

Report From the NEI/FDA Diabetic Retinopathy Clinical Trial Design and Endpoints Workshop

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Invited speakers and discussants are listed on page 5128.

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On June 26, 2015, the National Eye Institute (NEI) and the US Food and Drug Administration (FDA) together held the second workshop on diabetic retinopathy (DR) clinical trial design and endpoints at the National Institutes of Health in Bethesda, Maryland. Diabetic retinopathy, a diabetes-related eye disease, is a leading cause of blindness among adult Americans. The condition is characterized by pathologic changes in blood vessels in the retina, including abnormal growth, swelling, and blockage of retinal blood vessels, leakage of fluid, and progressive loss of vision, if unchecked. Multiple clinical stages of the disease are currently recognized, including mild, moderate, and severe nonproliferative retinopathy and proliferative retinopathy (Fig. 1). Though laser treatment and surgery are commonly used to treat diabetic macular edema (DME)—a condition marked by swelling of the macula, the region of the retina responsible for sharp central vision and the ability to discern fine details—recent years have witnessed the approval of new biological drugs for DME and nonproliferative retinopathy with DME; these drugs confer therapeutic benefits without the side effects of laser treatment.

The workshop, which followed a comprehensive symposium held in November 2006,¹ was aimed at providing an overview of the current research and clinical landscape of DR diagnosis and treatment and determining optimal designs and appropriate outcome measures for clinical trials of DR. Held under the auspices of the Association for Research in Vision and Ophthalmology (ARVO) and the Juvenile Diabetes Research Foundation (JDRF), the workshop convened basic researchers and clinicians in ophthalmology, health researchers, patient advocates, and FDA regulators to help establish standards for carrying out clinical trials that could lead to FDA-approved future potential treatments for DR and methods to monitor treatment response. More than 100 stakeholders from related fields attended the workshop, organized as a series of presentations by experts that were followed by panel discus-

sions and questions from the audience. The workshop was chaired by Dr. Thomas Gardner, MD, professor of ophthalmology at the Kellogg Eye Center, University of Michigan, Ann Arbor; Dr. Lloyd Paul Aiello, MD, PhD, director of the Beetham Eye Institute, Joslin Diabetes Center, Boston; and Dr. Lee Jampol, MD, professor of ophthalmology at Northwestern University, Chicago. Dr. Helen Nickerson, PhD, JDRF program director, and Dr. Frederick Ferris III, MD, clinical director of the NEI, together opened the workshop with introductory remarks.

Dr. Nickerson hailed recent advances in the treatment of certain forms of DR but emphasized the need for early-stage treatment as an approach to prevent vision loss, given the well-recognized challenges faced by patients in maintaining blood glucose levels in check. She acknowledged the caveats associated with early treatment, namely, the analysis of safety risks versus therapeutic benefits to patients and the difficulty of establishing reliable biomarkers for early-stage monitoring of disease progression and treatment response. To that end, she urged the gathering to engage in a vigorous discussion of various aspects of clinical trial design and endpoints.

Dr. Ferris reiterated the broad focus of the workshop, compared to the previous symposium, and encouraged the speakers and discussants to highlight all aspects that impinge upon clinical trial design and endpoints for DR. He noted that the open-forum design of the workshop, in contrast to the typical one-on-one meetings between investigators and FDA regulators, would allow unfettered exchange of ideas between academic and industry researchers, clinicians, patient advocates, and the FDA.

DR. HEATHER STUCKEY

The day's first speaker voiced the concerns of patients facing the daily challenges posed by DR. Dr. Stuckey, D.Ed, assistant



professor of medicine and public health researcher at Penn State University College of Medicine, Harrisburg, was diagnosed with type 1 diabetes in 1982. "I didn't realize the impact at the time. When you're young, you think you're infallible," she said. At age 23, she received laser treatment for DR and described the procedure as painful. Though the treatment was sight saving, she experienced the loss of peripheral vision and contrast sensitivity that can accompany surgical and laser treatment of the retina. She described her daily challenges, such as bumping into objects while navigating rooms and struggling with poor night vision. "It's not an insignificant thing . . . why can't we find a better solution?" she added. She reported findings from a 17-country survey of 10,000 individuals that was aimed at understanding the perspectives and attitudes of diabetes patients, health care workers, and family members. The patient voices from around the world underscored the fear, challenges, and human toll associated with diabetes, in particular complications such as DR. She concluded the talk with an entreaty to the assembled group: "I plead you to find a way to prevent us from having to go through this painful procedure," she said, alluding to laser treatment.

Highlights

Diabetic retinopathy is still addressed with a laser treatment procedure that can be painful. Although the procedure is sight saving, new research methods to restore the retina and/or prevent DR would help alleviate worry about laser treatments and eye complications.

The assembled stakeholders—ophthalmologists, health care professionals, patients—must work toward innovations in DR prevention and improvement of quality of life for those living with diabetes.

