distortion, related intraocular pressure elevation, or involvement of intraocular structures, more definitive management is usually considered. Pigment dispersion or direct tumor invasion into the anterior chamber angle is thought to induce secondary glaucoma, and cataract formation usually develops in close association to the tumor. Other findings associated with iris melanomas including heterochromia, spontaneous hyphema, and uveitis have been reported with less frequency. UBM not only provides detailed imaging of iris tumor dimensions and characteristics but, as well, can define anterior and posterior tumor margins in relation to other ocular structures. Such information is essential to assess growth patterns and to provide information if intervention is to be considered (Fig. 15.14).

Management of Iris Melanoma. Although features such as tumor size, iris margin distortion, intrinsic tumor vascularity, and sector cataract formation may support a diagnosis of malignancy, documented growth with or without associated ocular morbidity usually determines the need for intervention. Sector iridectomy, occasionally combined with cataract removal, is an appropriate approach to therapy for tumors with no more than 2 to 3 clock hours of involvement. As well, brachytherapy, in most instances, employing I-125, has been employed in the treatment of certain iris melanomas and has provided satisfactory local tumor control with acceptable anterior segment preservation. The application of plaque radiotherapy employing a safety margin around the tumor would seem to gain a theoretic advantage in this form of intervention.

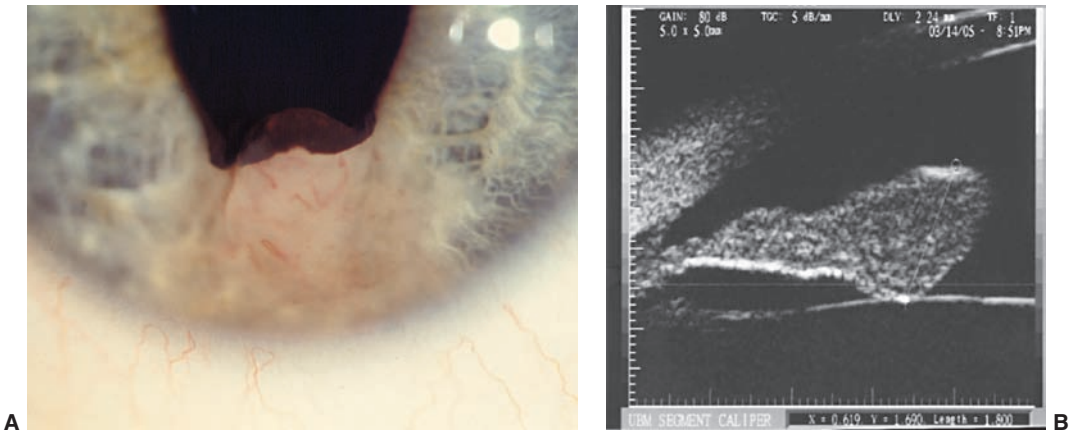

FIGURE 15.14: Clinical appearance of an iris melanoma that had shown progressive pupillary distortion over 2 years. **(A)** Pigmented vascularized mass involving the iris in the 6:00 position. **(B)** Ultrasound biomicroscopy of the same tumor occupying full-thickness iris with early angle involvement measuring 1.8 mm at its thickest point. This tumor underwent I-125 plaque radiotherapy, which achieved good local control.

Lesions extending into the ciliary body can be managed by iridocyclectomy or plaque radiotherapy.[26] Large or diffuse tumors of the iris with intractable glaucoma are often best managed with enucleation.[27]

Uveal Melanoma Prognostication. The COMS showed that large tumors treated by enucleation had similar survival rates with or without pre-enucleation radiotherapy. This large prospective randomized trial also demonstrated that medium-sized tumors had similar outcomes after enucleation or iodine-125 plaque radiotherapy.[5] Advances in primary tumor control have resulted in a shift to globe-preserving modalities, but despite such advances, the prognosis for survival remains unchanged. Until recently, clinical and histologic prognostic indicators were used to predict tumor-related survival. Tumor size, patient age, diffuse configuration, and cell type have been used to characterize tumor aggressiveness. Many other cytopathologic features including mitotic rate, nucleoli variability, vascular patterns, and periodic acid-Schiff staining of nucleolar DNA have been implicated to help determine the natural history of uveal melanoma.[28]

More recently, an evaluation of the tumor cytogenetics has revealed that aberrations of chromosomes 3, 6, and 8 are consistently found in patients with uveal melanoma.[29] Monosomy 3 is detected in about half of uveal melanomas and is highly predictive of metastasis.[30] Different chromosome 6 abnormalities are associated with either a higher or lower incidence of metastasis, and about 25% of uveal melanomas show a better prognosis if they contain a gain in 6p. An 8q gain in monosomy 3 melanomas carries a worse prognosis than monosomy 3 loss alone.[31] This preliminary analysis has provided a basis for more accurate techniques such as gene expression profiling (GEP), which has revealed evidence for the existence of two distinct classes of uveal melanoma.[32] Class 1 disease has a somewhat better prognosis than Class 2 disease. It is still uncertain if the origin of these two tumor types arises from unique cell lines or whether Class 1 tumors can in fact progress to Class 2. A certain level of discordancy between GEP predictions and survival, testing inconsistency, sampling error, cost, and ethics will guide the ultimate approach to the understanding of uveal melanoma tumorigenesis. Although there is not as yet an established successful treatment to alter the course of uveal melanoma, the predictive value of molecular testing will play a large part in establishing the surveillance patterns and potential for early systemic intervention.

TNM Classification of Uveal Melanoma. Cancer staging is pivotal to the battle on cancer, and one of the significant achievements of the COMS was to produce a system of tumor description which became the standard characterization for uveal melanoma used by more than 45 eye cancer centers throughout North America. Although the COMS tumor size categories have been utilized for more than a decade, recent evaluation of tumor metrics, gleaned from a tumor database of more than 7,000 uveal tumors, has redefined the most recent (7th edition) of tumor, node, metastasis (TNM) staging compiled through the collaboration between the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC). This system classifies the extent of disease based mostly on anatomic information regarding the extent of the primary tumor (T), regional lymph nodes (N), and distant metastases (M). For the present edition, T categories represent tumor size derived from a large collaborative database. The second criterion for T staging is the anatomic extent of the tumor as related to involvement of the ciliary body and extrascleral tissues. Ten-year survival rates for the four size categories (T1–4) were 90%, 78%, 58%, and 40%, respectively, among 7,585 uveal melanoma patients. The overall assessment of the tumor is based on accepted standards for a clinical ophthalmic examination, certain biometrics, which have been included by consensus, and a description of node involvement and/or the presence or absence of metastases. Stages 1 to 3 include uveal melanoma patients with no evidence of metastases and stage 4 uveal melanoma patients are those who harbor metastases. Ten-year survival rates for the seven stages 1, 2A and B, 3A to C and 4 were 88%, 80%, 68%, 45%, 26%, 21%, and 0%, respectively, among 5,470 uveal melanoma patients with data available for ciliary body and extrascleral tissue involvement in addition to tumor size.

Pathologic features and prognostic indicators have also been included in the recent edition of TNM classification and staging. Because of its importance in standardizing the evaluation of uveal melanoma, all publications related to uveal melanoma analysis are now required to employ this descriptive standard. Because of the ever-evolving changes in evidence to support the management of eye cancer, schemes such as the current TNM classification and staging of uveal melanoma will require timely validation in order that clinicians can manage eye cancer in an optimal fashion.

Conclusion

Over the last two decades, intraocular melanoma, with its variable presentation, has become easier to diagnose and is being defined with greater accuracy. Local tumor control is generally successful and can be achieved with various interventions. To increase long-term survival and improve life quality, however, there is a need to combine local management of this malignancy with measures to detect and treat micrometastatic disease. Direct and indirect approaches to activating antitumor immunity are being pursued in certain immunotherapeutic treatment models. Continuing genetic description relating to the normal and aberrant control of cellular growth and replication will improve our understanding of oncogenesis and will bear directly on our understanding of choroidal tumor production. Angiomanipulatory research aimed at inhibiting or modifying tumor-related angiogenesis coupled with the discovery of novel drug delivery systems continues to hold promise as a mechanism to modify both local and metastatic disease processes. Our continuing investment in the field of ocular oncology must be to encourage the appropriate scientific application of such novel approaches to the control of this and other malignancies.

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16 Optic Neuritis

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I. OVERVIEW

The treatment of optic neuritis has been explored in several randomized clinical trials (RCTs).[1–20] In the Optic Neuritis Treatment Trial (ONTT),[1–10] the largest trial to date, high-dose intravenous methylprednisolone (IV MP) treatment accelerated visual recovery but had no impact on final visual outcome. Three smaller RCTs of optic neuritis[11–13] found similar results. Two RCTs of intravenous immunoglobulin (IVIG), one in acute optic neuritis[14] and the other in chronic residual optic neuropathy following optic neuritis,[15] failed to demonstrate any treatment benefit. A study of IVIGs in corticosteroid (CS)-refractory optic neuritis demonstrated a beneficial effect on visual outcome.[16] The ONTT also found that high-dose IV MP treatment temporarily retarded the development of clinically definite multiple sclerosis (CDMS).[2,3,4,10] Four RCTs of interferon beta 1a,[17,18] interferon beta 1b,[19] and glatiramer acetate[20] in the treatment of acute optic neuritis and other "clinically isolated" neurologic syndromes that predict MS found that this treatment significantly reduced the development of CDMS and the accumulation of magnetic resonance imaging (MRI) abnormalities typical of MS.

The major findings of these trials are as follows: (1) neither CS nor IVIG treatment appears to have a meaningful effect on visual outcome and CS treatment has no long-term impact on neurologic outcome; (2) continuous interferon beta 1a, beta 1b, and glatiramer acetate treatment of acute optic neuritis reduces the development of new MS-like neurologic manifestations and accumulation of MS-like MRI abnormalities, but there is no evidence that it reduces long-term neurologic disability; and (3) acute optic neuritis, even if untreated, has a relatively benign neurologic course as compared to other clinically isolated neurologic syndromes (spinal cord and brain stem lesions causing weakness, diplopia, and ataxia).

II. IMPACT OF CORTICOSTEROID OR INTRAVENOUS IMMUNOGLOBULIN TREATMENT ON VISUAL OUTCOME IN OPTIC NEURITIS

The treatment of acute optic neuritis with oral, IV, and retrobulbar CS was common before the first publication of the ONTT in 1992,[1] based largely on anecdotal and small trial evidence.[1]

The ONTT was the first large RCT to study the effect of IV MP and low-dose oral prednisone (OP) on acute optic neuritis. In the ONTT, 457 patients with acute optic neuritis were randomized to three groups: (1) IV MP 250 mg four times a day for 3 days, followed by OP 1 mg/kg for 11 days; (2) OP 1 mg/kg for 14 days; or (3) placebo. Acute optic neuritis was defined as a monocular visual deficit of no more than 8 days' duration with an ipsilateral afferent pupillary defect in a patient aged between 18 and 46 years. Patients were entered into the trial only if they had had no previous episodes of optic neuritis in that eye, no previous CS treatment for MS, and no other systemic condition associated with optic neuritis apart from MS.

The ONTT end points were visual acuity, visual fields (Humphrey and Goldmann),

color vision (Farnsworth-Munsell 100-hue), contrast sensitivity (Pelli-Robson chart), and other neurologic deficits as assessed by a neurologist. All patients underwent brain MRI and blood tests for antinuclear antibody and treponemal antigen, and a chest x-ray directed at sarcoidosis. Lumbar puncture was optional and less than half the cohort underwent it. The examining neurologists were masked to treatment but the patients who received IV MP knew that they had received it.

Neither CS regimen produced any benefit on visual outcome. Visual function improved more rapidly in the IV MP group, but the difference was relatively trivial. These findings held up in the follow-up evaluations up to 15 years after study entry. Patients who had been treated with OP without a preceding regimen of IV MP had a *doubling of the recurrence rate of optic neuritis in the affected and the contralateral eye*. The IV MP group had a reduction in the development of CDMS after 2 years, but that effect had evaporated by 3 years after study entry.

The implications for clinical practice derived from the ONTT are that the IV MP regimen, chosen because it was common in the treatment of organ transplant rejection, had no impact on visual recovery and only a temporary effect on conversion to MS. OP had no impact on visual recovery and doubled the recurrence rate of optic neuritis in the same or contralateral eye.

Similarly defined cohorts of 66 optic neuritis patients in an English RCT[11] and a Japanese RCT[12] also found no benefit on visual recovery of an IV MP regimen similar to that of the ONTT. A Danish RCT[13] of 60 patients found that oral MP 500 mg/day for 3 days with a 10-day taper had exactly the same impact on visual recovery as did the ONTT IV MP regimen.

Like IV MP, IVIG appears to have no meaningful impact on visual recovery in optic neuritis. In a Danish RCT[14] of 68 patients with acute optic neuritis, five infusions of IVIG 0.4 g/kg body weight administered on days 0, 1, 2, 30, and 60 after symptom onset produced no benefit in standard measures of visual function at 6 months. An IVIG RCT from the Mayo Clinic,[15] using a similar regimen, showed that there was no meaningful impact on visual function in 55 patients with persistent visual dysfunction from optic neuritis in MS. In an IVIG nonrandomized open label prospective study conducted at a Detroit medical center,[16] 23 patients with optic neuritis refractory to CS treatment (defined as visual acuity ≤20/400 at 60–90 days after onset of neuritis) received IVIG 0.4 g/kg body weight on days 0 to 5 followed by once-monthly infusion for 5 months. There was significant improvement in the VA of the IVIG group, with 78% reaching visual acuity of 20/30 or better with only 12.5% of the control group responding similarly.

III. IMPACT OF BETA INTERFERON ON THE CONVERSION OF OPTIC NEURITIS TO MULTIPLE SCLEROSIS

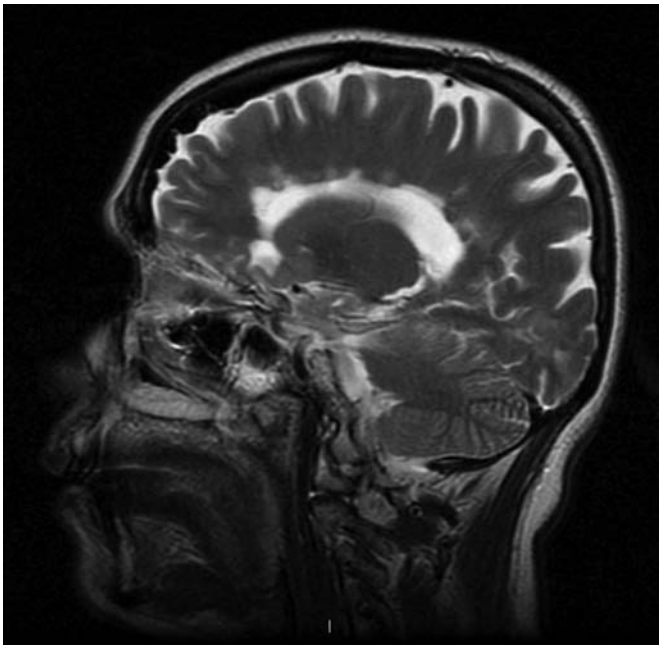
Multiple trials of patients with relapsing-remitting multiple sclerosis (RRMS) have established that chronic beta interferon 1a (Avonex, Biogen Idec; Rebif, EMD Serono) and 1b (Extavia, Novartis Pharmaceutical Corp; Betaferon, Schering) or glatiramer acetate (Copaxone, Teva Pharmaceutical) treatment reduces the clinical relapse rate and reduces the accumulation of MRI signal abnormalities over a 2- to 3-year period.[21] Because these agents also experimentally attenuate the immune process involved in MS, they have been called "immune-modulating agents" (IMAs).

It was logical, then, to explore whether chronic treatment with any of the IMAs, begun shortly after onset of acute optic neuritis, brain stem, or spinal cord manifestations (called "clinically isolated syndromes") and brain MRI abnormalities typical of MS, would reduce the conversion to CDMS and the accumulation of MRI abnormalities.

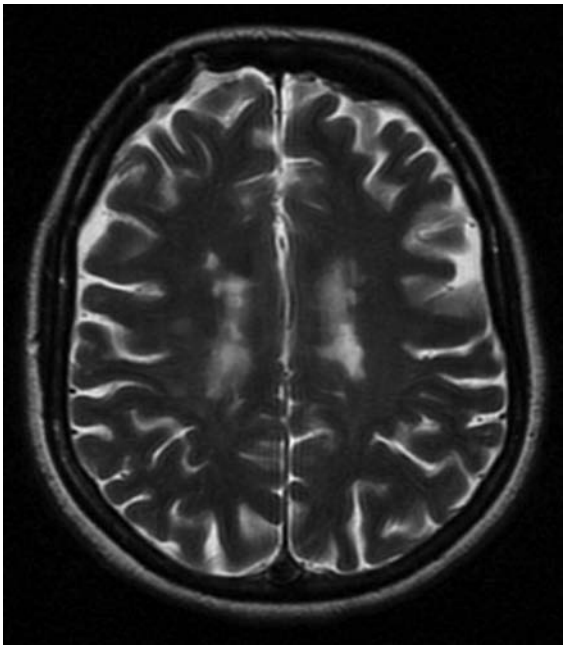
Two beta interferon 1a trials, one conducted in the United States with Avonex (Controlled High Risk Avonex Multiple Sclerosis Study = CHAMPS group),[17] the other in Europe with Rebif (Early Treatment of Multiple Sclerosis = ETOMS trial),[18] a beta interferon 1b trial conducted in Europe with Betaferon

(Betaferon/Betaseron in Newly Emerging MS for Initial Treatment = BENEFIT),[19] and a multinational study with glatiramer acetate (PreCISe)[20] included patients who had at least two MRI signal abnormalities typical of MS (the ONTT had shown that such abnormalities would predict a high likelihood of later development of CDMS) (Fig. 16.1).

There are many clinical trials designed to determine whether initiation of interferon

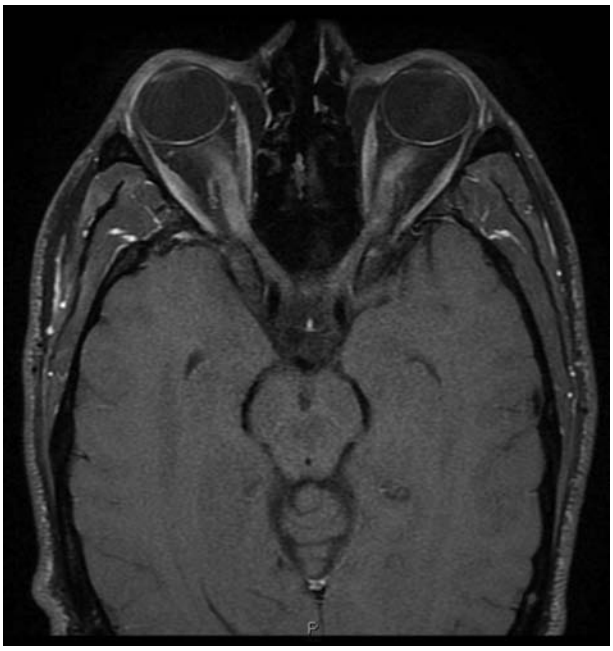


A



B

FIGURE 16.1 Magnetic resonance imaging (MRI). **(A)** Sagittal T2-weighted images. **(B)** Axial T2-weighted images. This shows multiple focal high-signal abnormalities characteristic of multiple sclerosis (MS). Such abnormalities, which are found in approximately 50% of patients with typical acute optic neuritis even if they have no history or physical evidence of other neurologic deficits, markedly increase the likelihood that a patient with optic neuritis will later develop clinically definite MS ("high-risk MRI"). **(C)** Axial T1-weighted MRI with contrast showing bilateral Optic Nerve (ON) enhancement due to bilateral optic neuritis.