DR. LLOYD PAUL AIELLO

Dr. Aiello presented introductory remarks, providing an overview of the potential impact of the DR disease burden and recent therapies on the design of future clinical trials. He began with a historical overview of the treatment of proliferative DR (PDR) in the 1960s, when pituitary ablation was commonly used to treat the condition. In those days, diabetes resulted in approximately 50% blindness and mortality rates. The advent of laser treatment in the 1960s altered the clinical landscape, ultimately resulting in more than 95% reduction in severe vision loss from PDR and a 50% reduction in moderate vision loss from DME. These changes made laser treatment for PDR and DME the worldwide standard of care for nearly half a century, saving sight in millions of people. In the late 1990s, a molecular understanding of the pathogenesis of DR uncovered the role of the protein called vascular endothelial growth factor (VEGF) in the growth and permeability of retinal blood vessels and in causing DME. Soon, anti-VEGF drugs were developed and gained FDA approval. These drugs, such as ranibizumab, known by the trade name Lucentis, and aflibercept, known by the trade name Eyelea, became the treatment of choice for DME, particularly for cases involving the center of the macula and reduced vision. Subsequently, due to their effect of slowing or reversing DR severity, these drugs were approved for treating nonproliferative DR in eyes with DME.

Dr. Aiello recalled the striking results obtained from the now familiar RIDE/RISE clinical trials—among several landmark trials of anti-VEGF drugs for DR treatment—that showed therapeutic benefits of ranibizumab, compared with laser treatment. He also recalled published results from a trial by the

Invited Speakers and Discussants [Commercial Relationship Disclosure]

Frederick L. Ferris, National Eye Institute [None]
Heather L. Stuckey, Penn State University [None]
Lloyd Paul Aiello, Joslin Diabetes Center [Kalvista (I, C), Merck (C), Genzyme (C)]
Thomas W. Gardner, University of Michigan [Kalvista (C), NovoNordisk (C), Puretech Health (C)]
Lee M. Jampol, Northwestern University [None]
Helen D. Nickerson, Juvenile Diabetes Research Foundation [None]
Ronald Klein, University of Wisconsin-Madison [None]
Barbara E. K. Klein, University of Wisconsin-Madison [None]
Jennifer Sun, Joslin Diabetes Center [Genentech (F), Boston Micromachines (F), Optovue (F), Kalvista (F), Eleven Biotherapeutics (C), Novartis (C), Merck (R)]
Wiley A. Chambers, U.S. Food and Drug Administration [None]
Eva M. Rorer, U.S. Food and Drug Administration [None]
Paul P. Lee, University of Michigan [Alcon Research Institute (C), Novartis (C)]
Ronald P. Danis, University of Wisconsin-Madison [EyeKor, Inc. (I, E), Chengdu KangHong Pharmaceuticals (C), GSK (C), IONIS Pharmaceuticals (C), ProQR (C)]
Glenn J. Jaffe, Duke University School of Medicine [Heidelberg Engineering (C), Genentech (C), Neurotech USA (C)]
Antonia M. Jossen, Charite Universitätsmedizin Berlin [None]
Adam R. Glassman, Jaeb Center for Health Research [None]
Michael Larsen, University of Copenhagen [Novartis (C), Bayer (C), Roche (C), Astra-Zeneca (C), Novo Nordisk (C), Allergan (C), Eli Lilly (C)]
Peter H. Scanlon, University of Oxford [None]
Michael S. Ip, University of California - Los Angeles [Omeros (C), Thrombogenics (C), Boehringer Ingelheim (C)]

Diabetic Retinopathy Clinical Research (DRCR) Network that showed that 44% to 63% of patients who received anti-VEGF drugs did not require any laser treatment to keep DME in check during the first year following treatment. Further, 5 years after treatment, approximately one-third of patients on anti-VEGF drugs displayed a gain of 15 or more letters on standardized eye charts, with approximately half of patients displaying a gain of 10 or more letters. Vision loss on the same eye charts was minimal for these patients. Around 75% of these patients showed a visual acuity > 20/32, and 56% of these patients did not require laser treatment over 5 years.² Additional data from the DRCR Network trials showed that anti-VEGF drugs could slow the progression of moderately severe nonproliferative DR (NPDR). Compared with a sham treatment and prompt laser, ranibizumab and prompt laser treatment led to a 6-fold increase in the number of patients who showed a two-level improvement or more on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, a well-established standardized eye chart for testing visual acuity; conversely, the drug almost halved the number of patients who showed a two-level or more worsening on the scale.³ These and other results eventually led to the FDA approval of ranibizumab and aflibercept for DR in patients with DME in 2015. These advances defined the direction of future research.

One important reason to press forward with research on DR is the global prevalence of diabetes. Dr. Aiello reviewed epidemiologic data showing that nearly 400 million people worldwide are currently afflicted with the disease, with almost 600 million patients predicted by 2035. In the United States alone, 11.3% of adults are affected by diabetes. India has long figured among the countries with the highest prevalence of diabetes, and China has witnessed soaring rates in recent decades, rising from less than 1% in 1980 to 11.6% in 2013. Today, China has the highest worldwide prevalence of

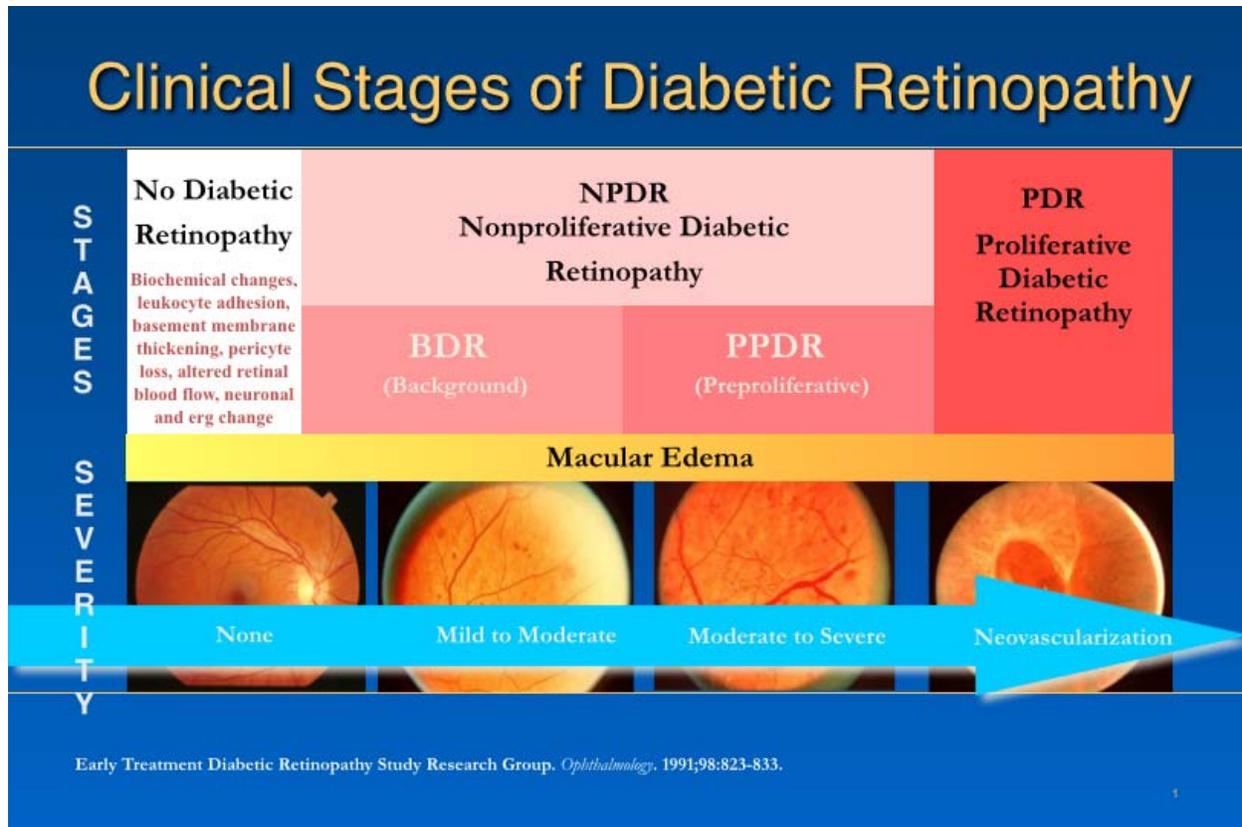


FIGURE 1. Stages of progression of diabetic retinopathy. Image courtesy of Lloyd Aiello.

diabetes, with 114 million adults afflicted with the disease. Studies show signs of an unrelenting epidemic in China: early onset of diabetes at lower body mass index compared with Americans, with approximately 40% of individuals ages 18 to 29 years diagnosed with prediabetes. However, Dr. Aiello noted, there are also hopeful signs from other parts of the world, where effective and timely screening programs have helped curtail the toll of the disease. In England and Wales, for example, DR was no longer the leading cause of blindness among working-age adults for the first time in 50 years, as reported in 2014.

Surveys have repeatedly shown that the fear of blindness rates among the top concerns of patients with diabetes. A cure for diabetes, such an artificial bionic pancreas, has remained elusive for decades. Though continuous glucose monitoring has been associated with lower hemoglobin A1c, a marker of blood glucose level, studies have shown that such technology is not typically used by substantial numbers of patients, particularly from economically disadvantaged backgrounds. A recent randomized trial by the DRCR Network on the effect of education during ophthalmologist visits on diabetes control among 1875 patients revealed no significant difference in hemoglobin A1c levels after a 12-month period between those who received the educational intervention and those who received usual care.⁴ The intervention included A1c testing, feedback to primary care doctors, personalized risk assessment, additional diabetes management materials, and follow-up, in addition to usual care.

Together, these findings highlight the need and challenges for early intervention in DR. Though most recent advances have focused on late stages of the disease, many changes begin prior to clinical manifestation of the disease, including

biochemical changes, leukocyte adhesion, basement membrane thickening, altered retinal blood flow, and neuronal and electroretinogram changes. Approximately 45% of patients with DR continue to require laser treatment after 5 years, and half of patients do not gain 10 or more letters of visual acuity. Moreover, treatment advances have increased the life span of people with diabetes who may consequently need long-term visual care. Given these factors, late-stage intervention may impose a high treatment burden and lead to potentially worse outcomes. Hence, Dr. Aiello noted, cost-effective, accessible, and efficacious early treatments that pose low risk to patients are direly needed, analogous to the successful measures adopted for diseases such as polio and smallpox.

Developing such treatments depends on new approaches to clinical trial designs and surrogate biomarkers that can predict visual and anatomic outcomes in DR. These biomarkers should be able to accurately determine the risk of disease, identify patients at risk of vision loss, monitor disease progression, identify patients likely to respond to treatments, monitor treatment response, and, pertinent to the day's proceedings, evaluate early-stage clinical trial outcomes.