C

FIGURE 16.1 (continued)

at the time of a first clinical demyelination event is of value. The design of most of these studies is similar and we will therefore elaborate on the CHAMPS trial which was one of the seminal studies.[17] In the CHAMPS trial, 393 patients who had a first isolated, well-defined neurologic event consistent with demyelination and involving the optic nerve (unilateral optic neuritis), spinal cord (incomplete transverse myelitis), or brain stem or cerebellum (brain stem or cerebellar syndrome) were enrolled to the study. Patients had to have two or more clinically silent lesions of the brain on MRI characteristic of MS. Patients were randomized to two groups: (1) IV MP 1g/day for 3 days followed by OP 1 mg/kg for 11 days and 30 μg of interferon beta 1a (Avonex, Biogen) by intramuscular (IM) injection once a week; (2) IV MP 1 g/day for 3 days followed by OP 1 mg/kg for 11 days and matching placebo by IM injection once a week. The CHAMPS trial end points were development of clinically definite MS and findings on MRI of the brain (number of new and enlarging lesions, volume of lesions on T2-weighted MRI, and number of gadolinium-enhancing lesions on T1-enhanced MRI scans). All patients underwent neurologic examination at the end of the first month, at month 6, and every 6 months thereafter. Additional examinations were performed within 7 days after the patient reported new visual or neurologic event. Patients in whom clinically definite MS developed discontinued treatment and were withdrawn from the study. Findings on MRI served as a secondary end point. A screening MRI of the brain was performed to determine the patients' eligibility and then at 6, 12, and 18 months in patients who were still in the study at these times. Avonex was found to reduce the 3-year conversion to MS from 50% to 35% as well as the accumulation of MRI signal abnormalities. The effect of treatment was similar among subgroups classified according to the type of the initial event and the number of lesions on T2-weighted MRI scan at screening. Because approved treatments for MS were available, it was not ethical to keep patients in their assigned groups once clinically definite MS was diagnosed. Thus, the trial design could

not provide any direct data on the long-term effects of interferon beta 1a on the rate of exacerbation or the progression of disability.

The ETOMS trial[18] of 309 patients found a 2-year reduction in the conversion to MS from 45% to 34% in patients treated with Rebif. The BENEFIT trial[19] of 487 patients found a 2-year reduction in conversion to MS from 45% to 28% in patients treated with Betaferon corresponding to an absolute risk reduction of 17%. Patient-reported physical health and health-related quality of life remained essentially unchanged over time, with no difference between the interferon and the placebo groups. The PreCISe multinational study[20] of 481 patients found a 2-year conversion rate reduction from 42.9% to 24.7% in patients treated with glatiramer acetate.

Although the RRMS trials: the CHAMPS, ETOMS, BENEFIT, and PreCISe studies have clearly shown a reduction in neurologic relapses and MRI accumulation, the effect is not striking. More importantly, no RCT has been carried out long enough to determine whether any of the IMAs has a beneficial effect on long-term neurologic disability. Many investigators have postulated that there should be such a benefit because a rapid early relapse rate[22] and an early accumulation of MRI signal abnormalities[23] have been associated with a higher long-term disability rate. Another basis for this presumption is that axonal loss, which occurs within inflammatory MS plaques,[24] is believed to be associated with long-term disability.[25] If IMAs can suppress inflammation, the argument goes that they should reduce axonal loss.[25] However, a massive retrospective study[26] did not support this postulate. Data were collected in British Columbia between 1985 and 2008 from 868 patients who were treated with interferon beta. They were compared to an untreated contemporary cohort of 829 patients and historical (preinterferon era) cohorts of 959 patients. Follow-up was 5 years for the interferon group and 4 and 10 years for the untreated contemporary and historical groups, respectively. The main outcome measure was time from interferon treatment eligibility (baseline) to a confirmed and sustained EDSS (Expanded Disability Status Scale; Table 16.1) score of 6. The observed outcome rates for reaching the score of 6 were 10.8%, 5.3%, and 23.1% in the three cohorts, respectively. These differences were not statistically significant and study conclusions were that among patients with RRMS, administration of interferon beta was not associated with a reduction in progression of disability.

The implications of these facts on the management of acute optic neuritis are still unclear.[27] Some commentators have stated that therapy with beta interferon 1a should be recommended to all patients with acute optic neuritis who have an MRI scan showing signal abnormalities typical of MS, even when there is no history or current physical finding suggestive of MS. Extrapolating from the equivalently beneficial effects on RRMS of beta interferon 1b and glatiramer acetate, other observers have suggested that physicians should not limit the recommendation to beta interferon 1a, but consider treating with *any of the IMAs*. A less aggressive position is to wait to see if the disease is active, as determined by a brief interlude to relapse or rapid accumulation of MRI signal abnormalities.[27] This latter position is based on the robust evidence that the natural history of untreated optic neuritis is much better than that of clinically isolated acute brain stem or spinal cord manifestations (see Section IV).

In the past two decades, there has been an expansion in therapeutic options for RRMS. The widespread practice is to start one of the interferons or glatiramer acetate in newly diagnosed patients. New drugs such as oral fingolimod, BG-12, teriflunomide, and natalizumab are being considered as first-line or second-line agents for patients with very active or refractory disease.[28,29]

IV. THE NATURAL HISTORY OF OPTIC NEURITIS

The greatest contribution of the ONTT has been to verify the relatively "benign" long-term visual and neurologic outcome in patients with acute optic neuritis. In the ONTT, visual function remained remarkably stable after the 1-year measurement. At 15 years after study entry, 72% of eyes affected with optic neuritis

TABLE 16.1 EDSS (Expanded Disability Status Scale)

A method of quantifying disability in multiple sclerosis and monitoring changes over time.

Steps 1.0 to 4.5: People with MS who are able to walk without any aid and based on measures of impairment in eight FSs: pyramidal, cerebellar, brain stem, sensory, bowel/bladder, visual function, cerebral (mental) functions, other

Score	Description
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal in two FSs
3.0	Moderate disability in one FS, mild in three to four FSs, no walking impairment
3.5	Moderate disability in one FS and more than minimal in several others, no walking impairment
4.0	Significant disability but self-sufficient, able to walk without aid or rest for 500 m
4.5	Significant disability, able to walk full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 330 m
5.0	Disability severe enough to impair full daily activities and ability to work a full day. Able to walk without aid/rest for 200 m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid/rest for 100 m
6.0	Requires walking aid to walk about 100 m
6.5	Requires two walking aids to walk about 20 m
7.0	Wheelchair, though wheels self in standard wheelchair and transfers alone. Unable to make more than few steps
7.5	Transferring but cannot carry in standard wheelchair for a full day and may require a motorized wheelchair
8.0	Restricted to bed or chair and pushed in a wheelchair. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of the day, has some effective use of arms
9.0	Confined to bed; can communicate and eat
9.5	Confined to bed, totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

FS, functional system; MS, multiple sclerosis.

had a visual acuity of ≥20/20. Of the 294 participants who completed the 15-year examination, 66% had a visual acuity of ≥20/20 in both eyes. More than 99% of patients would have been eligible for a driving license. After the initial period of recovery from the optic neuritis, visual acuity remained stable in most patients over 15 years. Patients who develop MS are more likely than those who do not develop MS to exhibit abnormal findings on tests of visual function. However, even in those with MS, vision is normal about 60% of the time. Recurrent optic neuritis occurred in either eye (with equal frequency in initially affected and unaffected eyes) in 35% of patients, but visual loss was not greatly diminished by recurrent episodes of optic neuritis. These results are comparable to other large series that had less rigorous monitoring than the ONTT.[30,31]

At 15 years, only 50% of ONTT patients had developed CDMS.[10] The risk was strongly related to the presence of lesions on baseline MRI. The probability was 25% for patients with no lesions and 72% for patients with one or more lesions. There was no appreciable difference in the risk of developing MS among the three original ONTT treatment groups. The risk of developing MS was highest in the first 5 years and then decreased. Among patients without MS at the 10-year examination, the probability of developing MS by the 15-year examination was 32% when one or more baseline lesions were present versus 2% when no lesions were present. Among the 113 patients with MS for whom an EDSS score was available at the 15-year examination, 66% had a score of less than 3 and only 13% had a score of 6 or higher and were nonambulatory. EDSS scores were similar at the 10-year and 15-year follow-up visits. Because most patients who developed MS were treated with IMA therapies, the study could not determine the degree of disability that occurs without treatment.

A large natural history study conducted in France[32] showed that lower long-term disability was associated with complete recovery from the initial episode, a long latency until a relapse occurred, and with few relapses within the first 5 years.

MS initiated by optic neuritis appears to have a relatively favorable prognosis relative to MS initiated by other clinically isolated syndromes (spinal or brain stem). A long-term Swedish study found that clinically isolated syndromes of brain stem or spinal cord dysfunction have a threefold greater rate of severe disability than does optic neuritis.[33] Thus, typical optic neuritis—even with MS-like lesions on MRI—does not always lead to CDMS; if it does, the disability is relatively mild. Previous observers had suspected this and called optic neuritis–initiated MS "benign MS."

The ONTT has also confirmed that brain MRI is the best predictor of whether CDMS is likely to follow optic neuritis.[4] A single ≥2 mm diameter high T2 MRI signal abnormality was enough to increase the 15-year risk of developing CDMS from 25% to 72%.[10] In the ONTT, the number of MRI signal abnormalities (MRI "lesion load") was not correlated with long-term neurologic disability.[6] But in other studies, long-term neurologic disability has been correlated with MRI lesion load,[23] infratentorial lesions,[34] early accumulation of MRI signal abnormalities,[23] and early development of brain stem and spinal cord manifestations.[33]

In the ONTT, blood tests directed at connective tissue disease and syphilis, and a chest x-ray directed at sarcoidosis, were unrevealing.[1] MRI disclosed a pertinent abnormality other than MS (a pituitary tumor) in only 1 of 457 studies. Lumbar puncture disclosed signs of autoimmune inflammation in some cases, but these signs had relatively little predictive value compared to MRI in terms of whether the patient would later develop CDMS.

V. CONCLUSIONS

The major clinical trials in acute optic neuritis have provided the following information:

1. *Impact of CS Treatment*. A single standard IV MP/CS regimen (MP 1 g/day for 3 days, OP for 11 days) mildly accelerates visual recovery in acute optic neuritis but does not affect final visual outcome. Low-dose OP (1 mg/kg) without preceding IV MP is harmful in that it significantly increases the recurrence rate of optic neuritis. High-dose OP (oral MP 500 mg/day for 3 days with a 10-day taper) probably accelerates visual recovery to the same degree as the standard IV MP/CS regimen. One-time administration of CS has no long-term benefit on the rate of conversion to CDMS. Whether periodic retreatment with a CS regimen would be beneficial is yet unknown.

2. *Impact of Immunomodulatory Treatment*. Continuous beta interferon 1a (Avonex, Rebif), beta interferon 1b (Betaferon, Extavia), or glatiramer acetate (Copaxone) treatment reduces the conversion to CDMS and the accumulation of MRI signal abnormalities in patients with optic neuritis and other clinically isolated syndromes accompanied by at least two typical MRI signal abnormalities at outset. However, *there is no evidence that this*

prophylactic treatment has any effect on the long-term neurologic disability of MS.

3. *Visual and Other Neurologic Outcomes in Optic Neuritis*. The 15-year visual and neurologic outcomes in patients with acute optic neuritis without a prior diagnosis of MS are relatively favorable. Even among those patients who are not treated with IMAs, fewer than 5% will become visually or neurologically disabled. Only 1/2 of patients will even receive the diagnosis of CDMS 15 years after the initial bout of optic neuritis; most will have minimal disability and an EDSS score of less than 3. MRI scan is the most powerful ancillary study to predict the likelihood of developing CDMS. IMA treatment can be most reasonably justified in patients with optic neuritis who develop brain stem or spinal cord manifestations within a short interval after developing optic neuritis, or perhaps in those with an initially high MRI "lesion load" or rapid accumulation of MRI signal abnormalities. These considerations have prompted the notion that patients with isolated optic neuritis and normal MRI scans undergo repeat MRI scanning within a 3- or 6-month interval to determine if pertinent signal abnormalities have appeared.

Current Practices

On the basis of the mentioned trials, treatment guides regarding the use of CSs have been published by the American Academy of Neurology,[35] and numerous reviews have discussed the optimal management of patients with isolated optic neuritis in both the ophthalmology and neurology literature. Several surveys among neurologists and ophthalmologists were conducted in the United States,[36] Canada,[36,37] Australia,[36,38] New Zealand,[36,38] Thailand,[36] Denmark,[36] and France[36] and were published in 2008. The results of these surveys indicated that more than 90% of practitioners were familiar with the ONTT, recognized its importance, accepted its findings, and offered a standard regimen of IV MP followed by OP to patients with typical acute optic neuritis. Respondents often recommended steroids for the wrong reasons: more neurologists than ophthalmologists recommended steroid treatment to improve visual outcome, while more ophthalmologists than neurologists recommended steroid treatment to reduce the long-term risk of MS. Despite the findings of the ONTT that low-dose OP doubles the frequency of recurrent optic neuritis, between 14% and 60% of practitioners were still using low-dose oral CSs.

The use of IMAs after an attack of acute isolated optic neuritis is still subjected to debate from the standpoint of clinical efficacy and cost-effectiveness. Treatment with IMA after acute isolated optic neuritis is variably underwritten by the government depending on the country. Most ophthalmologists and neurologists indicated that they do not recommend IMAs to patients with acute optic neuritis who have a normal baseline MRI, but believe that IMAs are indicated for patients with acute optic neuritis and an abnormal MRI. Not surprisingly, more ophthalmologists than neurologists are unfamiliar with the neurology-led ETOMS, CHAMPS, BENEFIT, and PreCISe studies. Conversely, more neurologists are unfamiliar with the main findings of the ONTT, an ophthalmology-led trial.

Notwithstanding these facts, the following guidelines are generally accepted as reasonable:

1. Exclude "atypical" optic neuritis associated with underlying infectious or noninfectious inflammatory disorders like syphilis, herpes zoster, Wegener's granulomatosis, sarcoidosis, cat scratch disease, idiopathic pachymeningitis, and neuromyelitis optica (NMO), which must be managed according to the underlying diagnosis. Use history, physical findings, and ancillary studies to determine this.

Typical optic neuritis must be differentiated from NMO, an autoimmune disease involving the optic nerve and spinal cord. In NMO, antibodies directed at the aquaporin 4 moiety, which governs a water channel on the cell membrane of astrocytes, trigger a humoral immune response that weakens the blood–brain barrier. There are several clinical

differences between optic neuritis associated with MS and NMO. Optic nerve involvement can be bilateral with poor recovery in NMO as opposed to MS in which optic neuritis is usually unilateral with very good recovery. MRI of the brain is usually normal in NMO and does not exhibit the white matter lesions of MS. Spinal cord MRI in NMO demonstrates longitudinally extensive lesions across more than three vertebral body lengths. In acute attacks of optic neuritis in NMO, cerebrospinal fluid counts can be very high with neutrophil predominance and high protein. Unique cerebrospinal fluid oligoclonal bands detected in 85% of MS patients are present in only 20% to 30% of NMO cases. Acute attacks of NMO are treated with IV MP. But patients who do not show improvement may benefit from plasma exchange. Prophylactic immune therapy may be indicated for NMO-seropositive patients and relapsing disease. The IMAs are not only ineffective in treating NMO; there is evidence that interferons may aggravate the disease. Instead, uncontrolled trials suggest that B-cell depletors such as azathioprine, mycophenolate, and rituximab seem to improve on the natural history of the disease.

2. If the diagnosis is "typical optic neuritis" (no underlying disorder except perhaps MS), consider performing a brain MRI largely to determine whether there is ample imaging evidence of subclinical demyelinization ("high-risk MRI"). If the MRI is normal, consider ordering NMO antibody and performing lumbar puncture.

3. To patients with a high-risk MRI, offer IV MP 1 g/day for 3 days followed by OP 1 mg/kg for 11 days, explaining that there is only a short-term benefit. To patients without high-risk MRI, explain that there is no evidence for any benefit of this treatment, besides shortening the duration of visual loss.

4. In patients with high-risk MRI, discuss the option of starting IMAs. The benefit of such treatment lies in slightly reducing the accumulation of MRI signal abnormalities and the development of MS-like relapses. There is no evidence that this treatment reduces long-term disability.

Principal Optic Neuritis Treatment Trial Findings

1. CS treatment of typical acute optic neuritis had no long-term benefits. It slightly hastened visual recovery. In patients with high-risk MRI scans (multiple high-signal abnormalities typical of MS), the 2-year conversion to MS was reduced by 50%, but by 3 years after trial entry, the conversion to MS was equal in CS-treated and placebo-treated patients. Treatment with OP without a preceding regimen of IV MP was harmful in that it doubled the recurrence rate of optic neuritis.

2. Brain MRI was by far the best predictor of whether a patient with optic neuritis would develop clinically definite MS. That is, a single cerebral high-signal abnormality measuring at least 2 mm in diameter raised the 15-year risk of MS from 25% to 72%.

3. The long-term visual outcome after optic neuritis was favorable. At 15 years after study entry, 69% of patients had 20/20 or better visual acuity in the affected eyes, as many as 86% had 20/20 or better visual acuity in one eye. Over 15 years, optic neuritis recurred in 35% of patients, but these recurrences did not substantially lower long-term visual function.

4. The long-term nonvisual neurologic outcome after optic neuritis was favorable compared to that of patients whose initial demyelinating event involves the brain stem or spinal cord. After 15 years, 50% of patients had developed clinically definite MS. Among patients whose entry MRIs were high risk, only 72% had developed clinically definite MS. Among the patients who developed MS, only 14% had severe neurologic disability (nonambulatory status).

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17 Thyroid-Associated Orbitopathy: An Evidence-Based Approach to Diagnosis and Management

Harmeet S. Gill MD, FRCSC

I. MANAGEMENT OF GRAVES' DISEASE

Overview

Graves' disease (GD) is a systemic, organ-specific, autoimmune condition that primarily affects the thyroid gland, pretibial skin, and the orbit. The endocrinologic manifestations should be distinguished from the ophthalmologic manifestations. Although they tend to be closely associated and typically present within months of one another, each appear to run an independent clinical course. In this chapter, the endocrinologic manifestations are referred to as dysthyroidism and the ophthalmologic manifestations as thyroid-associated orbitopathy (TAO). About 30% to 50% of GD patients will demonstrate signs of TAO during their course of disease.