The gold standard for monitoring retinopathy, the ETDRS fundus photography method, typically covers only approximately 30% of the entire retinal surface despite acquisition of seven overlapping fields. New ultrawide-field imaging modalities can image 82% of the entire retinal surface using one image acquired in 0.25 second. Predominantly peripheral lesions identified using these new technologies, which are located outside the ETDRS photography fields, have been reported in some patients, and these lesions have been shown to substantially increase the risk of DR worsening by two or more steps on the ETDRS scale as well as increase the risk of

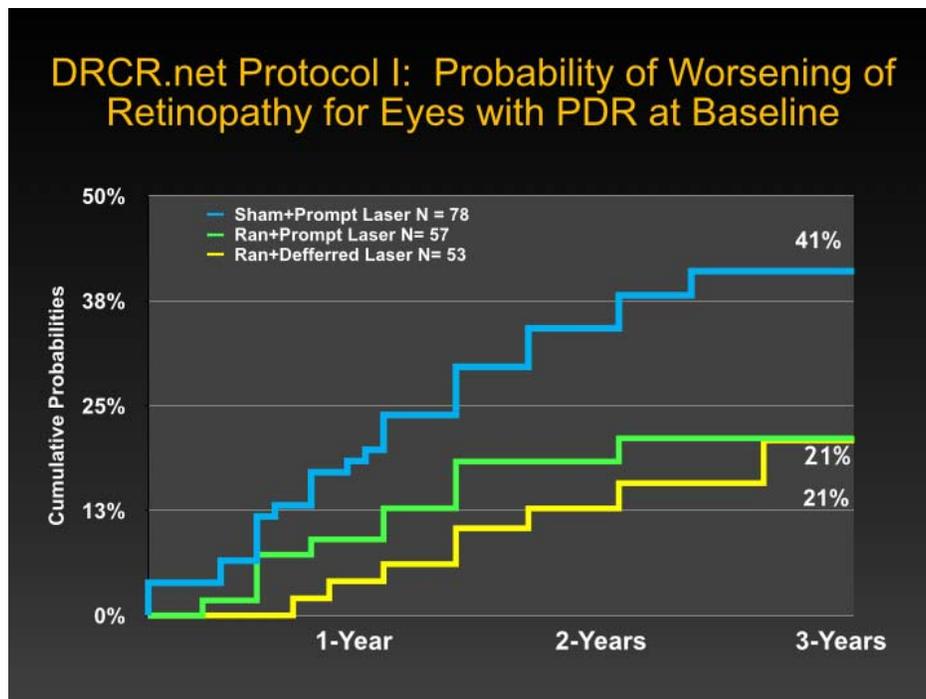


FIGURE 2. Peripheral retinal lesions outside the standard ETDRS visual fields might serve as potential surrogate biomarkers in early-stage trials of DR. Image courtesy of Lloyd Aiello.

onset of PDR by approximately 3-fold over 4 years.⁵ These findings suggest that the ETDRS grading criteria may need to be modified to incorporate peripheral lesions (Fig. 2).

Hence, Dr. Aiello concluded, currently accepted endpoints must be clearly defined, and conditions for acceptable future endpoints must be delineated. Also, he added, methods to identify, assess, and validate surrogate biomarkers and the impact of these new biomarkers on clinical trial design should be discussed and established.

Highlights

Molecular understanding of the pathogenesis of DR has led to the development and approval of safe and effective anti-VEGF drugs to treat DME.

Given that nearly 400 million people worldwide are diagnosed with diabetes and 600 million people are predicted to have the condition by 2035, as well as the rising prevalence of diabetes in countries such as China and India, there is a pressing need for early intervention in DR, prior to clinical manifestation of the disease.

Surrogate biomarkers to predict anatomic and visual outcomes in DR and novel clinical trial designs and endpoints are needed to facilitate development of safe and effective early interventions.

DR. WILEY CHAMBERS

Dr. Chambers, MD, Supervisory Medical Officer, Division of Transplant and Ophthalmology Products of the FDA's Center for Drug Evaluation and Research, presented the agency's requirements for approving clinical drug trials in ophthalmology, with particular regard to past clinical trials of DR, and reviewed acceptable endpoints for such trials. The Food, Drug, and Cosmetic Act of 1938 was passed in response to severe adverse events tied to the use of products that had been marketed without prior review. Citing a couple of well-known

examples of ophthalmic products, Dr. Chambers reminded the gathering that the entry of unapproved products into the market can result in disastrous consequences to patients, thus underscoring the primacy of safety concerns in the FDA regulatory process. The Act prohibits the transportation of unapproved drug products across state lines and requires substantial evidence of safety and efficacy for the approval of new drugs. Dr. Chambers explained the distinction between Investigational New Drugs, which are experimental therapies that may be approved for subsets of selected patients through clinical trials, and the standard approval process for new drugs that would essentially approve the drugs for use in all patients.

Dr. Chambers noted that the Act's "substantial evidence" requirement for approval of new drug products is not open to interpretation. Ultimately, FDA approval depends on whether a product's benefits outweigh its risks in the intended population for the designated indication as demonstrated in replicated, adequate, and well-controlled studies. Such studies must be carried out by scientific experts with the relevant training and experience required to determine whether the product has the purported effects under the stipulated conditions suggested or proposed in the labeling. The identity, strength, purity, quality, and dosage form of new drug products must be established and standardized for consideration for approval. The federal code of regulations lists Good Manufacturing Practices, and facilities used to manufacture new drug products must comply with those practices. Dr. Chambers noted that the FDA considers seven factors in deciding whether a given drug study is adequate and well controlled as required by the Act: clear statement of goals; design that incorporates a valid comparison with a control to enable an evaluation of the drug's quantitative effects; assurance that patients included have the condition(s) for which approval is sought; a method of minimizing bias in assigning patients to treatment and control groups; methods to minimize bias among subjects, observers, and analysts; reliable and well-

defined methods of evaluation of subjects' responses; and analysis of results that are adequate to assess the drug's effects.

Currently, ranibizumab and aflibercept injections are approved for the treatment of DR in patients with DME. In both cases, Dr. Chambers noted, approval was based on replicated, adequate, and well-controlled trials showing a statistically significant greater percentage of patients who improved by two or more steps on the ETDRS grading scale, compared with patients who did not receive treatment. Dr. Chambers explained the reasons behind the approval of the drugs. Because the ETDRS scale is well established and step changes on the scale are associated with changing risks of long-term vision loss (higher scores on the scale represent higher risks of vision loss), this outcome measure was found acceptable. Further, more than one study found statistically significant, clinically meaningful superiority for the drugs in the study population.

Dr. Chambers noted that approval typically requires more than one trial, given the law's requirement for replicability, but exceptions may be made when a single trial shows overwhelmingly convincing evidence or if the eligible study population is limited. He hastened to add that the high prevalence of DR means that the FDA is unlikely to approve new drugs for DR based on a single trial. The working definition of statistical significance, arguably far from perfect, is based on two-sidedness and 95% confidence intervals. Superiority should be demonstrated over current practice, which is often the standard of care for a particular condition. The use of two steps on the ETDRS scale reduces the chances of assessment artifacts. Dr. Chambers reminded the gathering that the FDA is willing to consider both prevention and regression of DR as potential outcome measures, drawing an analogy to infectious diseases.

Dr. Chambers broadly categorized endpoints as anatomic endpoints, which are often structural; objective endpoints, which use specific instruments; subjective endpoints, which need interpretation; and patient-reported outcomes on single questions or on multiple domains. The anatomic endpoints that the FDA considers acceptable final—not surrogate—endpoints of drug trials are improvement of DR; prevention of DR progression, cytomegalovirus retinitis progression, or retinal detachment; resolution of cell and flare, or conjunctival redness; and re-epithelialization of cornea with elimination of bacteria. Among the acceptable objective endpoints are intraocular pressure and improvements in refractive power, pupil size, or tear production. Dr. Chambers listed specific thresholds for each of these objective endpoints while cautioning that being able to measure an endpoint does not render it clinically meaningful. Among the subjective endpoints that need interpretation are measures of visual function, such as visual acuity, color vision, visual fields, and contrast sensitivity. Patient-reported outcomes include itching, pain, ocular irritation, ocular dryness, and quality-of-life measures, which is a composite outcome. Dr. Chambers noted that none of the currently reviewed patient-reported measures in ophthalmology drug trials have been validated or approved by the FDA. The agency has issued a guidance document for manufacturers who wish to develop patient-reported outcome measures to support labeling claims.⁶ In addition, Dr. Chambers mentioned the possibility of accelerated drug approval based on surrogate endpoints, defined in the regulation as one “that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit.” Such approval is used only in serious or life-threatening conditions and must be superior to current treatments. Drugs on accelerated approval must be studied after marketing to verify clinical benefits. Dr. Chambers noted that no ophthalmic drugs have been approved based on

surrogate endpoints. In many cases, he added, some surrogate endpoints have been used as final endpoints through labeling for specified populations without requiring final validation.

Finally, Dr. Chambers raised an array of questions that the ophthalmology community might consider in seeking FDA approval of new drugs: Does a candidate treatment reverse DR? Can the time of its effectiveness be determined? Does the treatment cure DR? How many treatments are necessary? Is the treatment effect long-lasting? These are some of the common criteria that the FDA would consider in approving any new drugs for DR.

Highlights

Food and Drug Administration approval of new drug products for DR would depend on whether the products' benefits outweigh their risks in the intended population for the designated indication as demonstrated in replicated, adequate, and well-controlled studies, which must be carried out by scientific experts with the relevant training and experience required to determine whether the product has the purported effects under the stipulated conditions suggested or proposed in the labeling.

Both prevention and regression of DR may be considered as potential outcome measures in DR clinical trials.

Prior to seeking FDA approval, researchers and drug developers might consider an array of factors for candidate drug products for DR, including the ability of the products to reverse or cure DR, the ability to determine the products' window of effectiveness, the number of treatments required, and the duration of the treatment effect.