Demographics

GD is typically diagnosed between the third to fifth decades of life, with a possible second peak incidence during the seventh decade of life. Women are four to eight times more likely than men to be affected.[1,2] The incidence of TAO is 14 per 100,000 in adults,[3] 0.1 per 100,000 in prepubescent children, and 3.0 per 100,000 in postpubescent children.[4] There is no known pattern of inheritance, but a genetic predisposition to autoimmune disease triggered by environmental factors is likely.[5] The most significant environmental factor is cigarette smoking. Genes such as *CTLA4*, *TNF*, *CD40*, *PTPN22*, and *ICAM1* may contribute to disease susceptibility.[6,7]

Thyroid Physiology

The thyroid gland produces hormones including thyroxine (T4) and triiodothyronine (T3), which help regulate body temperature, energy levels, sleep, appetite, metabolic rate, and many other bodily functions. The pituitary gland produces thyrotropin, also called thyroid-stimulating hormone (TSH), when serum concentrations of T4 and T3 are low and decreases TSH production when levels are high. The thyroid gland has receptors for TSH (TSH-R) and produces T4 and T3 in response to serum TSH concentration.

Graves' Pathophysiology

Thyroid gland follicular cells and orbital fibroblasts share a common antigen, the TSH-R.[8–10] Autoantibodies known as thyroid-stimulating immunoglobulins (TSI) or thyrotropin receptor antibodies bind TSH-Rs. "Activating" antibodies are more prevalent and result in T4 and T3 overproduction (hyperthyroidism), while "blocking" antibodies found in up to 15% of subjects can result in hypothyroidism. Some patients will develop goiter or thyroid gland enlargement. TAO occurs because an immune response, consisting of both humoral and cell-mediated pathways, is triggered. Autoreactive T-lymphocytes target orbital fibroblasts and then antigen-presenting cells, including B-lymphocytes, release cytokines and chemokines that activate cell-surface receptors like CD-40. This results in overproduction of hyaluronan, a glycosaminoglycan (GAG) secreted by the connective tissue network

surrounding extraocular muscles.[11] The hydrophilic GAGs cause edematous expansion of eye muscles and other orbital tissues. Some orbital fibroblasts and muscle cells will differentiate into adipocytes (adipogenesis), further increasing the orbital volume.[12] A heterogeneous population of orbital fibroblasts among patients may provide the basis for variability in clinical activity. In addition to their function as antigen-presenting cells, B-cells are also precursors to antibody-producing plasma cells.

Histological findings of TAO include fibroblast proliferation, lymphocyte and plasma cell infiltration, GAG accumulation, edema, and fibrosis.[13,14] The most common immune cells that infiltrate orbital tissue are T-lymphocytes, B-lymphocytes, and mast cells.[14] A second orbital antigen implicated in TAO is insulin-like growth factor 1 receptor (IGF-I-R).[15] Autoantibodies against IGF-I-Rs may be responsible for the chemokine release that triggers an orbit-specific homing signal to the rest of the immune system.[16] Bone marrow–derived fibrocytes are fibroblast-like cells detectable in orbital tissue of patients with GD that recruit various inflammatory mediators.[17] They are absent in healthy subjects. Some in vitro studies suggest that oxidative stress and high concentrations of oxygen-free radicals are also involved in TAO pathogenesis.[18,19] The underlying molecular and immune pathways that eventually lead to spontaneous resolution of disease remain unknown.

Clinical Features of Systemic Disease

Symptoms from GD can present suddenly or progress over longer periods of time delaying diagnosis. Dysthyroidism most commonly manifests as hyperthyroidism (90% or greater), but some patients will be euthyroid or hypothyroid or have Hashimoto's thyroiditis.[3] Signs and symptoms of hyperthyroidism are summarized in Table 17.1. Pretibial myxedema presents as a nonpainful erythematous and indurated dermatopathy over the shins.

TABLE 17.1 Clinical features of hyperthyroidism

Tachycardia
Palpitations
Anxiety
Tremulousness
Thyroid gland enlargement
Sensitivity to heat, diaphoresis
Hair thinning or loss
Weight loss with increased appetite
Diarrhea
Insomnia
Difficulty concentrating
Fatigue and muscle weakness
Brittle nails
Menstrual irregularity in women
Breast enlargement in men
Thyroid storm *(rare but fatal)*

Clinical Features of Thyroid-Associated Orbitopathy

Orbital inflammation and fibrosis can cause significant disfigurement of the eye, vision loss, and decreased quality of life. Most patients (90%) will demonstrate upper eyelid retraction, many (70%) will demonstrate periorbital edema, some (30%) will demonstrate restrictive strabismus and diplopia, and few (5% or less) will suffer decreased visual function from compressive optic neuropathy.[2,3] The common manifestations of TAO are summarized in Table 17.2. Bilateral symmetrical or asymmetrical disease can occur (see Figs. 17.1, 17.2 and 17.3A). Upper eyelid retraction is initially caused by beta-adrenergic stimulation from thyrotoxicosis but persists because of inflammation and scarring of the levator palpebrae superioris muscle. Inflammation of the conjunctiva, extraocular muscles, and orbital fat results in chemosis, diplopia, and exophthalmos, respectively. Exophthalmos exacerbates upper and lower eyelid retraction. Upper eyelid lag on downgaze, lagophthalmos, and exposure keratopathy are common findings. Enlargement of multiple extraocular muscles with relative

TABLE 17.2 Manifestations of thyroid-associated orbitopathy

Anterior segment
Exposure keratopathy
Conjunctival hyperemia
Chemosis
Elevated intraocular pressure
Posterior segment
Optic disc edema or pallor (rare)
Eyelids
Upper eyelid retraction (most common)
Lower eyelid retraction
Eyelid lag on downgaze
Eyelid edema/fullness
Lagophthalmos
Orbit
Restrictive strabismus and diplopia
Exophthalmos
Globe subluxation

sparing of muscle insertions is typical.[20] The inferior and medial recti tend to be enlarged more than the superior and lateral recti. The enlarged recti muscle bellies are best visualized on a coronal orbital image (see Fig. 17.4). Abnormally enlarged extraocular muscles are seen in up to 90% of patients radiographically, but diplopia occurs in only one-third.[21] Imaging is helpful to distinguish fat-predominant versus muscle-predominant orbital expansion. Significant crowding at the orbital apex can result in congestive and compressive optic neuropathy. This is particularly dangerous in the absence of exophthalmos. Signs of compressive optic neuropathy include decreased visual function, optic disc edema or pallor, color desaturation, or an afferent pupillary defect. TAO is more severe in older patients and in males.[22] Compressive optic neuropathy does not occur in children.[4] Rarely, patients suffer concomitant autoimmune myasthenia gravis, which presents as variable blepharoptosis, diplopia, or saccadic fatigue.

Natural History of Disease

A period of worsening signs and symptoms lasts for 6 to 12 months followed by a plateau and burning-out period over 18 to 24 months.[23] The "inflammatory" or "active" phase represents maximum activation of the immune system, which is followed by a period of fibrosis and scarring. After the disease has burnt out, the term "inactive" or "quiescent" disease may be used. There are some rare reports of a chronic or relapsing disease course.[24] Cigarette smoking, including second-hand exposure, increases the risk, severity, and duration of TAO by tenfold.[25,26]

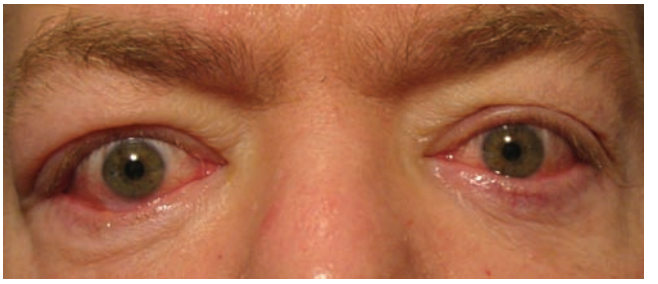


FIGURE 17.1 Mild-to-moderate asymmetrical disease. Bilateral upper eyelid swelling, conjunctival injection, and chemosis. Right upper and lower eyelid retraction.

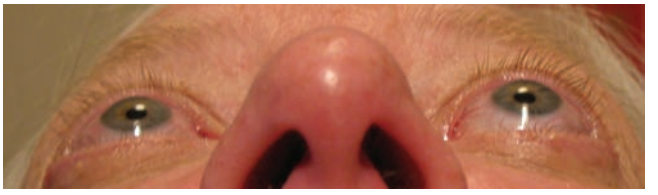
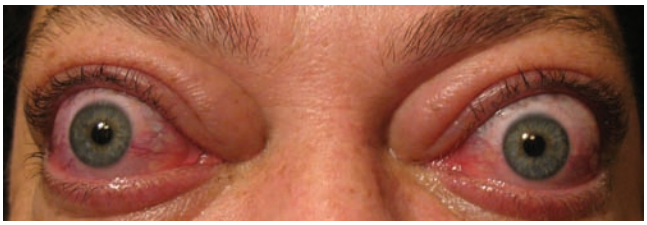
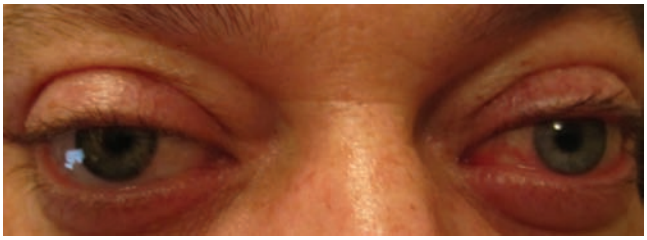


FIGURE 17.2 Moderate-to-severe asymmetrical disease. Submental view of left exophthalmos.



A



B

FIGURE 17.3 **(A)** Vision-threatening symmetrical disease. Upper and lower eyelid swelling and retraction, conjunctival injection and chemosis, restrictive strabismus and exophthalmos, and compressive optic neuropathy. **(B)** Six months after high-dose steroids, surgical decompression, strabismus repair, and eyelid retraction repair.

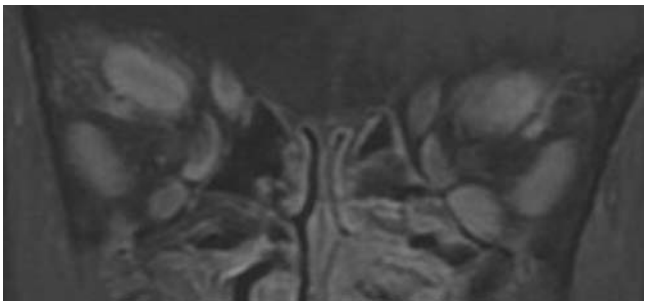


FIGURE 17.4 Coronal T1-weighted, fat-suppressed, gadolinium-enhanced magnetic resonance image of enlarged extraocular muscle bellies from vision-threatening thyroid-associated orbitopathy.

Ophthalmologic Examination

A comprehensive evaluation includes testing visual function, pupillary responses, intraocular pressure, optic discs, extraocular motility, exophthalmometry, cornea, conjunctiva, margin-to-reflex distances, and determination of lagophthalmos for each eye. Visual function tests include best-corrected visual acuity, color testing (red saturation or Ishihara plates), and perimetric testing. An important objective of this evaluation is to determine both "activity" and "severity" of disease.

Disease activity refers to the degree of inflammatory reaction to autoantigen presently taking place. This was quantified in the late 1970s using an ordinal score called the NOSPECS index (N, no signs or symptoms; O, only signs, no symptoms; S, soft-tissue involvement; P, proptosis; E, extraocular muscle involvement; C, corneal involvement; S, sight loss).[27] This index was later modified to a continuous total eye score.[28] Since the late 1990s, the clinical activity score (CAS) developed by Mourits et al. has become popular.[29] The European Group on Graves' Orbitopathy (EUGOGO) consensus statement recommends a CAS of three or more out of seven (the first seven clinical parameters) as a threshold for active disease (see Table 17.3).[30]

Disease severity describes the actual physical sequelae (i.e., optic neuropathy, exophthalmos, and eyelid retraction) that occur and can be categorized as vision-threatening, severe, moderate, or mild. These sequelae are present during active or inactive disease.

Work-Up and Treatment for Dysthyroidism

From the panel of possible thyroid function tests, the most valuable for diagnosing and monitoring dysthyroidism are serum-free T4 and TSH. Most patients with GD are

TABLE 17.3 Clinical activity score (CAS) to quantify disease activity

PAIN	1. Retrobulbar pain
	2. Pain on attempted up- or downgaze
REDNESS	3. Redness of the eyelids
	4. Redness of the conjunctiva
SWELLING	5. Swelling of the eyelids
	6. Chemosis
	7. Swollen caruncle or plica
IMPAIRMENT	8. Increase in exophthalmos by ≥2 mm over 1–3 mo
	9. Decrease in eye movement in any direction by ≥ five degrees over 1–3 mo
	10. Decrease in pinhole visual acuity by 1 or more lines on the Snellen chart over 1–3 mo

The European Group on Graves' Orbitopathy (EUGOGO) recommends a CAS of three or more out of seven (the first seven clinical parameters) as a threshold for active disease. Bartalena et al.[30] [www.eugogo.eu].

comanaged with internists or endocrinologists whose goals are to stabilize thyroid function with antithyroid drugs (ATDs) and to help in the decision-making process regarding if and when thyroid ablation is required. Oral thioamides (methimazole, carbimazole, or propylthiouracil) are commonly used, and randomized, controlled studies support initial therapy with methimazole for efficacy and tolerability.[31] The ATD administration regimens are either titration or a block-and-replace strategy. Thyroid ablation, whether by surgical thyroidectomy or radioiodine (I-131), is typically used when thyroid levels are unstable on ATDs. Thyroidectomy (total, near total, or subtotal) may be preferable for patients that exhibit a goiter or thyroid gland enlargement, but risks include hypoparathyroidism and permanent damage to the recurrent laryngeal nerve. The main disadvantage of radioiodine ablation is the increased risk and severity of TAO in susceptible patients.[32] This phenomenon is worse in smokers and likely related to the high concentration of thyroid antigens released during necrosis of thyroid follicular cells. An oral administration of 5 to 15 mCi results in an absorbed radiation dose of 50 to 100 Gy. A study of 450 patients shows that the rate for TAO progression during radioiodine ablation is 15% but can be mitigated with a short course (1 to 3 months) of oral steroids.[33] Posttreatment hypothyroidism should also be avoided.[34] Patients who are nonsmokers and lack evidence of TAO can probably undergo radioiodine ablation without steroid prophylaxis. A recent randomized, placebo-controlled study found that Ginkgo biloba extract decreases radiation-induced genotoxic damage during radioiodine therapy.[35]

Currently, the choice of treatment for dysthyroidism is based on expert opinion rather than level 1 evidence.[36] There is an ongoing debate regarding whether or not thyroid ablation has any effect on TAO progression. Removing the bulk of shared antigens should theoretically reduce the severity of disease.[37] Total thyroid ablation (TTA) is a combined strategy in which surgical thyroidectomy is followed immediately by radioiodine ablation for remnant tissue. The long-term follow-up data from a randomized study comparing thyroidectomy alone versus TTA showed that TAO symptoms resolved more quickly in the TTA group, but overall outcomes were comparable.[38] Euthyroid maintenance seems to prevent TAO progression.[39] However, based on the current evidence, thyroid ablation is believed to treat dysthyroidism alone and has little to no effect on the course of ophthalmologic disease.[33]

Work-Up for Thyroid-Associated Orbitopathy

Antibodies generated against thyroid peroxidase (TPO) and thyroglobulin are detectable in patients with GD. However, the blood test most valuable for monitoring TAO activity is TSI.[40] This antibody titer correlates strongly with CAS but does not correlate with thyroid function tests (T4, TSH) or TPO antibody.[41] A recent cross-sectional study showed that 98% of 108 patients with active TAO had a positive TSI assay.[42] Furthermore, TSI levels were higher in moderate-to-severe versus mild disease ($p < 0.001$) in this study. A trend-based

analysis of TSI is preferable to using specific values as thresholds for intervention. When the TSI levels begin to decrease and plateau, this indicates disease stabilization. The values typically never return to normal levels. Neuroimaging with computed tomography or magnetic resonance imaging can help confirm the diagnosis of TAO, especially for euthyroid patients (see Fig. 17.4).

Differential Diagnosis

It is not uncommon for patients with dry eye symptoms alone and no prior history of GD or other autoimmune disease to have occult TAO.[43] Although the diagnosis of TAO is often apparent, a differential diagnosis includes myasthenia gravis, orbital myositis, orbital tumors, chronic progressive external ophthalmoplegia, and orbital arteriovenous fistulas. Once the diagnosis has been confirmed, TAO activity and severity will determine whether observation alone or treatment with medication, radiation, or surgery is required.

II. TREATMENT OF THYROID-ASSOCIATED ORBITOPATHY

Overview

The purpose of this section is to provide guidelines regarding the treatment of TAO based on the best available evidence. The information has been organized by treatment modality and the implications for practice are highlighted prior to a detailed review of the relevant studies. Areas of future research are summarized at the end of each subsection. (See Appendix A for a summary of clinically relevant studies of treatment for TAO.)

Smoking cessation is the single most important intervention for every patient regardless of disease severity.[44] The majority of patients can be managed conservatively with close monitoring and reassurance while awaiting spontaneous recovery. Some patients will require an immunosuppressive or surgical intervention for vision-threatening disease, eyelid swelling, exophthalmos, diplopia, or exposure. The order of surgical intervention is to perform orbital decompression first, followed by strabismus surgery, followed by eyelid surgery as needed (see Figs. 17.3 and 17.5). Some patients will eventually require a combination of these procedures for functional and/or aesthetic rehabilitation.[45] Any surgical intervention performed during the active phase will worsen orbital inflammation, and so rehabilitative surgery is considered after quiescence. Vision-threatening cases are initially managed with high-dose steroid (HDS) therapy with some requiring adjunctive surgical decompression of bony orbital walls and intraorbital fat. Retrobulbar irradiation (RI) is less effective as a first-line intervention but may be useful in refractory cases. One approach to quantification of treatment response is presented by Bartalena et al.