DR. RONALD KLEIN

Providing an epidemiologic perspective, Dr. Klein, MD, began by explaining the need for accurate estimates of prevalence and incidence of DR. Because prevalence and incidence data are needed to accurately track disease trends, determine necessary patient services and associated costs, design clinical studies, and identify age-, sex-, and race-related disparities in care, data on the prevalence, severity, incidence, and progression of DR must be collected in a systematic manner in population-wide studies. Among the regional studies of prevalence are the Beaver Dam Eye Study, the Chinese Eye Study, the Los Angeles Latino Eye Study, the New Jersey 725 Study, and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). The Atherosclerosis Risk in Communities Study is a multicenter study that has provided DR prevalence and incidence data, and the National Health and Nutrition Examination Survey (NHANES) is a federally sponsored, cross-sectional, nationwide survey of noninstitutionalized, civilian individuals in the United States that also provides DR prevalence and incidence data.

All the above-mentioned studies use the current gold-standard method for diagnosing DR, namely the grading of color stereoscopic film or digital fundus photographs (30°) with seven overlapping standard retinal fields. Dr. Klein described the Airlie House classification scheme, a standard method of grading fundus photographs for DR that has been used in gathering prevalence and incidence data. The classification scheme typically examines the presence and extent of a number of lesions, including retinal microaneurysms, venous loops, and hard and soft exudates, among others. Based on the classification, a severity level for a given individual's eye is assigned, ranging from no DR (10) to PDR (81–85), depending on the presence of certain lesions and combinations of lesions. For a given individual, a combined

severity score is obtained by assigning greater weight to the more severely affected eye. The severity score reflects ranking on the ETDRS DR severity scale, which is itself based on the Airlie House classification scheme. The ETDRS severity scale is rank ordered as a series of steps from 1 to 23, and directional step changes on the scale reflect improvement or worsening of DR.

The NHANES study, carried out from 2005 to 2008, examined fundus photographs of 5371 individuals, of whom 1006 had diabetes, which was defined either by self-report of a previous diagnosis of diabetes or by a glycated hemoglobin A1c level of 6.5% or more in previously undiagnosed individuals. Diabetic retinopathy was defined by the presence of one or more retinal microaneurysms or retinal blot hemorrhages in at least one eye, and was considered vision threatening if severe NPDR, PDR, and/or clinically significant DME was present. The prevalence measures were statistically weighted to provide a representative prevalence estimate of DR among adults with diabetes who were 40 years of age or older in the United States. The estimated prevalence for DR was 28.5%, representing 4.2 million people, and the estimated prevalence for vision-threatening DR was 4.4%, representing 655,000 people. The survey also showed racial differences in prevalence: Non-Hispanic blacks had a 47% (190%) higher crude prevalence than their non-Hispanic white counterparts, and Mexican Americans had a 29% (130%) higher crude prevalence than their non-Hispanic white counterparts. (In parentheses are the corresponding values for vision-threatening diabetes.⁷) Dr. Klein noted that despite the survey's many strengths, NHANES did not include institutionalized individuals and did not distinguish between type 1 and type 2 diabetes; moreover, the area in the fundus photos was less than that captured by seven 30° images.

The Eye Disease Prevalence Research Group (EDPRG), which provided alternative estimates of DR prevalence in the year 2000, estimated a 61% increase in the prevalence of any DR (6.6 million people) and a 78% increase in vision-threatening DR (1.2 million people) by 2020.⁸ However, findings from the Beaver Dam Eye Study and the National Health Interview Survey suggest that the EDPRG projections may lead to an overestimate of DR disease burden.

Dr. Klein noted that there are no national estimates of incidence or progression of DR, and most available estimates come from old, regional studies. Dr. Klein recalled findings on the 10-year cumulative incidence of DR among patients with type 1 and type 2 diabetes from the WESDR study, carried out from 1980 through 1982 to 1990 through 1992.⁹ When the study was repeated during a second 10-year period from 1994 through 1996 to 2004 through 2006, a statistically significant lowering of DR progression as well as decreased incidence of PDR and DME was observed.

In summary, Dr. Klein noted, the estimated prevalence of PDR and clinically significant DME both appear to be on the wane, likely due to improved clinical management of blood pressure and sugar levels among patients with type 1 and type 2 diabetes. The estimated prevalence of visual impairment appears to be on the wane among non-Hispanic whites with type 1 diabetes, likely due to earlier detection and treatment of vision-threatening retinopathy. Demographic changes, such as increasing prevalence of DR among Mexican Americans and African Americans, may explain the increase in visual impairment reported in the NHANES study. Most projections of the worldwide future prevalence of DR are based on the assumption of unchanging risk profiles, clinical management practices, and life expectancies for people with diabetes. Dr. Klein cautioned that such an assumption may lead to erroneous estimates. Finally, Dr. Klein noted the need for improved worldwide epidemiologic surveillance and screening

methods for DR and for the incorporation of new imaging techniques into classification schemes and severity scales.

Highlights

The 2005 to 2008 NHANES estimated the prevalence of DR to be 28.5%, representing 4.2 million people among adults with diabetes who were 40 years of age or older in the United States; for vision-threatening DR it was 4.4%, representing 655,000 people.

The NHANES also showed racial differences in prevalence: Non-Hispanic blacks had a 47% (190%) higher crude prevalence than their non-Hispanic white counterparts, and Mexican Americans had a 29% (130%) higher crude prevalence than their non-Hispanic white counterparts. (In parentheses are the corresponding values for vision-threatening diabetes.)

The EDPRG, which provided alternative estimates of DR prevalence in the year 2000, estimated a 61% increase in the prevalence of any DR (6.6 million people) and a 78% increase in vision-threatening DR (1.2 million people) by 2020.