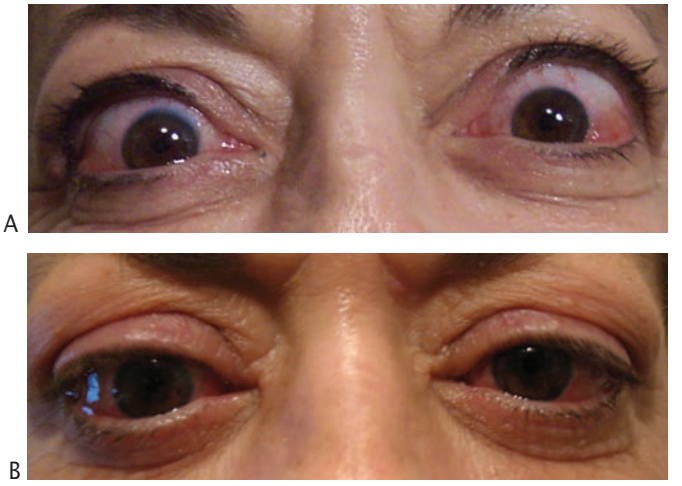


FIGURE 17.5 **(A)** Bilateral upper eyelid retraction left greater than right. **(B)** Two months after bilateral upper eyelid recession (posterior transconjunctival mullerectomy).

TABLE 17.4 Management of thyroid-associated orbitopathy based on disease severity

Vision-threatening disease (compressive optic neuropathy or severe corneal exposure)
High-dose steroid therapy
– intravenous > oral
Surgical orbit decompression
– bony walls (1-, 2-, or 3-wall)
– intraorbital fat
Retrobulbar irradiation
Newer biologics (rituximab)
Severe disease (restrictive strabismus)
Prismatic correction
Botulinum A toxin injection
Strabismus surgery
Moderate disease (eyelid retraction with exposure keratopathy)
Botulinum A toxin injection
Upper eyelid recession
Lower eyelid elevation (± spacer graft, ± midface elevation)
Mild disease (dry eyes, mild keratopathy, chemosis, eyelid edema, mild eyelid retraction)
Ocular lubricants (tears, ointments)
Selenium supplementation

(EUGOGO) using major and minor criteria.[33] (See Table 17.4 for an overview of management options based on disease severity.)

Immunosuppressive Therapy

The primary goal of TAO management is to minimize inflammatory damage while awaiting disease resolution. Systemic glucocorticoid therapy is the most effective intervention to accomplish this goal. Steroids directly inhibit the proinflammatory cytokines and other inflammatory mediators released during the active disease phase, but confer no benefit during the inactive fibrotic phase. They improve soft-tissue swelling, motility disturbance, and compressive optic neuropathy but do not significantly decrease exophthalmos. Both orally administered and intravenous (IV) pulses of HDSs can be used, but the latter seems to be better tolerated and more effective.[46] Many retrospective and nonrandomized studies found IV more effective than oral administration, but had drawbacks such as use of oral agents during the interpulse period or concomitant radiotherapy.[47–50] A prospective, randomized, controlled study comparing IV and oral HDS over 12 weeks for moderate-to-severe TAO found that IV administration resulted in a more rapid and significant improvement in CAS ($p < 0.01$), exophthalmos ($p < 0.038$), extraocular muscle changes ($p < 0.02$), optic neuropathy ($p < 0.001$), intraocular pressure ($p < 0.04$), visual acuity ($p < 0.03$), quality of life ($p < 0.0001$), and overall treatment response (72% versus 49%) ($p < 0.001$).[51] In another single-blind, prospective, randomized, controlled study, 70 patients with active and severe TAO received either 0.5 g of methylprednisolone IV once weekly for 6 weeks then 0.25 g for 6 weeks (cumulative dose 4.5 g) or 100 mg daily of oral prednisone for 1 week tapered by 10 mg per week for a total of 12 weeks.[52] The IV group had a 77% response rate compared with 51% for oral HDS ($p < 0.01$). One biological explanation for this finding is that IV therapy more effectively reduces circulating dendritic cells, which are potent antigen-presenting cells involved in the primary immune response of TAO.[53] IV HDSs also significantly decrease serum TSH-R autoantibody levels in patients with GD.[54] The response rate achieved using IV pulse therapy is about 80% compared with 50% for oral HDSs.[30] However, the specific dosing strategies for IV administration are variable.[51,55] Weekly pulse therapy is probably preferable to consecutive daily administration in order to minimize the risk of adverse events, the most significant being hepatic failure.[56] Hepatic failure occurs when the cumulative dose of IV methylprednisolone exceeds 8 g.[57] The morbidity and mortality of IV HDSs are 6.5 and 0.6%, respectively.[56] Patients should be followed closely for adverse events, and any indication of hepatic dysfunction demands liver enzyme testing. Less serious and more common side effects include weight gain, cushingoid features, hypertension, hirsutism, psychosis, osteoporosis, and gastrointestinal (GI) problems.[28] These are all worse with oral compared with IV administration.[51] Prophylactic H2 receptor blockers are helpful to

reduce GI symptoms. Overall, HDSs decrease the quality of life for most patients.[58] Contraindications to HDSs include uncontrolled diabetes, severe hypertension, recent hepatitis, and pregnancy. As the disease stabilizes and the dose is tapered, rebound inflammation can occur.[30]

Local steroid therapy by periocular or orbital injection is less effective than systemic administration but improves eye motility and soft-tissue swelling.[59] It can be considered in select cases, but should never be used for compressive optic neuropathy.[60] Ebner et al. performed a multicenter, prospective, randomized, placebo-controlled study of periocular triamcinolone injections for early TAO and found that eye motility and size of extraocular muscles improve with treatment.[61] However, the ideal role for local steroid therapy is adjunctive or in cases when systemic HDSs are contraindicated.

Other systemic immunosuppressive agents for TAO include octreotide, cyclosporine, azathioprine, colchicine, cyclophosphamide, and methotrexate.[62,63] Octreotide is a somatostatin analog that inhibits lymphocyte proliferation and was shown to have a modest benefit in improving CAS in two prospective, randomized, double-blind, placebo-controlled trials.[64,65] Cyclosporine inhibits cytotoxic T-cell activity and, as single-drug therapy, was found less effective than oral prednisone in a randomized, controlled study by Prummel et al.[28] The combination of both agents, however, was more effective than either agent alone. Dry eye symptoms are common manifestations of TAO likely caused by exposure and evaporation of tears.[66] The treatment armamentarium for dry eyes is vast including various lubricating tears, gels, ointments, and relatively recently topical cyclosporine A (CsA). A prospective, randomized, controlled study compared topically administered CsA with lubricants to lubricants alone for dry eyes from TAO and found no advantage of CsA therapy.[67]

Implications for Practice

Immunosuppressive therapy is effective during the inflammatory phase of TAO. Systemic glucocorticoids are the best first-line agents, and IV pulses of steroids are superior to other steroid regimens. Cyclosporine and other immunosuppressives may have a role in combination therapy or as steroid-sparing agents for select cases.

Areas of Future Research

There is a lack of evidence for superiority of a particular IV HDS dosing regimen in TAO. The potential role of combination therapy using HDSs, other immunosuppressives, and newer immunomodulating drugs for refractory cases needs to be explored.

Retrobulbar Irradiation

Radiation therapy has been used to treat TAO for more than 65 years and, in its early stages, was directed at the hypothalamus and pituitary gland. Later, it was determined that therapeutic benefit resulted from suppression of orbital inflammation.[22] Orbital lymphocytes and fibroblasts are highly radiosensitive.[68] RI has been studied for vision-threatening or severe TAO either alone or in combination with HDSs during active TAO. Diabetes and severe hypertension are relative contraindications for RI because they increase the risk of retinopathy. The risk of cataract formation and development of secondary tumors is believed to be low (1% or less). The most common delivery regimen is a cumulative dose of 20 Gy per eye, fractionated in 10 daily doses. However, lower doses are equally effective and better tolerated. Gerling et al. compared 2.4 Gy and 16 Gy in a double-blind randomized study for TAO and found no difference in clinical response.[69] Randomized, placebo-controlled studies have shown a response rate of about 60% after RI, with the main benefit limited to diplopia.[68,70] Prummel et al. conducted a prospective, double-blind, randomized, placebo-controlled study of RI for 88 patients with mild-to-moderate TAO and found a small benefit in extraocular motility but no difference in overall quality of life.[71] A recent meta-analysis of randomized, controlled trials also found no advantage of RI over sham irradiation in CAS, with improvement limited to diplopia alone (odds ratio 4.88, 95% confidence interval 1.93–12.34, two trials).[72]

Overall, a debate continues regarding the role of RI for TAO.[73–75] Gorman et al. found no significant difference between eyes in 42

patients where only one orbit was irradiated with 20 Gy in a randomized, double-blind, internally controlled, prospective study.[76] This led the authors to suggest abandonment of RI for TAO. However, the lack of a significant difference detected between treated and untreated eyes might have been because the untreated orbit was inadvertently exposed to 2 Gy or more of radiation.[77] Randomized, controlled studies have shown similar efficacy between oral prednisone and RI.[78] It is unlikely that a prospective study comparing IV HDSs and RI will be undertaken based on the current evidence. The combined effect of oral HDSs and RI is greater than either modality alone,[79,80] suggesting the best role for RI may be as adjunctive treatment in refractory cases.

Implications for Practice

RI is effective for diplopia but is not commonly used as a first-line intervention. It may improve compressive optic neuropathy or act as a steroid-sparing agent in refractory cases. Level 1 evidence suggests that exophthalmos, eyelid retraction, and soft-tissue changes do not improve with radiotherapy.

Areas of Future Research

The role of RI as a steroid-sparing agent or as part of combination therapy for refractory cases needs clarification with prospective comparative studies. A randomized study comparing IV HDSs alone and IV HDSs with RI may be useful.

Surgical Decompression

There are many philosophies and surgical techniques for orbital decompression but all involve removing one or more bony walls, intraorbital fat, or a combination of these based on disease severity.[81] The result is a prolapse of orbital contents into adjacent sinuses permitting the globe to return to its normal anatomical position. The lack of standardization and variable quality of published reports makes it difficult to establish universal guidelines. Most studies are retrospective cohort or case series and cannot demonstrate superiority of any particular technique.[81] This is because variables such as surgical timing, follow-up intervals, disease activity, methodology, and outcome measures are inconsistent. Even the indications for surgery (compressive optic neuropathy versus exophthalmos) are variable with unique treatment goals. Apical crowding causing compressive optic neuropathy demands maximum decompression of the orbital apex (posterior inferior and medial walls) to relieve pressure on the optic nerve (see Fig. 17.6). Exophthalmos can be lessened by removing one or more bony walls and intraorbital fat so that the orbital volume expands and the globe is retroplaced. Some patients will require both optic nerve compression and exophthalmos treatment. There is inter-subject variability in orbital anatomy, and so a case-by-case analysis of preoperative imaging is invaluable. The surgeon should consider globe-to-orbit volume ratio, extraocular muscle-to-intraorbital fat volume ratio, and the fibrosis of orbital tissues during planning.

Bony orbital decompression can be performed by transcutaneous, transconjunctival, transcaruncular, transpalpebral, coronal, and swinging eyelid approaches as described in the oculoplastics literature.[82–85] Studies in the otolaryngology (head and neck surgery) literature describe endonasal medial wall techniques.[86] Rarely, neurosurgeons may perform a transcranial orbital roof decompression.[87] A disadvantage of an endonasal approach to the medial wall is trauma to the nasal mucosa and turbinates, with no clear advantage over the transcaruncular orbital approach. A transconjunctival approach to the inferior orbital floor allows bony removal and prolapse of orbital contents into the maxillary sinus. Globe ptosis (hypoglobus) and new-onset strabismus (NOS) can be decreased by leaving the anteromedial floor (strut) intact.[88] A Caldwell-Luc transantral approach to remove the floor and medial wall has lost favor due to a relatively high rate (60% or greater) of NOS and other complications.[89–91] However, preservation of 10 mm of the orbital floor and periorbita supports a normal globe position and decreases the rate of NOS.[92] Removal of the lateral wall alone is more effective when the temporalis fascia is incised and is less likely to cause NOS. However, there are risks including cerebrospinal

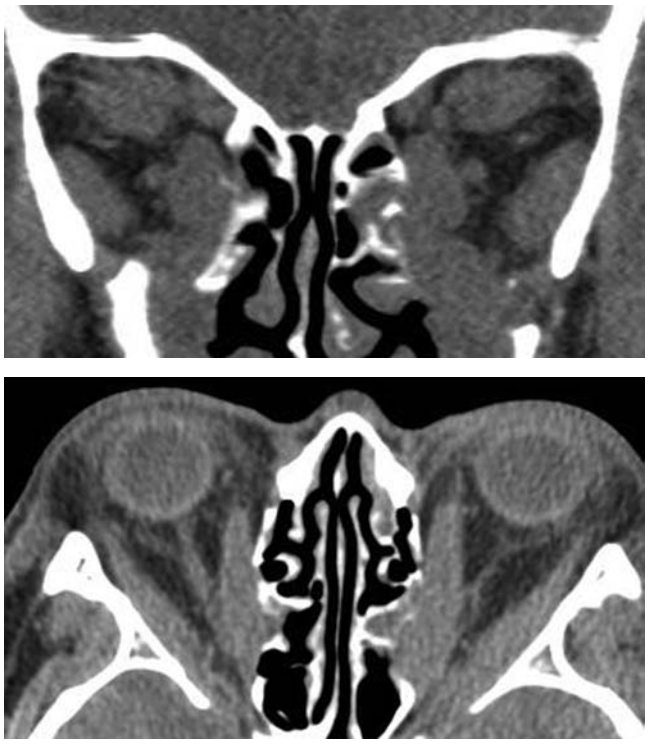


FIGURE 17.6 Coronal **(A)** and axial **(B)** computed tomography images of maximal orbital apex (posterior inferior and medial wall) decompression for compressive optic neuropathy.

fluid leak and injury to the frontal branch of the facial nerve. Complications common to most decompressive surgeries include vision loss from damage to the optic nerve or its blood supply, globe ptosis, cheek numbness, cerebrospinal fluid leak, vision-threatening orbital hemorrhage, and diplopia from NOS.[93,94] There is some consensus that removal of the medial and lateral orbital walls (two-wall, balanced decompression) with or without fat removal may be the most effective technique with the least complications.[30] Intraorbital fat decompression alone without bony removal has a low complication rate and may be an option for fat-predominant disease.[95] Most techniques result in 3 to 5 mm of exophthalmos reduction,[96] but ultimately the comfort and experience of the surgeon and unique patient characteristics will guide decision-making.

A Cochrane review evaluated randomized, controlled trials comparing two or more surgical methods of orbital decompression with removal of bony wall, orbital fat, or a combination of both with any form of medical decompression.[97] Two studies were identified but both had methodological limitations and could not support definitive recommendations for clinical practice. Based on disease pathophysiology, it is intuitive that immunosuppression with HDSs should precede any surgical intervention. However, Wakelkamp et al. performed a prospective randomized study comparing surgical decompression and HDSs as a first-line intervention for compressive optic neuropathy.[98] The majority (82%) of patients in the surgery arm of this study did not respond and ultimately required HDSs and/or RI. This study clearly reinforces that HDSs should be the first-line intervention during active disease.

Implications for Practice

Maximum surgical decompression of the orbital apex is indicated for compressive optic neuropathy when medical treatment fails. Exophthalmos causing severe corneal exposure or disfigurement is lessened by removing bony orbital walls and/or intraorbital fat.

Areas of Future Research

Prospective, randomized, controlled studies comparing different surgical techniques are

difficult to perform due to surgeon preference and unique patient characteristics. Future studies should, however, attempt to control for patient demographics and disease activity and severity and consider outcome measures such as exophthalmos reduction, visual function improvement, CAS, complication rate, and quality of life.

Rehabilitation and Reconstruction

Once TAO is in the quiescent phase, rehabilitative and reconstructive surgery can be considered. The natural history of TAO suggests that 20% of patients will spontaneously improve, 65% will remain static, and 15% will worsen over time.[99] Orbital decompression for cosmesis is an acceptable indication. HDSs and RI will not lessen exophthalmos. The appearance of exophthalmos can be improved in certain patients using orbitofacial implants without any bony or fat removal. Strabismus surgery follows orbital decompression since the latter can cause diplopia. Conversely, recessing multiple extraocular muscles can cause exophthalmos. Prior orbital decompression may decrease the success rate of strabismus surgery.[100] The goal is to restore single binocular vision in primary and downward gaze. Forced ductions performed under anesthesia help determine the amount of restriction for each muscle. Interestingly, sometimes larger recessions are needed for smaller deviations, while smaller recessions prove sufficient for larger deviations. Resections are typically avoided in TAO. The myriad of surgical techniques described underscores the difficulty in treating TAO-related strabismus.[101,102] Nonsurgical treatment options for strabismus include botulinum A toxin injection and prismatic correction. The duration of action for botulinum A toxin is about 3 months. This intervention may be helpful in nonsurgical candidates or those with debilitating diplopia during active disease and/or awaiting decompressive surgery. Strabismus surgery is performed prior to eyelid surgery because recession of vertical muscles can worsen eyelid retraction.

When upper or lower eyelid retraction with exposure keratopathy and/or lagophthalmos persists, surgical correction is the mainstay of treatment.[103] The retractors of the upper eyelid, the levator palpebrae superioris and Muller's muscles, can be recessed, lengthened, or excised through an anterior or posterior approach to help correct the deformity. For mild–moderate upper eyelid retraction, a posterior transconjunctival mullerectomy with or without levator aponeurotomy is usually sufficient (see Fig. 17.5).[104,105] For more severe retraction, the levator aponeurosis can be repositioned through an anterior lid crease approach. Elner et al. have shown that a graded full-thickness anterior blepharotomy results in a predictable and reproducible improvement.[106] In 50 upper eyelids with differing retraction severity, 93% had symptom resolution and normalization of margin-to-reflex distances. Lower eyelid retraction repair often involves lateral canthal tightening and spacer material such as hard palate or acellular dermal matrix (human or porcine). A blepharoplasty and/or browplasty for eyelid fullness is typically performed last. Nonsurgical options for upper eyelid retraction include injection with botulinum A toxin,[107] triamcinolone acetonide,[108] or hyaluronic acid fillers.[109]

Implications for Practice

Orbital disfigurement, diplopia, and lid function can be improved with bony decompression, orbitofacial implants, strabismus repair, or eyelid surgery as needed. The surgical interventions should proceed in that order when TAO is inactive. Botulinum A toxin injection is helpful for nonsurgical treatment of strabismus or upper eyelid retraction.

Areas of Future Research

Many groups are currently investigating the underlying immunopathologic changes in extraocular muscles and eyelid retractors. Prospective comparative studies investigating whether specific nonsurgical treatments reduce the subsequent need for rehabilitative surgery are lacking.