The WESDR, the Beaver Dam Eye Study, and the National Health Interview Survey suggest that the EDPRG projections may overestimate the DR disease burden because the estimated prevalence of PDR and clinically significant DME both appear to be on the wane, likely due to improved clinical management of blood pressure and sugar levels among patients with type 1 and type 2 diabetes.

There is a need for improved worldwide epidemiologic surveillance and screening methods for DR and for the incorporation of new imaging techniques into classification schemes and severity scales of DR.

DR. JENNIFER SUN

Dr. Sun, MD, MPH, discussed past findings on the progression and regression of DR from major clinical trials, and described the effects of various treatments on the natural history of DR worsening. One striking observation from recent clinical trials of intravitreal anti-VEGF treatment of DME has been the finding that treatment with anti-VEGF often leads to an amelioration of DR severity in patients. To illustrate the point, Dr. Sun presented an example of color fundus photographs from a patient whose DME was treated with ranibizumab and who also showed a three-step improvement in DR severity on the ETDRS scale after 1 year of monthly treatments. Such findings have raised the question whether intravitreal anti-VEGF treatment decreases rates of DR worsening and increases rates of DR improvement, and, if so, at what rates and at what minimal course of treatment. Also of interest is the optimal time point at which anti-VEGF treatment must be initiated to achieve desired DR severity outcomes (indicating a potential optimal therapeutic window) and the possibility of non-anti-VEGF intravitreal agents that have similarly salutary effects on DR outcomes.

To address the question of the specific effects of anti-VEGF treatment for DME on DR severity, Dr. Sun presented data from three groups of phase III clinical trials: the DRCR Network protocol I, the VIVID and VISTA trials (aflibercept), and the RIDE/RISE trials (ranibizumab) for DME. At baseline, most of the patients enrolled in these trials had moderate to severe NPDR, and after around 2 years of treatment with anti-VEGF agents, showed a decrease in the rates of two-step or more as well as three-step or more worsening of DR on the ETDRS scale. Compared with patients receiving laser treatment, fewer patients who received the anti-VEGF agents in the VIVID/VISTA trials also required panretinal laser photocoagulation, an outcome that indicates an advanced, proliferative stage of