Novel Therapies

The treatment options discussed thus far improve symptomatology and/or decrease inflammatory damage to orbital tissue but do

not influence the underlying TAO pathophysiology. In contrast to nonspecific immunosuppressives like HDSs, immunomodulating agents presented over the past decade target specific immune cells and pathways. Many of these drugs, developed for other autoimmune disorders like rheumatoid arthritis, are being applied to TAO. For example, etanercept, a recombinant human soluble TNF alpha receptor fusion protein, improved CAS and severity in 10 TAO patients.[110] One-third, however, developed disease recurrence after discontinuation of therapy. Infliximab is a monoclonal antibody against TNF alpha that may be beneficial in TAO, but there are currently no prospective comparative studies.[111] The most promising agent thus far has been rituximab, an anti-CD20 chimeric humanized monoclonal antibody that targets CD20-positive B-cells.[112] In addition to depleting B-cells, rituximab alters antigen presentation, cytokine release, and T-cell activity through various mechanisms. The pilot study by Salvi et al. of 9 patients treated with rituximab (administered as two 1 g IV doses, separated by a 2-week interval) and 20 patients with IV HDSs (0.5 g weekly for 16 weeks) showed that CAS improved more with rituximab ($p < 0.05$).[112] A prospective, noncomparative study of 12 patients by Silkiss et al. showed an improved CAS in moderate-to-severe TAO, which persisted at the 1-year follow-up.[113] Interestingly, this study and others have found that rituximab improves clinical activity but does not affect serum TSI values.[114] Khanna et al. treated six patients with vision-threatening TAO unresponsive to steroid therapy with rituximab who demonstrated an improved CAS (5.5 +/- 0.8 to 1.3 +/- 0.5) at 2 months ($p < 0.03$) and resolution of compressive optic neuropathy.[115] However, their results were confounded by various other decompressive treatments that were used concurrently in several patients. The most common side effects attributable to rituximab are GI.[116] A very small, but serious risk of developing fatal progressive multifocal leukoencephalopathy also exists.[117] Bahn and colleagues are currently recruiting 30 patients for a randomized, placebo-controlled study of rituximab for TAO (NCT00595335, www.clinicaltrials.gov). Thus far, rituximab has been used for severe, vision-threatening disease but based on its mechanism of action may prove to be more effective if initiated earlier during the disease course.

Oxygen-free radicals play a pathogenic role in TAO.[18,19] Antioxidants are, therefore, potential therapeutic agents for active disease. Selenium is a trace mineral that was shown in a randomized, placebo-controlled study to be effective in patients with mild TAO for slowing disease progression and improving quality of life.[118] This was administered as oral sodium selenite 100 µg taken twice daily for 6 months. The main criticism of this study was that the serum concentration of selenium was not measured despite recruiting subjects from areas known to have higher rates of selenium deficiency. Pentoxifylline is an anti-inflammatory phosphodiesterase inhibitor that was also tested in this study but did not perform better than placebo. A nonrandomized, placebo-controlled study showed that antioxidant treatment with allopurinol and nicotinamide was helpful for moderate-to-severe TAO.[63] The long-term risks of various antioxidants need to be evaluated.

Implications for Practice

Rituximab is the newest addition to the treatment armamentarium for moderate-to-severe or vision-threatening TAO. The risk-to-benefit ratio for this drug has yet to be larified. Oral supplementation with selenium is effective in slowing the progression of mild TAO and improving quality of life.

Areas of Future Research

Clinical trials are currently underway to help define the role of rituximab in TAO. Other targeted immunomodulating therapies used in autoimmune diseases like rheumatoid arthritis are being applied to TAO. The effectiveness of any new drug needs to be weighed against tolerability, adverse effects, and cost. This is particularly important if we begin to use these agents at earlier, non-vision-threatening stages of disease.

III. SUMMARY AND TAKE-HOME MESSAGES

GD is a systemic, site-specific, autoimmune condition that targets the thyroid gland, orbit, and, less commonly, pretibial skin.

Hyperthyroidism occurs in more than 90% of GD patients at some point during the disease course. It predominantly affects middle-aged women, and up to half of all patients will experience TAO. Of all patients manifesting clinical signs of TAO, 10 to 15% will be euthyroid or hypothyroid. The visual deficits and disfigurement associated with TAO result in decreased quality of life and impairment for many patients.[119] However, GD is self-limiting, and so most patients are manageable with minimal intervention and reassurance. Close observation with regular follow-ups including a complete ophthalmologic examination and serum blood tests for T4, TSH, and TSI are required for monitoring. Coordinated care with internists or endocrinologists is helpful to restore and maintain euthyroidism with ATDs or ablative therapies. Susceptible patients (smokers or those with TAO) undergoing radioiodine ablation should be treated with a short course of oral steroids to prevent TAO progression. Thyroidectomy and ATDs have a neutral effect on TAO progression.

All patients must be counseled on the absolute need for smoking cessation, including second-hand exposure. Patients can be counseled on the potential benefit of selenium supplementation although the long-term risks are unknown. Some patients will need urgent surgical intervention for vision-threatening disease, but all reconstructive and rehabilitative surgery should be delayed until the clinical activity and TSI levels have stabilized. IV HDS pulse therapy is the first-line intervention for compressive optic neuropathy. The ideal dosing regimen has yet to be determined, but a 12-week course of a cumulative 4.5 g dose has an 80% response rate. Hepatic and cardiovascular health must be evaluated before initiation of therapy. Patients who continue to progress after 1 to 2 weeks should then undergo surgical decompression of the orbit. This intervention can improve both optic neuropathy and exophthalmos. Nonsurgical candidates may consider RI, which is most effective when given as combination therapy with HDSs. As single-agent therapy, RI mostly improves dysmotility. After the disease is quiescent, rehabilitative orbital, strabismus, and/or eyelid surgery can be considered. The evolving field of targeted biologic agents is encouraging. Ideally, these drugs will help change the natural progression of disease and obviate the need for steroids, radiation, or surgery. Potential strategies include blocking activated T-cells, depleting B-cells, inhibiting aberrant cytokine signaling, and blocking TSH-Rs and IGF-I-Rs. The ultimate goal is to treat the cause of disease rather than the consequences.

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APPENDIX A **Summary of Clinically Relevant Studies of Treatment for Thyroid-Associated Orbitopathy**

Reference	Study design/purpose	Study participants	Treatment protocol	Outcome	Conclusions/limitations
Marcocci (2011)[118]	Multicenter, randomized, double-blind, placebo-controlled study of selenium and pentoxifylline for mild TAO.	159 patients with mild TAO.	Sodium selenite (100 μg bid) 55/159, pentoxifylline (600 mg bid) 52/159, or placebo 52/159 for 6 mo.	CAS decreased in all groups but most significant with selenium. QOL ($p < 0.001$), eye involvement ($p = 0.01$), and progression of TAO ($p = 0.01$) all significantly better at 1 y with selenium.	Selenium improves QOL and ocular disease and slows progression of mild TAO.
Ponto (2011)[42]	Single-center, cross-sectional trial to assess TSI and TBII assays correlated with disease activity and severity.	108 patients with untreated TAO.	TSI, disease activity, severity of TAO, and TBII measured.	TSI detected in 98% of TAO, correlated with activity ($p < 0.001$) and severity ($p < 0.001$). TSI levels higher in severe than mild TAO ($p < 0.001$).	TSI is significantly associated with clinical activity of TAO and serves as a functional biomarker.
Silkiss (2010)[113]	Prospective, interventional trial of rituximab for TAO.	12 patients with CAS > 4.	Two doses of 1 g separated by 2 wk.	CAS improved at 1 mo and 1 y. TSI levels did not change.	Rituximab may be effective for TAO and a randomized comparative study is needed.
Aktaran (2007)[51]	Single-center, randomized, single-blind, controlled study comparing IVS with oral steroids for TAO.	52 patients with active TAO underwent steroid therapy for 12 wk.	IVS qwk (0.5 g then 0.25 g, for 6 wk each) versus oral prednisolone (72 mg for 2 wk then tapered).	CAS ($p < 0.01$), proptosis ($p < 0.038$), CON ($p < 0.001$), QOL ($p < 0.0001$) improved more rapidly and significantly with IVS versus oral.	IVS therapy is more effective and better tolerated compared with oral steroids for TAO.
Stan (2006)[64]	Single-center, randomized, double-blind, placebo-controlled study of octreotide for TAO.	29 patients with active TAO.	Four monthly doses of octreotide long-acting release (20 mg) or saline by intramuscular injection.	CAS change was 2.5 in the treatment group versus 1.0 in the placebo group ($p = 0.02$)	CAS improves significantly with octreotide versus placebo. However, small sample sizes in this study.

(continued)

APPENDIX A (Continued)

Reference	Study design/purpose	Study participants	Treatment protocol	Outcome	Conclusions/limitations
Kahaly (2005)[52]	Single-center, randomized, single-blind, controlled study comparing IVS with oral steroids for TAO.	70 patients with active TAO underwent steroid therapy for 12 wk. IVS 35/70 and oral 35/70.	IVS q wk (0.5 g, then 0.25 g, 6 wk each) versus oral prednisone (100 mg daily for 1 wk tapered by 10 mg each wk).	77% of IVS versus 51% of oral steroid group had sustained improvement at 3 mo ($p < 0.01$). VA ($p = 0.01$), chemosis ($p < 0.01$), and QOL ($p < 0.001$) greater for IVS group.	IVS therapy is more effective and better tolerated than oral steroids for TAO.
Wakelkamp (2005)[98]	Single-center, randomized, controlled study to compare IVS therapy with surgical decompression.	15 patients with CON from severe TAO.	6/15 underwent surgery and 9/15 IVS (2 wk) followed by oral steroids for 4 mo.	VA and CAS improved in 56% of IVS group and 17% of SD group. 82% of surgery group did not respond.	Steroid therapy is a better first-line intervention for CON from TAO compared with surgical decompression.
Ebner (2004)[61]	Multicenter, randomized, placebo-controlled study of periocular steroid injection for TAO.	41 patients with early TAO.	24/41 in the treatment group underwent four injections of triamcinolone (40 mg/ml) of 20 mg q wk; 17/41 were in the placebo group.	The area of binocular vision without diplopia by Goldmann perimetry increased in the treatment group (107.1) compared with the control group (-4.5). The size of EOM was reduced in the treatment group.	Periocular triamcinolone injection improves motility and reduces EOM size in early TAO. The subgroup analyses make it difficult to generalize results.
Prummel (2004)[71]	Single-center, randomized, double-blind, placebo-controlled study of orbital irradiation for mild TAO.	88 patients with mild TAO.	44/88 received radiotherapy and 44/88 were sham irradiated. Ten divided fractions of 2 Gy daily were delivered over 2 wk.	52% of treated patients versus 27% of sham patients had improved eye motility at 1 y ($p = 0.02$). QOL was similar between groups.	Radiotherapy is effective for mild TAO but does not confer increased QOL.
Elner (2004)[106]	Single-center, noncomparative, interventional study of full-thickness anterior blepharotomy.	50 eyelids with upper lid retraction and exposure.	All underwent a graded, full-thickness, anterior blepharotomy.	Upper lid position ($p < 0.001$), lagophthalmos ($p < 0.001$), and keratopathy ($p < 0.01$) improved.	Graded anterior blepharotomy for upper lid retraction is safe and effective.

Gorman (2001)[76]	Single-center, randomized, double-blind, internally controlled trial of orbital irradiation for TAO.	42 patients with moderate-to-severe TAO.	One randomly selected orbit treated with 20 Gy external beam therapy and the contralateral orbit treated with sham. Therapies reversed after 6 mo.	Volume of EOM, volume of orbital fat, globe position, eyelid fissure width, range of eye motility, and diplopia fields had no significant difference between groups.	The authors concluded that orbital irradiation is not effective for TAO. However, it is possible that the contralateral orbit received up to 2 Gy during treatments.
Pliego-Mald (2000)[90]	Single-center, randomized, controlled study to compare two surgical decompression techniques.	44 orbits in patients with inactive TAO and exophthalmos (>22 mm).	Walsh-Ogura (26/44) and Kennedy's (18/44) techniques were compared.	Walsh-Ogura transantral approach was associated with more complications. Both techniques are equally effective in reducing exophthalmos ($p < 0.05$).	Transantral decompression has more complications such as new-onset diplopia compared with endonasal approaches.
Mourits (2000)[70]	Single-center, randomized, double-blind, placebo-controlled study of orbital irradiation for TAO.	60 patients with severe TAO.	30/60 underwent radiotherapy (20 Gy in 10 fractions) and 30/60 had sham irradiation.	60% of treated versus 31% of sham patients had improved diplopia at 24 wk ($p = 0.04$).	Diplopia improves in moderate-to-severe TAO with orbital irradiation therapy. There is little to no reduction of exophthalmos or lid swelling.
Prummel (1993)[78]	Single-center, randomized, double-blind, placebo-controlled study comparing oral steroids and retrobulbar irradiation.	56 patients with moderate-to-severe TAO.	28/56 received 3 mo oral prednisone with sham irradiation and 28/56 received 20 Gy retrobulbar irradiation and placebo capsules.	Both groups demonstrated a similar response to treatment at 24 wk. Eye motility improved in the irradiation group only ($p = 0.003$).	Oral steroids and retrobulbar irradiation are equally effective as first-line therapy.

CAS, clinical activity score; CON, compressive optic neuropathy; EOM, extraocular muscle; IVS, intravenous steroids; QOL, quality of life; SD, surgical decompression; TAO, thyroid-associated orbitopathy; TSI, thyroid-stimulating immunoglobulin; TBII, thyroid-stimulating hormone receptor inhibitory immunoglobulin; VA, visual acuity.

18 Traumatic Optic Neuropathy: An Evidence-Based Perspective on Management

Harmeet S. Gill MD, FRCSC and Robert A. Kersten MD, FACS

Introduction

Approach to Traumatic Visual Loss

Patients can undergo visual loss after a traumatic insult to the eye or periorbital structures. First and foremost, we recommend establishing whether the injury falls into one or more of the following categories in order to guide management.

A. Globe injury. (Fig. 18.1A)
   The management is primary repair of involved structures.
B. Optic nerve dysfunction. **look for decreased visual acuity and afferent pupillary defect*
   1. *Orbital compartment syndrome*. Signs of elevated orbital pressure include proptosis, high intraocular pressure, decreased eye motility, and decreased retropulsion ("tight" orbit). This may occur secondary to hemorrhage, edema, or air within the orbital space. The two main mechanisms of injury to the optic nerve are ischemic compartment syndrome (when orbital pressure exceeds mean arterial pressure) and mechanical optic nerve "stretch" from globe proptosis (Fig. 18.1B).

The management is *immediate* lateral canthotomy and cantholysis.

   2. *Direct optic nerve injury*. Secondary to bone fragment or foreign body. (Fig. 18.1C).
   3. *Indirect optic neuropathy*. Little anatomical disruption of orbital structures.

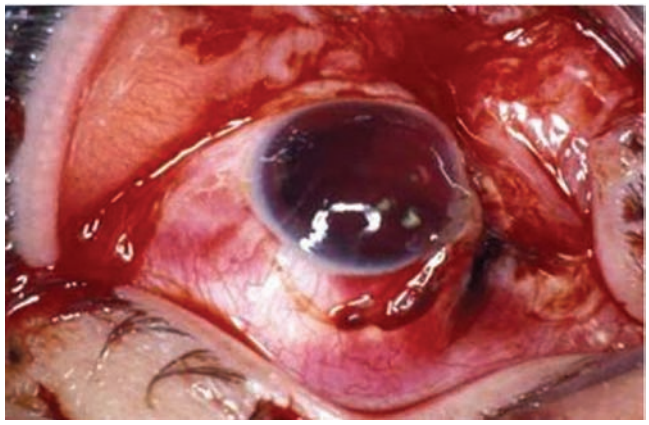
The purpose of this chapter is to provide guidelines regarding management for direct and indirect traumatic optic neuropathy.

Demographics

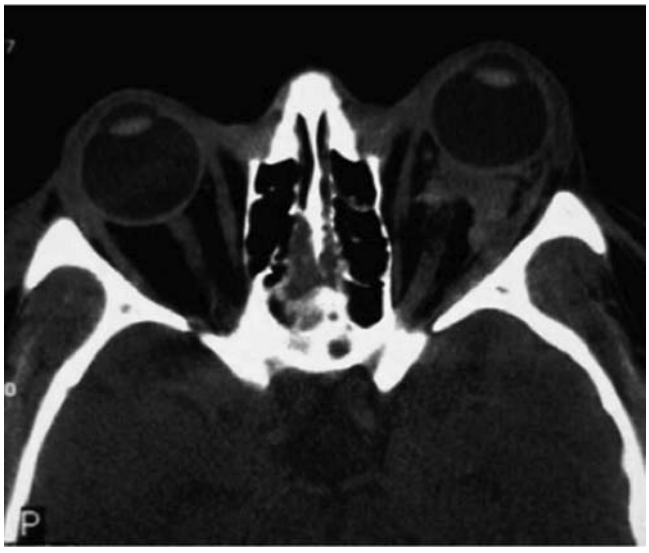
Any optic nerve dysfunction secondary to trauma is referred to as traumatic optic neuropathy (TON). This is an uncommon but severe cause of visual loss that can follow blunt or penetrating injury to the orbital or craniofacial structures. Most patients are young males in their early thirties.[1] Common causes include high-speed vehicle collisions, falls, and physical assault with various weapons.[2] Up to 20% of ocular combat injuries are associated with TON.[3] The incidence varies between 0.5% and 5% after closed head injury, and rates are higher in patients with concomitant zygomaticomaxillary complex (ZMC) and other facial fractures.[4–6] The prevalence of TON is about one in one million persons.[2]

Clinical Features

The majority of patients with TON will suffer immediate visual decline while up to 10% report delayed or progressive loss of vision.[1,7] Visual deficit can present as decreased acuity, color vision, or variable field defects. Most patients will have 20/400 or worse acuity,[8] and up to one-third may present with no perception of light.[2] However, patients may be unconscious or unresponsive in the setting of severe head trauma precluding assessment of visual acuity. The presence of an afferent pupillary defect and otherwise normal ophthalmic examination is suggestive of TON. Pupillary responses can be difficult to assess in the presence of analgesic opioids causing miosis. It is imperative that reversible causes of vision loss (i.e., retinal



A



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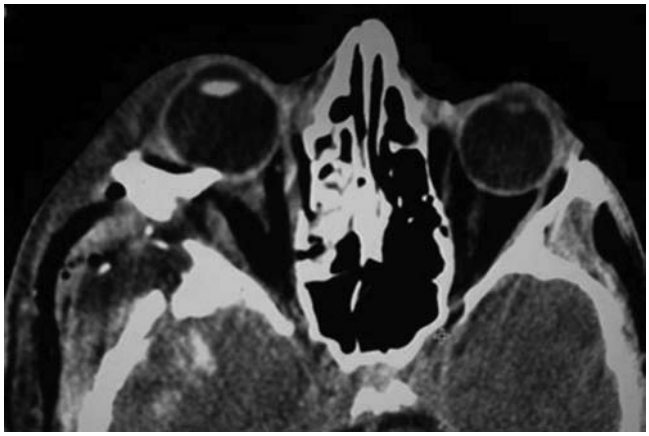


C

FIGURE 18.1 **(A)** Traumatic globe rupture with full-thickness scleral defect. **(B)** Axial computed tomographic (CT) image demonstrating left orbital hemorrhage, proptosis, and mechanical stretching of the optic nerve. **(C)** Axial CT image showing right intraorbital bone fragment.

detachment, retrobulbar hemorrhage) and neurologic causes of a nonreactive, mydriatic pupil are ruled out. Visual evoked potential testing (pattern or flash) has been studied as a surrogate for visual acuity in TON patients but is often unrecordable and of limited benefit.[9,10] Poor prognosticators for visual recovery include no light perception (NLP)

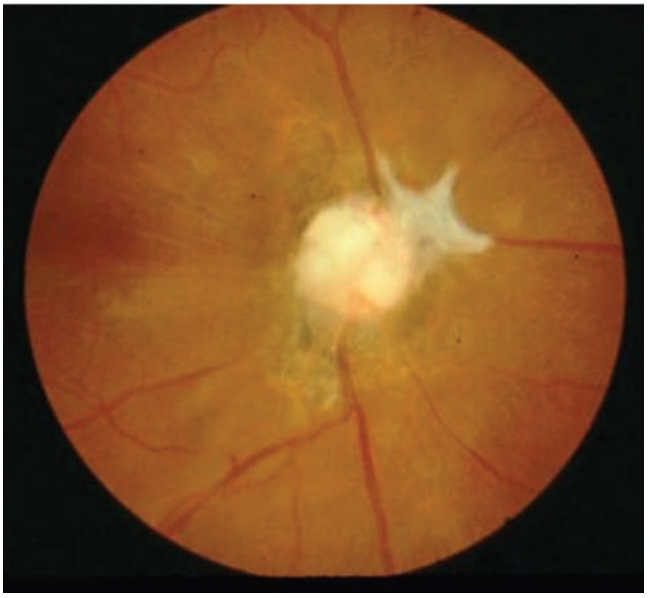


FIGURE 18.2 Optic nerve atrophy and axonal loss is seen 4 to 6 weeks after trauma.

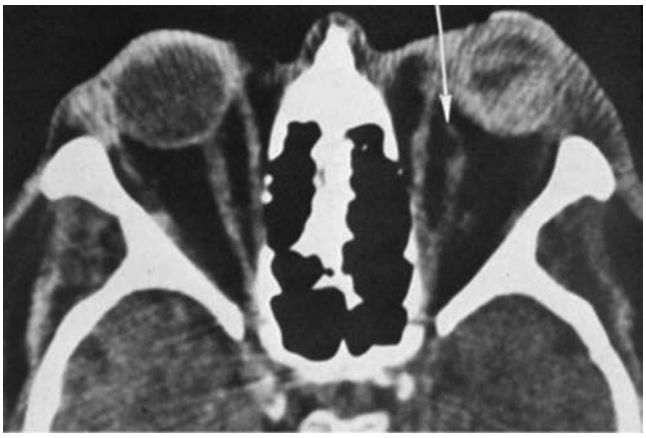
at presentation[11] and an afferent pupillary defect greater than 2.1 log units.[12] Patients with loss of consciousness or lack of visual improvement after 48 hours also tend to have a poor visual prognosis. In the acute setting, the appearance of the optic nerve will vary depending on the anatomical site of involvement but after 4 to 6 weeks demonstrates signs of atrophy and axonal loss (Fig. 18.2).[4] Reduced retinal nerve fiber layer thickness can be detected at this time using optical coherence tomography.[13,14]

Mechanisms of Injury

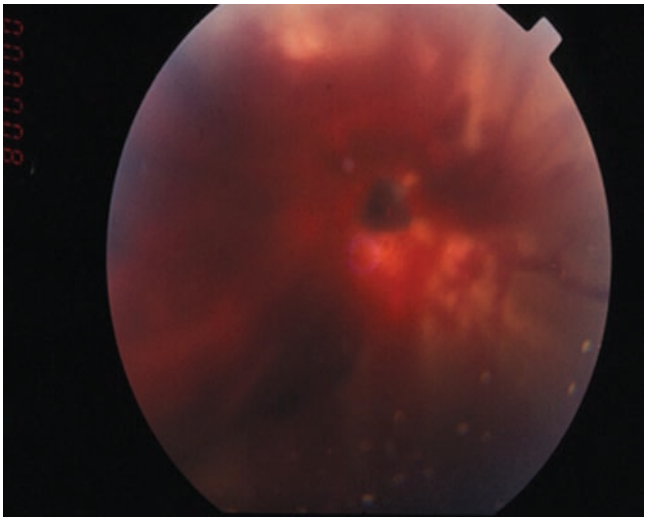
The mode of injury (direct versus indirect trauma) is often used to classify TON. Direct TON results from a penetrating orbital foreign body or bone fragment that transects or impinges on the optic nerve (Fig. 18.1C). These patients usually suffer immediate, severe, and irreversible loss of vision. In the absence of obvious anatomical disruption, more subtle injury to the optic nerve microvasculature and/or shearing injury to axons occurs.[15,16] This is called indirect TON, which typically results from blunt trauma to the frontal bone at the supraorbital rim with transmission of force across the orbital roof concentrated at the orbital apex and optic canal combined with deceleration injuries. An example is a patient hitting his or her head on the pavement after a fall. Most clinical studies focus on the management of indirect TON, which is much more common and typically portends a better visual prognosis than direct TON. Other mechanisms causing optic nerve axonal loss, common to both direct and indirect trauma, include avulsion, compression, swelling, ischemia, and concussion. A computed tomographic (CT) scan with 1 mm cuts of axial and coronal planes of the orbit (and/or head, facial bones) is helpful in the setting of orbitofacial trauma and can help differentiate direct versus indirect TON. The optic canal is formed by the sphenoid bone, which can be fractured in up to 50% to 80% of TON cases.[17] The presence of blood in the adjacent sphenoid sinus raises the clinical suspicion of an optic canal fracture. The falciform anterior clinoid process on an axial CT series is a useful landmark to help identify the optic canal.

Optic Nerve Anatomy

Knowledge of the anatomy and course of the optic nerve and its relationship with other orbitocranial structures is necessary



A



B

FIGURE 18.3 **(A)** Axial computed tomographic (CT) image showing complete avulsion of the left optic nerve from the globe. **(B)** Intraocular hemorrhage seen during funduscopic examination.

to understand why TON occurs and how it is treated. The optic nerve can be separated into anterior (optic nerve head) and posterior (intraorbital, intracanalicular, and intracranial) segments. Injury to the anterior optic nerve or its blood supply may occur at its point of insertion into the eye after forceful globe rotation. With complete or partial avulsion of the nerve from the globe, an intraocular hemorrhage at the nerve head is seen during funduscopic examination (Fig. 18.3). Injury to the nerve anterior to the central retinal artery entry point will disrupt retinal circulation causing occlusive retinopathy or retinal hemorrhages. More posterior injury is, however, much more common and the optic nerve and fundus will appear normal. The disruptive forces following closed head injury are concentrated at the orbital apex and optic canal, making the intracanalicular optic nerve the most vulnerable segment. The dural sheath that surrounds this segment is tightly adherent to the periosteum within the optic canal. Axonal loss may result from the primary insult of bony impingement following an optic canal fracture, shearing injury, or disruption of nerve microvasculature. A secondary insult then follows. Optic nerve swelling within the canal produces a localized compartment syndrome that precipitates ischemic damage and further axonal loss.[7] The intracranial optic nerve segment

lies near the falciform dural fold and is perhaps the second most common site of injury. This segment is more commonly implicated in cases of bilateral TON.[18]

Goals of Treatment

The primary insult typically results in irreversible axonal death. The overriding goal of intervention is to improve or preserve visual function by minimizing the effect of secondary insults, including optic nerve swelling, vasospasm, ischemia, and release of neurotoxic factors. The four main options are high-dose systemic corticosteroid therapy, optic canal decompressive surgery (OCDS), a combination of steroids and surgery, or observation alone (no treatment). There is sound biologic rationale for considering these options. High-dose systemic corticosteroids decrease inflammatory mediators and surgical expansion of the bony optic canal creates space for a swollen nerve, minimizing the damaging effect of compressive forces. However, some data suggest that such interventions may actually do more harm than good. Furthermore, there are relatively high rates of spontaneous visual recovery (50% or greater) following indirect TON with observation alone. Steroids and surgery have not been shown to produce significantly better results. Neuroprotective therapies are emerging that may prove effective for TON, superseding both steroids and surgery.

There remains a lack of consensus regarding which management option for TON is best. It is difficult to draw meaningful conclusions from the literature, which is mostly comprised of small, retrospective studies without controls and with differing recruitment criteria, treatment regimens, time to diagnosis of TON, and initiation of therapy. The purpose of this chapter is to provide clinically relevant guidelines regarding the treatment of TON based on the best available evidence. In each section, the implications for practice are highlighted prior to a detailed review of the relevant studies. Areas of future research are summarized at the end of each section.

High-Dose Systemic Corticosteroid Therapy

The main rationale for using high-dose corticosteroid therapy in TON is to reduce optic nerve swelling and prevent axonal loss. Additional benefits may include antioxidant, free radical scavenging, prevention of lipid peroxidation, or other neuroprotective effects on the injured nerve.[19,20] The most commonly studied corticosteroid for TON is intravenous (IV) methylprednisolone. Dexamethasone has also been used by some groups.[17,21] There are several systemic risks of high-dose corticosteroids that include sepsis, pneumonia, gastrointestinal bleeding, hepatic failure, and wound complications. Rarely, serious life-threatening infections (i.e., mucormycosis) have been reported after high-dose steroid therapy for TON.[22] Some early experimental animal models of spinal cord injury showed that methylprednisolone improves neurologic recovery.[23] The therapeutic doses used in such studies helped develop protocols for the clinical studies that followed. In 1982, Anderson et al. first reported the use of corticosteroid therapy for six patients with TON.[24] Half demonstrated visual recovery, but this study provided only anecdotal evidence. Several additional small, retrospective case series without controls followed, which also suggested that steroids may be an effective treatment option for TON.[17,25,26] However, there was a lack of consensus regarding steroid type, dosage, and timing. In 1990, a large prospective study was published in the neurosurgical literature that validated high-dose steroid therapy as a treatment option for traumatic nerve injury.

The National Acute Spinal Cord Injury Studies

In 1985, the National Institutes of Health (NIH)-sponsored National Acute Spinal Cord Injury Studies (NASCIS) II trial[27] was initiated to determine if high-dose corticosteroid therapy improves neurologic recovery following acute spinal cord injury (ASCI). This multicenter, randomized, double-blind, placebo-controlled trial recruited 487 patients

that suffered ASCI within 12 hours who met the inclusion criteria. Patients with involvement of the nerve root or cauda equina only, those with gunshot wounds, pregnant patients, those addicted to narcotics, those receiving maintenance steroids for other reasons, those under 13 years of age, those having already received corticosteroids pre-randomization, or those suffering life-threatening morbidity were excluded. Patients were randomly assigned to one of three treatment arms within 12 hours after injury: high-dose methylprednisolone (162/487), naloxone (154/487), or placebo (171/487). The treatment protocol for IV methylprednisolone consisted of a loading dose (30 mg/kg) over 15 minutes followed by a continuous infusion of 5.4 mg/kg/hour for 23 hours. Naloxone is an opiate receptor antagonist that was given as a 5.4 mg/kg bolus followed by 4 mg/kg/hour for 23 hours. Motor and sensory functions were assessed by systemic neurologic examination at admission, 6 weeks and 6 months after injury. At 1-year follow-up, the mean difference in motor scores between steroid and placebo groups was significant (5.20, 95% confidence interval [CI] 0.53–9.87). This was not the case for sensory scores (2.41, 95% CI -1.72–6.54). Treatment benefit was limited to patients who began methylprednisolone therapy within 8 hours after injury. There was a trend toward higher rates of gastrointestinal bleeding and wound infections in the steroid group that was not statistically significant. The investigators concluded that high-dose methylprednisolone improves neurologic recovery after traumatic ASCI compared with placebo when administered within 8 hours of trauma. However, this study suffers several important limitations. The 8-hour stratification was based on post hoc data analysis of a subgroup of patients (129 of 487, 26%). When this stratification is removed, the methylprednisolone group actually had worse overall outcomes compared with placebo.[28,29] Other concerns include lack of proper randomization, with a bias in favor of steroid therapy. Finally, although neurologic improvement was statistically significant, it resulted in only minimal clinical improvement in daily functioning. The Third National Acute Spinal Cord Injury Study (NASCIS III) found that patients treated within 3 hours of injury could be maintained on continuous IV infusion for 24 hours, while those treated within 3 to 8 hours after injury benefited from 48 hours of continuous IV infusion.[30] This study found an increased risk of sepsis and pneumonia in the steroid group.

Extrapolating National Acute Spinal Cord Injury Studies to Traumatic Optic Neuropathy Management

The results of NASCIS II were extrapolated to TON management by the ophthalmic community leading to widespread use of high-dose corticosteroids. From 1990 to 2010, 43 case series (each with a minimum of 10 participants with TON) have been published.[31] From the cumulative 1,906 participants identified in these studies, 76% were treated with corticosteroid therapy either alone or in combination with OCDS. Drawing meaningful conclusions from the published case series is difficult because of numerous methodologic flaws. These include small sample sizes, retrospective analysis, lack of randomization, unknown time interval between injury and treatment initiation, and lack of consistent visual function assessment and follow-up. In the older studies, patients were treated relatively late postinjury (i.e., weeks) and had reportedly worse outcomes compared with newer studies, in which patients were treated more rapidly (i.e., hours to days) from injury onset. A debate regarding whether or not steroids should be used in TON has persisted. In addition to equivocal clinical evidence, the biologic rationale for using steroids is also questionable. The optic nerve is a white matter axonal tract whose cell bodies reside in the retina while the spinal cord is a mixed axonal tract made up of both white and grey matter. To clarify whether or not steroids are effective for TON, a large, multicenter, prospective study was organized in 1994 by 76 investigators in 16 countries known as the International Optic Nerve Trauma Study (IONTS).[1]

International Optic Nerve Trauma Study

The main purpose of this study was to determine whether high-dose corticosteroid therapy

or OCDS improves visual recovery after indirect TON.[1] It was designed as a multicenter, prospective, randomized clinical trial but converted to a nonrandomized, comparative interventional study after 2 years due to lack of enrollment. Participants comprised 133 patients with indirect TON (127 unilateral, 6 bilateral) that were evaluated within 3 days and treated within 7 days following injury. The three treatment arms for unilateral TON patients were corticosteroid therapy (85/133), OCDS (33/133), or observation (9/133). Methylprednisolone regimens were defined as megadose (greater than 5,400 mg/day), very high dose (2,000–5,400 mg/day), high dose (500–1,999 mg/day), moderate dose (100–499 mg/day), and low dose (less than 100 mg/day). Most patients received either a megadose (40%) or a very high dose (18%) regimen, and all of the patients in the surgical treatment arm, except one, received concomitant steroids; 104 cases were available for follow-up at 1 month and 40 cases at 6 months. The main outcome measure was improvement in best-corrected visual acuity (BCVA) after adjusting for baseline. BCVA improved by 3 lines or more in 52% of patients in the steroid group, 32% of patients in the surgery group, and 57% of patients in the observation group ($p = 0.22$). Dose or timing of steroid therapy was not associated with probability of visual recovery. The investigators concluded that neither corticosteroids nor OCDS had significantly better outcomes than observation alone. The most important criticism of this study is the bias toward treatment (94% of patients received corticosteroids at varying doses).[31] There was also a lack of uniform steroid dosing, timing of treatment, and indication for OCDS. Other case series have similarly found that 40% to 60% of patients with TON improve with steroids,[17,32,33] a rate comparable to spontaneous recovery without treatment.

Because the results of IONTS were inconclusive, a single-center, randomized, double-blind, placebo-controlled study was done by Entezari et al. in 2007 to determine if high-dose methylprednisolone therapy is better than observation alone for TON.[34] Patients with indirect TON evaluated within 7 days were enrolled. Unconscious patients, those with penetrating trauma, direct TON, hazy ocular media, presence of blow-out fracture, and candidates for OCDS were excluded. From 31 eligible participants, 16 received steroids and 15 placebo. Each participant was randomly assigned to either the placebo or the treatment arm. Treatment consisted of IV methylprednisolone (250 mg every 6 hours for 3 days) followed by oral prednisone (1 mg/kg daily for 14 days). Participants and clinicians performing ophthalmic examinations were masked to treatment assignment. Mean BCVA by logarithmic of the minimum angle of resolution (logMAR) was measured at presentation and at the 3-month follow-up. Recovery of visual acuity was defined as a decrease of at least 0.40 logMAR units after 3 months. Three-month follow-up data was available for all 31 participants. The mean final BCVA was 1.78 +/– 1.23 logMAR (Snellen equivalent 20/1,205) in the placebo group compared with 1.11 +/– 1.14 logMAR (Snellen equivalent 20/258) in the steroid group, which was not statistically significant ($p = 0.13$). The mean BCVA improved by 0.40 logMAR in eight eyes (53.3%) in the placebo group and in 11 eyes (68.8%) in the steroid group, which was not statistically significant ($p = 0.38$). The authors concluded that a high rate of spontaneous visual recovery occurs and there is no evidence that steroids provide any additional benefit compared with observation alone. The main limitations of this study were a relatively small sample size and the issue of many patients receiving treatment days after injury, at which point steroids may confer less benefit than an earlier intervention.

Cochrane Review: Steroids for Traumatic Optic Neuropathy

In 2011, Yu-Wai-Man and Griffiths performed a systematic review of randomized controlled trials (RCTs) to determine whether steroids are effective and safe in TON based on the best available evidence.[35] Trials were included if patients were diagnosed with either direct or indirect TON. Bilateral cases were excluded. Only RCTs for TON treated with the following regimens were included: 1. any steroid regimen versus

no treatment; 2. any steroid regimen versus any form of surgical optic nerve decompression, and 3. any steroid regimen versus a combination of steroids and surgery. The primary outcome measure was number of lines of visual acuity gained or lost at 3 and 6 months follow-up. Snellen ratios were converted to logMAR decimal values. Secondary outcome measures included other validated tests of visual function, adverse outcomes related to treatment, and validated quality-of-life measures. The authors searched databases including CENTRAL, MEDLINE, EMBASE, LILACS, mRCT, ClinicalTrials.gov, and Web of Science CPCI-S. There were no language or date restrictions in their search for trials and the last search was on November 23, 2010. Other resources were searched including reviews and book chapters and contacting trial investigators and experts to identify additional published and unpublished studies. Two review authors independently extracted data from and appraised the studies for methodologic quality. The risk for bias was assessed for parameters including generation of randomization sequence, allocation concealment, masking (blinding) clinicians, and extent of follow-up for each study. A total of 501 references were identified after deduplication. The only study that met inclusion criteria was by Entezari et al.[34] This study was graded as having a low risk of bias. Based on this review, the authors found no convincing evidence that steroids provide any additional visual benefit in TON. Similarly, Lee et al.[2] have studied epidemiologic data in the United Kingdom on TON incidence, management, and visual recovery and found no significant benefit of steroid or surgical therapy. They highlight a trend among physicians toward conservative management.

Steroids are Dangerous in Patients with Traumatic Brain Injury

In 2005, the Corticosteroid Randomization After Significant Head Injury (CRASH) study[36,37] by Edwards et al. was published. This was a multicenter, randomized, double-blind, placebo-controlled study whose purpose was to determine whether high-dose corticosteroid therapy is effective and safe in patients with acute head trauma. Adults with head trauma and a Glasgow Coma Scale score of 14 or less presenting within 8 hours of injury were recruited. This international collaboration planned to enroll 20,000 patients, but the data monitoring committee disclosed unmasked results leading to no further recruitment after 10,008 patients. Participants were randomly assigned to receive a 48-hour infusion of IV methylprednisolone (2 g over 1 hour loading dose followed by 0.4 g/hour for 48 hours) or placebo. The primary outcome measures were death within 2 weeks of injury and death or disability at 6 months. Analyses were done on an intention-to-treat basis. The effect measure used was relative risk (RR) with 95% CI for the overall risk and 99% CI for the results of subgroups. Homogeneity in treatment effects within subgroups was assessed with a chi-squared test on two degrees of freedom at a 5% significance level. Data at 6 months were obtained for 9,673 (96.7%) patients. The risk of death from all causes within 2 weeks was higher in the steroid group (21.1% versus 17.9%, $p = 0.0001$). This relatively higher mortality rate was independent of injury severity ($p = 0.22$) and time postinjury ($p = 0.05$). At 6 months follow-up, the risk of death was higher in the steroid group compared with placebo (25.7% versus 22.3%; RR 1.15, 95% CI 1.07–1.24, $p = 0.0001$). This was also true for the risk of death or severe disability (38.1% versus 36.3%; RR 1.05, 95% CI 0.99–1.10, $p = 0.079$). The timing or severity of injury was not significant. The authors concluded that high-dose corticosteroid therapy in the setting of acute traumatic brain injury is associated with increased rates of mortality and disability. A mechanism that explains why this occurs remains unknown. A Cochrane review of corticosteroids for acute traumatic brain injury had similar conclusions to CRASH.[38]

The results of the CRASH trial have largely resulted in the abandonment of high-dose corticosteroids in the setting of acute brain injury because of an increased mortality rate. These findings make it

particularly important to look for evidence of concomitant acute head trauma prior to considering therapeutic options for TON. In addition to the lack of supportive clinical data, several recent animal models of TON have shown either no effect[39] or a detrimental effect of high-dose methylprednisolone on retinal ganglion cell (RGC) survival and axonal regeneration.[40–42] In fact, Steinsapir et al. found that high-dose methylprednisolone exacerbated axonal loss following experimental optic nerve crush injury in rats in a dose-dependent fashion ($P < 0.02$).[41] Another animal model of high-dose methylprednisolone for optic neuritis also showed greater axonal loss in the steroid group compared with controls.[43] One experimental study showed that head trauma preceding optic nerve injury confers a neuroprotective effect to optic nerve axons, which is lost after administration of high-dose methylprednisolone.[44]

Implications for Practice

There is a relatively high rate of spontaneous visual recovery following indirect TON and no convincing evidence that high-dose corticosteroid therapy is more effective than observation alone. High-dose corticosteroid therapy is associated with an increased mortality rate in the setting of acute traumatic brain injury.

Areas of Future Research

It is unlikely that a large RCT evaluating high-dose corticosteroid therapy for TON will be undertaken given the significant risk profile and limited benefit that has been demonstrated thus far. Future clinical or animal studies that clearly demonstrate the harmful effects of high-dose corticosteroids may prove more useful in settling the debate regarding whether or not this therapy should be used for TON.

Optic Canal Decompressive Surgery

The optic nerve sheath is firmly adherent to the dural lining of the optic canal. Blunt trauma to the skull transmits deformative forces that are concentrated at the orbital apex and optic canal. These can damage the intracanalicular optic nerve segment from swelling, which exacerbates axonal loss through direct pressure and ischemia. A common rationale for performing OCDS is to reduce the pressure effect of tissue swelling on optic nerve axons. As previously discussed, up to 50% to 80% of TON cases may be associated with an optic canal fracture.[17] Some argue that TON following an optic canal fracture is an automatic indication for surgical intervention,[45] although the presence of a fracture has not been associated with poor visual recovery.[46,47] For some patients with TON and canal fracture, CT imaging will be suggestive of bone fragment transection or impingement of the optic nerve. If the fragment has transected the nerve, the injury will likely have resulted in acuity at or near NLP, a pronounced afferent pupillary defect, and irreversible loss of vision. The risks of surgery will outweigh potential benefits.[48] However, it can be difficult to differentiate transection from impingement based on the clinical exam alone. There are several case reports of bone fragment removal and subsequent visual recovery, likely because the fragment did not transect the nerve. Wu et al.[49] report such a case of NLP vision after bony impingement from an iatrogenic optic canal fracture during sinus surgery that improved to 20/50 with a combination of OCDS, steroids, and nerve growth factor. Nazir et al.[50] report a similar case in which the patient recovered vision from NLP to 20/20 after bone fragment removal and steroid therapy. These and other case reports provide anecdotal evidence supportive of bone fragment removal for iatrogenic TON following sinus endoscopic procedures. However, vision might have improved spontaneously in these cases without any intervention.[1] The presence of a hematoma within the optic nerve sheath tends to respond favorably to sheath fenestration or canal decompression, in which case surgery may be preferable to observation.[2,8] Any decision to intervene surgically for TON requires thoughtful analysis because many patients will recover vision without intervention and

the risks of operating near the intracanalicular optic nerve segment are significant. These include further injury to the optic nerve or its nutrient vessels, cerebrospinal fluid (CSF) leak, meningitis, injury to the carotid artery, and cavernous sinus hemorrhaging.[21]

Since the 1950s, there have been several anecdotal reports and small, retrospective case series showing conflicting results following OCDS for TON.[25,51,52] Cook et al.[33] performed a meta-analysis of 46 studies in the late 1990s and concluded that corticosteroids, OCDS, or a combination of both was beneficial for TON. However, their inclusion criteria were criticized because older reports stratified time to treatment in days, weeks, or months, whereas more recent reports were within hours.[31] As previously discussed, the IONTS[1] found OCDS was no better than observation alone. Three of 33 participants (10%) in the surgical treatment arm who underwent external OCDS developed a postoperative CSF leak, one of whom also developed meningitis. Jiang et al. reported that dural exposure occurred in 5% of patients who underwent endoscopic OCDS.[48]

Combination Therapy: Steroids and Optic Canal Decompressive Surgery for Traumatic Optic Neuropathy

Yang et al.[53] performed a single-center, retrospective comparative cohort study to determine whether combination therapy with OCDS and steroids is more effective than steroids alone. The medical records of 42 consecutive patients with TON after maxillofacial trauma were reviewed. Patients with penetrating ocular injuries or optic nerve avulsion were excluded. All patients were treated with IV methylprednisolone for 3 days following diagnosis (NASCIS II protocol). If visual acuity did not improve after the third day, OCDS (endoscopic) was recommended to the patient. All patients were followed for at least 3 months. The rate and degree of visual recovery considering initial visual acuity (IVA) at baseline and last follow-up were determined. Twenty-four of 42 patients (57%) received steroids combined with OCDS. The two groups were defined as nonsurgical (steroids alone) or surgical (combined therapy). Data gathered included patient age and gender, mechanism of injury, treatment modalities, IVA, radiologic presence of optic canal fracture, time elapsed before treatment, and length of follow-up. Visual acuity was converted into logMAR units. An equation was developed to define visual recovery as a percentage. They found that the severity of TON was greater in the surgical than the nonsurgical group ($p = 0.14$). IVA was a statistically significant factor that affected TON outcome ($p = 0.006$). In both groups, there was a strong tendency for patients without fracture to display a better improvement rate than those with fracture (51.6% versus 18.2%; $p = 0.08$). Regardless of the treatment type, patients treated within 7 days improved more than those treated later (61.88% +/– 20.41% versus 38.14% +/– 26.50%; $p = 0.56$). Patients in the surgical group with NLP had better improvement in rate and degree (31.3%; 59.34 +/– 22.18%) than those in the nonsurgical group (0%, 0%; $p = 0.272$). The authors concluded that IVA is the most important predictor of visual recovery for TON. They also suggest that patients presenting with NLP may benefit more from OCDS. Important limitations of this study include a small sample size, retrospective analysis, and selection bias. All patients received corticosteroid treatment, and rates of spontaneous visual recovery are unknown in this cohort.

Li et al.[54] performed a similar study to determine whether endoscopic OCDS combined with steroids is more effective than steroids alone for TON. This was a single-center, retrospective comparative cohort study and medical records of 237 patients with direct and indirect TON were reviewed. All patients were treated with high-dose IV dexamethasone (30 mg/day) for 3 days followed by 20 mg/day for 3 days and 10 mg/day for 3 days. Patients were separated into two groups based on immediate versus progressive visual loss. Group A comprised 108 patients suffering immediate blindness after trauma, of whom 89 consented to endoscopic OCDS. Group B comprised 129 patients with

gradual visual loss after trauma, of whom 87 consented to endoscopic OCDS. The main outcome measure was visual improvement, defined as a gain of 2 lines or more on the Snellen chart or improvement from light perception to hand motion, or hand motion to finger-counting. Of 237 patients recruited, all were treated with steroids and 176 also consented to endoscopic OCDS. The chi-square statistic was used to compare rates of visual recovery between the two groups. Patients were followed for at least 3 months postintervention. The total rate of visual improvement was 55% (96/176) in the combined group and 51% (31/61) in the steroid group, which was not statistically significant ($p = 0.615$). Rate of visual recovery in Group A patients was 38% (41/108) and in Group B patients was 67% (86/129) ($p = 0.001$). Of the 176 patients in the combined group, 141 underwent surgery within 7 days and showed a visual recovery rate of 60% (85/141), while 35 underwent surgery after 7 days and showed a visual recovery rate of 31% (11/35; $p = 0.002$). Major complications included severe bleeding after ophthalmic artery injury (one case, 0.6%), CSF rhinorrhea (three cases, 1.7%), and orbital infection (two cases, 1.2%), all of which resolved with appropriate management. No patient in their series demonstrated decreased vision after intervention. The authors concluded that endoscopic OCDS is safe and effective for TON. It should be employed with steroids as soon as possible for patients demonstrating progressive vision loss but may be less beneficial in those with immediate blindness. Important limitations of this study include a lack of randomization, unequal group sizes, retrospective analysis, selection bias, and definition of visual recovery. Furthermore, the time postinjury to surgical intervention varied greatly (days to months). The rate for spontaneous visual recovery without intervention is not known for this cohort. It is unclear whether the two groups (A and B) were derived after post hoc analysis. Lastly, cases of direct and indirect TON were combined. Some groups advocate that delayed endoscopic OCDS may be useful as a "salvage" operation when there is poor response to steroids and no demonstrable visual recovery,[55] while others find it more helpful earlier (within 72 hours of steroid therapy while visual loss is progressive).[56]

Cochrane Review: Surgery for Traumatic Optic Neuropathy

In 2011, Yu-Wai-Man and Griffiths[57] performed a systematic review of RCTs to determine whether surgical intervention is effective and safe for TON. All RCTs of TON in which any form of surgical intervention either on its own or in combination with steroids was compared with steroids alone or no treatment were included. These trials comprised patients with either direct or indirect unilateral TON. Studies of bilateral TON were excluded. The authors searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1950 to December 2010), EMBASE (1980 to 2010), LILACS (1982 to 2010), the *meta*Register of Controlled Trials (*m*RCT), ClinicalTrials.gov, NRR (2007 Issue 2), and reference lists of other reviews and book chapters on TON. They also contacted researchers in the field. There were no date or language restrictions in the electronic searches for trials. The electronic databases were last searched on December 2, 2010. Two authors independently assessed the titles and abstracts identified from the search strategy. However, no studies were found that met the inclusion criteria. The authors concluded that there is a relatively high rate of spontaneous visual recovery and no evidence that surgical decompression of the optic canal provides any additional benefit.

Summary

Overall, the OCDS literature is comprised of small, retrospective case series.[26,33,54] The main limitations of the available literature include a selection bias (tendency for patients with poorer baseline visual acuity [i.e. NLP] to be offered surgery), inclusion of direct TON cases which portend a worse overall prognosis compared with indirect TON, and use of concomitant corticosteroid therapy precluding ascertainment of the surgical effect alone. Furthermore, the wide range of surgical techniques described makes it difficult to compare results. Both

transcranial and extracranial (transethmoidal, transantral-ethmoidal, transsphenoidal) approaches for decompression of the optic canal may result in visual recovery in up to 70% of TON cases.[1,58,59] Some groups report better results with incision of the optic nerve sheath during OCDS.[60] The newer endoscopic extracranial techniques have lowered complication rates for both adults and children with TON.[21,54] The decision regarding which technique should be employed is usually based, however, on surgeon preference and experience more than evidence.[57] Patients tend to be offered a surgical intervention if they have poor baseline visual acuity or fail to improve with steroids, which underestimates potential benefits of OCDS.

Implications for Practice

There are no high-quality studies that show OCDS is superior to observation alone for improving visual recovery in TON. There are serious surgical risks including further optic nerve injury, CSF leak, carotid artery injury, cavernous sinus hemorrhaging, and meningitis. Certain clinical scenarios such as presence of an optic nerve intrasheath hematoma or bone fragment impingement may be more likely to benefit from surgical intervention.

Areas of Future Research

A prospective RCT comparing OCDS to observation alone is required to know whether or not this intervention is appropriate. However, patient recruitment for adequate power, universal surgical technique and expertise, and standardized timing to intervention across multiple centers are significant barriers to this endeavor.

Emerging Neuroprotective Therapies

Over the past two decades, there have been considerable advances in our understanding of cellular and molecular pathways involved in neuroprotection. Research mostly comes from the study of injured axonal tracts of the spinal cord and brain, vascular or age-related changes in brain matter, and various optic neuropathies such as hereditary, demyelinating, ischemic, glaucomatous, and traumatic. Clinical trials are currently being planned based on the promising results of various neuroprotective strategies. For example, a recent pilot study showed that IV infusion of bone marrow–derived autologous mesenchymal stem cell therapy is effective for preventing vision loss in progressive multiple sclerosis.[61] The limited efficacy of both steroid and surgical therapy for TON requires us to seek effective neuroprotective and axoprotective therapies.[62] The most promising strategies currently under investigation can be categorized as systemic neurotrophic agents, local neurotrophic agents, stem cell therapies, immunosuppressants, hormonal agents, electrical stimulation, hyperbaric oxygen, and temperature regulation.

The majority of data come from experimental animal models. For example, an optic crush study in rats showed a neuroprotective effect of transcorneal electrical stimulation.[63] An important mechanism of secondary neural tissue injury is related to glutamate excitotoxicity. Targeted agents inhibiting NMDA-mediated retinal excitotoxicity are effective at prolonging survival of optic nerve axons.[64] Numerous studies have shown a neuroprotective effect conferred by intravitreal injection of neurotrophic factors or agents that increase their concentration or efficacy. Examples of such agents that increase RGC survival after optic nerve transection include those that secrete mesenchymal stem cells,[65] induce neurotrophic factors, such as the dipeptide leucine–isoleucine (Leu-Ile),[66] or target and inhibit specific proteins like caspase-2.[67] Interestingly, human umbilical cord blood stem cells were transplanted intravitreally in rats and increased RGC survival.[68] A mouse model of optic neuritis showed that T-cell receptor ligand confers a neuroprotective effect.[69] FK506 is an immunosuppressant used for prevention of graft rejection in organ transplantation and prevents optic nerve axonal degeneration after injury.[70] Other animal models have shown that posttraumatic hypothermia provides short-term axonal protection.[71] Both local

and systemic hypothermia may be protective after traumatic brain injury by mitigating nerve swelling and ischemia.[72,73]

Attempts to translate animal research to clinical practice are currently underway. For example, erythropoietin (EPO) is a cytokine hormone that reduces neuronal apoptosis in several experimental models including optic nerve transection.[74] In their pilot study, Kashkouli et al.[75] found that IV EPO resulted in significantly greater visual recovery compared with observation alone in TON patients. Clinical studies in humans looking specifically at neuroprotective agents for TON are limited. Levodopa crosses the blood–brain barrier and is converted to dopamine, an important neurotransmitter in both the retina and the central nervous system. Administration of this agent has been shown to improve visual function in patients with amblyopia[76] and ischemic optic neuropathy[77] and in patients being treated for Parkinson's disease.[78] One study looking at the effectiveness of levodopa for TON is summarized below.

Levodopa for Traumatic Optic Neuropathy

In 2010 Razeghinejad et al.[9] performed a single-center, randomized, double-blind, placebo-controlled study to determine whether levodopa improves visual outcome of patients with indirect TON. Thirty-two adult and pediatric patients with indirect TON diagnosed within 6 days postinjury were enrolled. Patients were randomized based on the last digit of the medical record (odd digits assigned to the treatment group and the even digits to the placebo group). The treatment group consisted of 16 patients, the placebo group 10 patients, and six patients were lost to follow-up. Patients with direct TON, optic nerve avulsion, penetrating trauma, and optic canal or blow-out fractures were excluded. All patients were evaluated with pattern visual evoked potential (PVEP) testing and orbital CT scanning. All patients received high-dose methylprednisolone (one gram per day for 3 days) followed by oral prednisone (one mg/kg for 11 days, then tapered over 3 days). The treatment group received levodopa (adults: levodopa 100 mg/carbidopa 10 mg tablets, three times daily for 1 month; children: levodopa 1.5 mg/carbidopa 0.15 mg per day). The main outcome measures were BCVA converted to a logMAR scale and PVEP amplitudes. Patient demographics, exam and CT findings, treatment onset, and follow-up times were compared between groups, showing no statistically significant difference in any of these variables. They found that BCVA improved in the levodopa group after treatment (p = 0.009) but not in the placebo group (p = 0.34). BCVA after treatment in the levodopa group was 2.1 +/– 2.1 logMAR (Snellen equivalent 20/2,518) and in the placebo group was 3.9 +/– 1.2 logMAR (Snellen equivalent 20/158,866; p = 0.008). Nine patients (56.2%) in the levodopa group and one patient (10%) in the placebo group experienced improvement in visual acuity (p = 0.02). The frequency of unrecordable PVEPs was comparable in both groups (p = 0.09). For patients with NLP (54%), no significant difference was detected between groups (p = 1.00). No patients treated with levodopa complained of adverse effects related to treatment. The authors concluded that patients treated with levodopa within 6 days of injury had a better visual outcome compared with placebo. The main limitations of this study include small, unequal group sizes and the trend for the levodopa group for better pretreatment mean BCVA (p = 0.06). It remains unclear whether the treatment effect is attributable to levodopa alone or the combined effect with high-dose methylprednisolone. Optimal dose and duration of levodopa for TON is unknown.

Implications for Practice

All neuroprotective strategies are currently in the experimental stage. Potentially safe options that may be considered for select patients include levodopa and EPO therapy.

Areas of Future Research

Elucidating the detailed molecular pathways involved in axonal regeneration following traumatic and other optic neuropathies will greatly expand the treatment armamentarium. Most of this work is being done using animal models, but translation to clinical practice is occurring at an accelerated pace.

Summary and Take-Home Messages

Several of the clinically relevant studies regarding the management of TON have been summarized in chronologic order in Appendix A.

Decisions regarding the management of TON should be made on an individualized basis and a detailed informed consent regarding known risks and benefits of the various options discussed with the patient and caregivers. Direct TON typically results in severe, immediate, irreversible vision loss, and no treatment has been found effective to improve this prognosis. Baseline visual acuity is likely the most important predictor for visual recovery.[17,32,35] Spontaneous recovery of visual function following optic nerve injury is reported in 40% to 60% of patients with conservative therapy alone.[1,17,79,80]

Currently, there is no level I evidence supporting any treatment option for TON.[35,57] Barriers to high-quality evidence include the relatively low incidence of TON, difficulty with subjective visual testing, timely diagnosis, and a variable clinical course with a relatively high rate of spontaneous visual recovery. There are numerous anecdotal and retrospective reports that suggest a potential benefit of steroids or surgery, mostly limited to patients who are treated early. Drawing meaningful conclusions from such studies is difficult because of considerable variation in recruitment criteria, time elapse from trauma to therapy, mechanism and extent of injury, treatment regimen, and data collection. The large RCT that popularized high-dose steroids for ASCI when administered within 8 hours (NASCIS II)[27] demonstrated only a modest clinical benefit, and we now know that such therapy is associated with higher rates of mortality and disability in the setting of acute brain injury (CRASH).[36] Furthermore, the results of NASCIS II were extrapolated to TON, although the biologic rationale for doing so is questionable. Both controlled and uncontrolled trials of this regimen have shown no benefit for TON. The largest prospective case series (IONTS)[1] and the only randomized, controlled study[34] of high-dose corticosteroid therapy for TON have shown no better visual recovery outcomes than observation alone. Experimental optic nerve crush injury studies in animals suggest that high-dose steroids actually hinder axonal regeneration. Similarly, studies have not consistently shown routine OCDS to be beneficial for TON. There are specific clinical scenarios such as presence of a hematoma within the optic nerve sheath or a bone fragment impinging on (and not transecting) the optic nerve that may respond favorably to a surgical intervention.

Although the desire to intervene in the hopes of improving visual potential may drive some practitioners to administer high-dose corticosteroids or perform OCDS in the setting of TON, the evidence suggests that such therapy may do more harm than good. We have learned from large randomized clinical trials that doing something can sometimes be worse than doing nothing. The Ischemic Optic Nerve Decompression Trial showed that optic nerve sheath fenestration was ineffective for nonarteritic ischemic optic neuropathy.[81] Similarly, the Optic Neuritis Treatment Trial showed a higher recurrence rate in patients treated by standard-dose oral corticosteroids.[82] In light of the evidence, there is an increasing trend toward conservative management for TON.[2] We agree with this approach for now until emerging neuroprotective strategies are evaluated with larger randomized controlled studies.

APPENDIX A **Summary of clinically relevant studies of treatment for traumatic optic neuropathy**

Reference	Study design/ purpose	Study participants	Treatment protocol	Outcome	Conclusions/limitations
Razegh (2010)[9]	Single-center, randomized, double-blind, placebo-controlled study to determine if levodopa improves VA in patients with indirect TON.	32 adult and pediatric patients with indirect TON seen < 6 d from injury.	All received HDS. 16/32 levodopa, 10/32 placebo, 6/32 lost to follow-up.	VA improved in 56.2% of levodopa group and 10% of placebo group ($p = 0.02$)	Levodopa is safe and effective for TON when treatment initiated within 6 d of injury. However, there are small, unequal group sizes in this study, and it remains unclear whether concurrent HDS are needed for levodopa effect.
Li (2008)[54]	Single-center, retrospective, comparative, cohort study to compare combination therapy (OCDS + HDS) with HDS alone.	237 patients with direct and indirect TON.	All received HDS. Separated into two groups based on immediate versus progressive vision loss. Patients given choice to undergo OCDS.	176/237 consented to OCDS. VA improved in 51% HDS group and 55% in combined group.	OCDS is safe and effective. However, there were lack of randomization, unequal group sizes, selection bias, and retrospective analysis.
Entezari (2007)[34]	Single-center, randomized, double-blind, placebo-controlled study to compare HDS and observation for TON.	31 patients with TON seen within 7 d of injury.	16/31 received HDS and 15/31 received placebo.	VA improved in 68.8% of HDS group and 53.3% of placebo group ($p = 0.38$)	HDS is no more effective than observation. However, the study had small group sizes and treatment was delayed by days.
Edwards (2005)[36] (CRASH)	Multicenter, randomized, double-blind, placebo-controlled trial to study if HDS are safe and effective after acute head trauma.	10,008 patients with head trauma, GCS<15, seen within 8 h of injury.	Randomly assigned to 48 h infusion of IV methylprednisolone or placebo.	Risk of death within 3 wk higher in steroid group (21.1%) versus placebo (17.9%) ($p = 0.0001$). Similar findings at 6 mo follow-up.	HDS in setting of acute traumatic brain injury is associated with increased rates of mortality and disability.
Yang (2004)[53]	Single-center, observational, retrospective case series to study HDS response followed by OCDS in those who do not improve.	42 patients with TON from maxillofacial trauma. Minimum 3-mo follow-up.	18/42 treated with HDS alone. 24/42 who did not improve underwent OCDS.	VA improved in 5/23 NLP group, 13/19 LP or better group. VA improved in 44.4% of HDS group and 41.7% of HDS + OCDS group.	Initial VA predicts prognosis. OCDS may still help patients treated > 7 d after injury with NLP. However, the study had small sample size and was nonrandomized.

Thakar (2003)[55]	Single-center, interventional, prospective case series to study effectiveness of delayed OCDS.	35 patients with TON due to blunt head trauma treated by delayed OCDS.	All patients underwent OCDS and if poor VA persisted, then received 1 mg/kg prednisolone.	VA improved in 20/26 (77%) who had LP or better VA and 0/9 (0%) who presented with NLP.	Initial NLP vision predicts poor prognosis (with late surgery). However, this study had a small sample size and no control group.
Wang (2001)[11]	Single-center, observational, retrospective case series to compare HDS, OCDS, fracture repair, and observation.	61 patients with sudden or progressive loss of VA after blunt or penetrating injury.	HDS 25/61, OCDS 7/61, fracture repair 21/61, no treatment 13/61.	VA improved in 36%. 18/40 (45%) with blunt trauma improved and 4/21 (19%) with penetrating trauma.	VA prognosis worse if orbital fracture or NLP. Fracture repair or timing of surgery did not affect prognosis. However, this was a small study without detailed protocols outlining steroid or surgical therapy.
Levin (1999) (IONTS)[1]	Multicenter, comparative, nonrandomized, interventional study to compare HDS, OCDS, and observation alone.	127 patients with TON seen within 3 d of injury and a minimum 1 mo follow-up were enrolled.	HDS 85/127, OCDS 33/127, untreated 9/127.	VA improved (3 lines or greater) in 52% of HDS group, 32% surgery group, and 57% observation-alone group.	No significant difference detected among groups. However, this study was not randomized, controlled, or masked. Variable, inconsistent treatment regimens were employed.
Mine (1999)[83]	Single-center, observational, retrospective case series to identify prognostic factors and indications for surgery.	36 patients with indirect TON (unilateral and bilateral).	Dexamethasone 24/36, combination therapy (OCDS and steroids) 12/36.	VA improved in 58.3% steroid group, 83.3% in combination group.	Visual recovery not correlated with age or presence of optic canal fracture. Initial VA of HM or better carries greater likelihood for visual recovery compared with LP or worse. However, the study had unequal and small treatment groups.

(continued)

APPENDIX A (Continued)

Reference	Study design/ purpose	Study participants	Treatment protocol	Outcome	Conclusions/limitations
Chou (1996)[32]	Single-center, observational, retrospective case series to compare steroids, steroids and surgery, and observation alone.	58 patients with TON after blunt head trauma.	Dexamethasone (po or IV) 23/58, steroids and OCDS 25/58, no treatment 10/58.	VA improved in 56.5% steroid group, 60% in combination group, none in observation group.	NLP vision predicts worse prognosis. However, the study had small treatment groups.
Bracken (1990) (NASCIS II)[27]	Multicenter, randomized, double-blind, placebo-controlled trial to determine if HDS improve neurologic recovery after SCI.	487 patients evaluated within 12 h of acute SCI.	Methylprednisolone 162/487, naloxone 154/487, placebo 171/487.	At 1 y, motor scores improved in HDS subgroup treated within 8 h of injury ($p < 0.05$).	There is mild clinical improvement in motor scores with methylprednisolone compared with placebo. However, the 8 h stratification is based on post hoc data analysis.
Fujitani (1986)[84]	Single-center, observational, retrospective case series to compare steroids to OCDS.	110 patients with indirect TON (113 eyes).	Steroid group 43/113 and OCDS group 70/113.	VA improved in 44.2% of steroid group and 47.7% of surgery group ($p > 0.05$).	Early surgery for complete visual loss recommended when TON found soon postinjury. However, the study had unequal group sizes and unclear statistical analysis.
Anderson (1982)[24]	Single-center, observational, retrospective case series to determine effectiveness of steroids and OCDS.	7 patients with unilateral vision loss after blunt head trauma.	Dexamethasone 20-60 mg IV every 6 h. OCDS in 4/7 patients.	VA improved in 3/6 patients treated with steroids and 1/4 patients treated with OCDS and steroids.	Megadose steroids may help improve vision. However, the study had no control group, small sample, and variable steroid dosing.

HDS, high-dose corticosteroids; SCI, spinal cord injury; VA, visual acuity; HM, hand motions; LP, light perception; NLP, no light perception; GCS, Glasgow Coma Scale; TON, traumatic optic neuropathy; OCDS, optic canal decompressive surgery; IV, intravenous.

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GLOSSARY

5-FU	5-Fluorouracil
ACEI	Angiotensin-converting enzyme inhibitors
ACV	Acyclovir
AGIS	Advanced Glaucoma Intervention Study
AK	Astigmatic keratotomy
ALT	Argon laser trabeculoplasty
AMD	Age-related macular degeneration
AMS	Antigen matching study
ANCHOR	Anti-VEGF for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration
APT	Acyclovir Prevention Trial
AREDS	Age-Related Eye Disease Study
ARR	Absolute risk reduction
ASVD	Acute severe vision decrease
ATS	Amblyopia Treatment Study
ATT	Argon laser trabeculoplasty-trabeculotomy
BCVA	Best-corrected visual acuity
BRAVO	Ranibizumab for the Treatment of Branch Retinal Vein Occlusion
BRVO	Branch retinal vein occlusion
BVOS	Branch Vein Occlusion Study
C_3F_8	Perfluoropropane
CATT	Comparison of Age-Related Macular Degeneration Treatment Trials
CBA	Cost–benefit analysis
CCT	Central corneal thickness
CCTS	Collaborative Corneal Transplantation Studies
CDMS	Clinically definite multiple sclerosis
CDS	Cornea Donor Study
CEA	Cost-effectiveness analysis
CI	Confidence interval
CIGTS	Collaborative Initial Glaucoma Treatment Study
CK	Conductive keratoplasty
CLE	Clear lens exchange
CLEK	Collaborative Longitudinal Evaluation of Keratoconus
CMA	Cost-minimization analysis
CME	Cystoid macular edema
CNTGS	Collaborative Normal-Tension Glaucoma Study
CNV	Choroidal neovascular membrane
COMS	Collaborative Ocular Melanoma Study
CRA	Chorioretinal anastomosis
CRAO	Central retinal artery occlusion
CRP	C-reactive protein
CRUISE	Ranibizumab for the treatment of central retinal vein occlusion
CRVO	Central retinal vein occlusion
CS	Corticosteroid
CS	Crossmatch study
CSDME	Clinically significant diabetic macular edema
CT	Computed tomography
CUA	Cost–utility analysis
CVOS	Central Vein Occlusion Study
D5W	Dextrose 5% in water
DCCT	Diabetes Control and Complications Trial
DCNVA	Distance-corrected near visual acuity
DME	Diabetic macular edema
DRS	Diabetic Retinopathy Study
DRVS	Diabetic Retinopathy Vitrectomy Study
DS	Deep sclerectomy
EDIC	Epidemiology of diabetes interventions and complications
EFP	Extra-retinal fibrovascular proliferation
EGPS	European Glaucoma Prevention Study
EKT	Epithelial Keratitis Trial
EMGT	Early Manifest Glaucoma Trial
ERG	Electroretinogram

ETDRS Early Treatment Diabetic Retinopathy Study
EVA Electronic visual acuity
EVS Endophthalmitis Vitrectomy Study
FAZ Foveal avascular zone
FDA Food and Drug Administration
FFSS Fluorouracil Filtering Surgery Study
FNAB Fine needle aspiration biopsy
FT4 Free thyroxine
FVPED Fibrovascular pigment epithelial detachment
GLD Greatest linear diameter
GLT Glaucoma Laser Trial
GLTS Glaucoma Laser Trial Studies
HDLs High-density lipoproteins
HEDS Herpetic Eye Disease Studies
HHDC High human development countries
HLA Human leukocyte antigen
HMO Health Maintenance Organization
HRC High-risk characteristics
HRQL Health-related quality of life
HSV-1 Herpes simplex virus type 1
ICER Incremental cost-effectiveness ratio
ICG Indocyanine green
ICRs Intracorneal rings
ICL Implantable collamer lens
IGF-1 Insulin-like growth factor-1
ILM Internal limiting membrane
IMAs Immune-modulating agents
IOLs Intraocular lens
IONTS International Optic Nerve Trauma Study
IOP Intraocular pressure
IRMA Intraretinal microvascular abnormalities
IRT Iridocyclitis, receiving topical steroid
ISIS Intravitreous Steroid Injection Study
IVAN Alternative treatments to inhibit VEGF in age-related choroidal neovascularization
IVMP Intravenous methylprednisolone
KC Keratoconus
LALES Los Angeles Latino Eye Study
LAR Long-acting repeatable
LASEK Laser epithelial keratomileusis
LASIK Laser in situ keratomileusis
LDLs Low-density lipoproteins
LHDC Lower human development countries
LOCS Lens Opacities Classification System
LTK Laser thermal keratoplasty
MARINA Minimally classic/occult trial of anti-VEGF antibody in the treatment of age-related macular degeneration
MD Mean deviation
MHDC Middle human development countries
MIC Minimum inhibitory concentration
MIRA-1 trial Multicenter investigation of rheopheresis for AMD
MMC Mitomycin C
MP Methylprednisolone
MPS Macular Photocoagulation Study
MRI Magnetic resonance imaging
MS Multiple sclerosis
MVR Microvitreoretinal
NASCET North American Symptomatic Carotid Endarterectomy Trial
NASCIS National Acute Spinal Cord Injury Studies
NEI/NIH National Eye Institute of the United States National Institutes of Health
NIDDM Noninsulin-dependent diabetes mellitus
NIH National Institutes of Health
NNT Number needed to treat
NPDR Nonproliferative diabetic retinopathy
NVA Neovascularization of the angle
NVD Neovascularization of the disk
NVE Neovascularization elsewhere
NVI Neovascularization of the iris
OCT Optical coherence tomography
OH Ocular hypertension
OHTS Ocular Hypertension Treatment Study
ONSD Optic nerve sheath decompression
ONTT Optic Neuritis Treatment Trial
OP Oral prednisone
OR Odds ratio
PARD Pseudophakic and aphakic retinal detachment

PAS	Peripheral anterior synechiae
PBK	Pseudophakic bullous keratopathy
PCS	Prospective Cohort Studies
PDR	Proliferative diabetic retinopathy
PDT	Photodynamic therapy
PED	Pigment epithelial detachment
PEDIG	Pediatric Eye Disease Investigator Group
PEG	Polyethylene glycol
PERK	Prospective evaluation of radial keratotomy
PFCL	Perfluorocarbon liquid
PFO	Perfluoro-*n*-octane
PKC-DMES	Protein Kinase C β Inhibitor Diabetic Macular Edema Study
PKC-DRS	Protein Kinase C β Diabetic Retinopathy Study
PKC-DRS2	Protein Kinase C β Inhibitor Diabetic Retinopathy Study 2
PKC	Protein kinase C
PKP	Penetrating keratoplasty
PMA	Postmenstrual age
POAG	Primary open-angle glaucoma
PPPV	Primary pars plana vitrectomy
PPV	Pars plana vitrectomy
PRK	Photorefractive keratectomy
PRP	Panretinal photocoagulation
PRR	Prevalence rate ratio
PSD	Pattern standard deviation
PVD	Posterior vitreous detachment
PVR	Proliferative vitreoretinopathy
QALY	Quality-adjusted life year
QOL	Quality of life
RCS	Retrospective cohort studies
RCT	Randomized controlled trial
RD	Retinal detachment
RFS	Recurrence factor study
RGP	Rigid gas-permeable lenses
RISE/RIDE	Ranibizumab in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus
RK	Radial keratotomy
RL	Refractive lensectomy
RM-ROP	Risk model retinopathy of prematurity
RON	Radial optic neurotomy
ROP	Retinopathy of prematurity
RRMS	Relapsing-remitting multiple sclerosis
RRR	Relative risk ratio
rt-PA	Recombinant tissue Plasminogen activator
SAP	Standard achromatic perimetry
SB	Scleral buckling
SCORE	Standard of Care versus Corticosteroid for Retinal Vein Occlusion
SELEX	Systematic Evolution of Ligands by EXponential enrichment
SF_6	Sulfur hexafluoride
SKN	Stromal keratitis, not on the steroid
SKS	Stromal keratitis, on steroid treatment
SLT	Selective laser trabeculoplasty
SMAS	Specular Microscopy Ancillary Study
SOC	Standard of care
SPR	Scleral Buckling versus Primary Vitrectomy in Rhegmatogenous Retinal Detachment Study
SRF	Subretinal fluid
SRG	Standard reference gamble
T3	Triiodothyronine
TAT	Trabeculotomy-argon laser trabeculoplasty-trabeculotomy
TED	Thyroid eye disease
TON	Traumatic optic neuropathy
TSH	Thyroid-stimulating hormone
TTO	Time trade-off
TTT	Transpupillary thermotherapy
UBM	Ultrasound biomicroscopy
UCVA	Uncorrected visual acuity
VA	Visual acuity
VC	Viscocanalostomy
VEGF	Vascular endothelial growth factor
VFQ	Visual Function Questionnaire
VFs	Visual fields
VIM	Verteporfin in minimally classic
VIO	Verteporfin in occult (VIO) choroidal neovascularization
VIP	Verteporfin in photodynamic therapy
VIPER	Vitrectomy with Encircling Band vs Vitrectomy Alone for Pseudophakic Retinal Detachment Study
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy

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