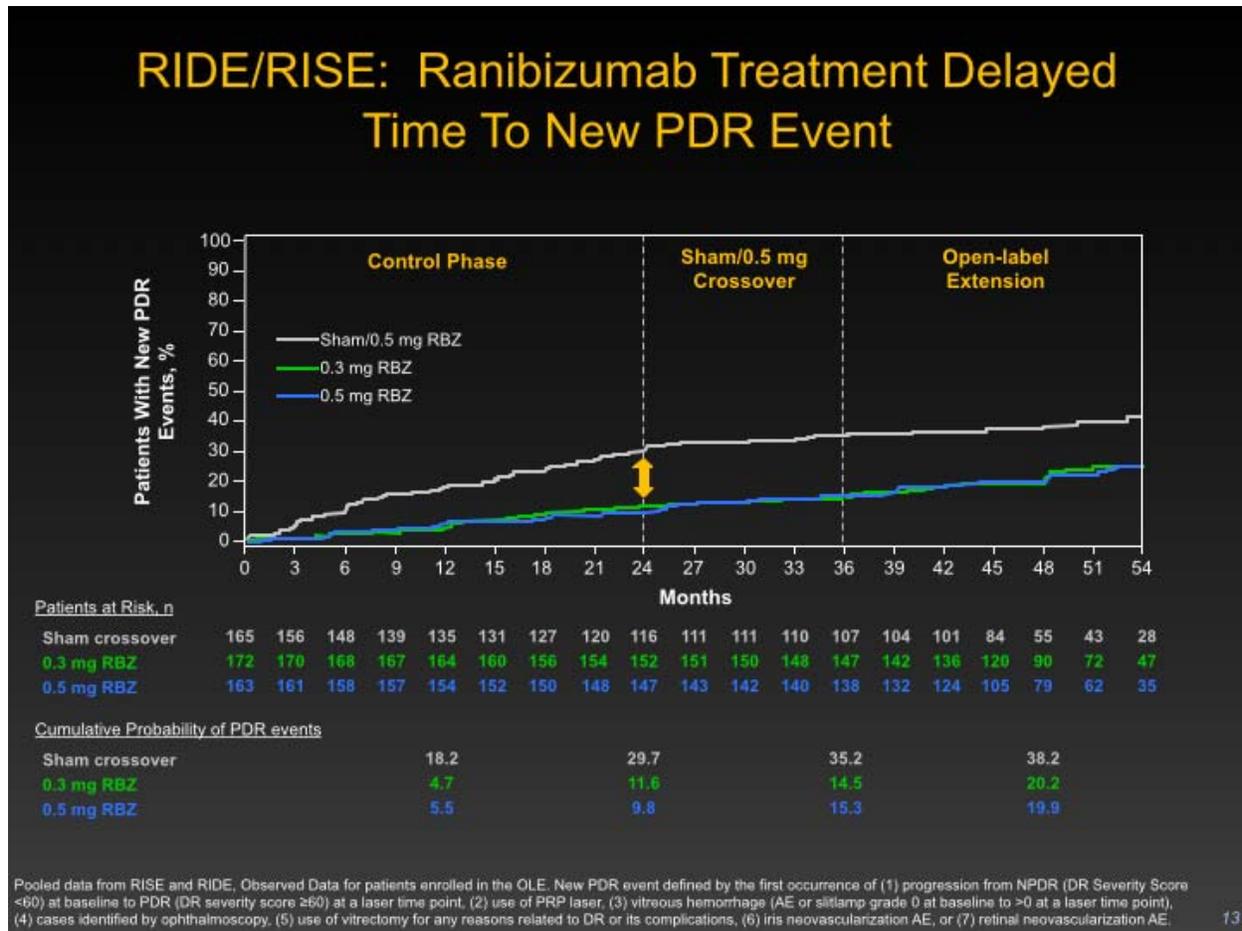


FIGURE 3. Trial of ranibizumab for eyes with PDR at baseline. Image courtesy of Jennifer Sun.

retinopathy, after approximately 2 years of treatment.¹⁰ Findings from the protocol I trial show that the cumulative probability of DR worsening—a composite measure including worsening on the ETDRS scale, onset or further development of PDR, need for panretinal photocoagulation, and intravitreal hemorrhage, among other outcomes—for eyes with NPDR as well as for eyes with PDR decreased over 3 years with ranibizumab treatment.¹¹ Similarly, the RIDE/RISE trials revealed that ranibizumab treatment delayed the onset of PDR (Figs. 2, 3). The RIDE/RISE trials also showed that nearly 97% of patients treated with ranibizumab displayed either stable or improved DR after 2 years of treatment.^{12,13} The VIVID/VISTA trials corroborated these findings by showing two-step or more and three-step or more improvements in DR after approximately 2 years for patients treated with aflibercept.

Taken together, the trials demonstrate not only a clear benefit for anti-VEGF agents but also that sustained improvement of DR occurs rapidly—as early as 3 months after treatment—and can be sustained throughout 36 months of treatment, as shown by the RIDE/RISE trials. The open-label extension study, carried out as a part of the RIDE/RISE trials, provides clues to whether less than monthly injections of ranibizumab might achieve similarly rapid and sustained improvement of DR in patients. This study suggested that DR severity improvement can be maintained with less frequent injections. Dr. Sun presented a case example of an eye with severe NPDR that received ranibizumab and showed a three-step improvement of DR severity after 36 months of continuous monthly therapy, continuing to maintain the

improvement at 48 months, despite receiving only four injections between months 36 and 48.

The RIDE/RISE trials revealed that a 2-year delay in initiating anti-VEGF treatment can result in worse visual acuity outcomes. The trial also provided clues regarding DR severity outcomes: A sham-treated group that was administered ranibizumab beginning at 24 months for a period of 1 year showed an improvement in DR severity in many patients, but the improvement in this group after 1 year of treatment did not match that seen among the patients originally selected to receive ranibizumab from the beginning of the trial at their 1-year follow-up visit. The rate of new PDR events is also higher in eyes for which ranibizumab therapy is delayed by 2 years as compared with eyes that receive immediate ranibizumab treatment. Together, these findings suggest the presence of a therapeutic window for anti-VEGF agents for achieving optimal DR severity outcomes. A delay of 2 or more years in initiating anti-VEGF treatment might lead to worse long-term DR severity outcomes.

Finally, Dr. Sun presented data from the MEAD study and the DRCR Network protocol B, both showing the beneficial effects of intravitreal steroids on DR severity. The MEAD study showed decreased rates of two-step or more worsening of DR severity on the ETDRS scale for patients who received a dexamethasone implant.¹⁴ The protocol B study of triamcinolone monotherapy showed decreased rates of progression of retinopathy, defined as a composite outcome that included progression from NPDR to PDR, administration of panretinal photocoagulation, vitreous hemorrhage, and a two-step or more worsening on the

ETDRS scale between baseline and follow-up after 2 years, for patients who received steroid, as compared with laser-treated patients.¹⁵ These findings suggest that steroids, as well as anti-VEGF drugs, might be effective in treating DR.

In conclusion, Dr. Sun pointed out that while the ETDRS scale is well established for monitoring DR progression in eyes with baseline NPDR, it is not designed to monitor changes in PDR. Thus, she emphasized the need to develop new outcome measures for evaluating such changes in clinical trials and additional needs to determine how endpoints based on visual function are associated with DR in the early stages of the disease, as well as how such endpoints vary with DR severity over time.

Highlights

Landmark clinical trials have shown not only a clear benefit for anti-VEGF agents in DR treatment but also that sustained improvement of DR can occur rapidly.

There is evidence that improvements in DR severity obtained with initial monthly dosing can be maintained in many eyes with less frequent injections of anti-VEGF drugs.

The presence of a therapeutic window for anti-VEGF agents to achieve optimal DR severity outcomes underscores the importance of timely intervention, and a delay of 2 or more years in initiating anti-VEGF treatment might lead to worse long-term DR severity outcomes.

Results from several clinical trials suggest that steroids, like anti-VEGF drugs, might be effective in improving DR severity and reducing PDR-related outcomes.

DR. JENNIFER SUN

Dr. Sun focused her second presentation on future perspectives in DR treatment, underscoring the recurring theme that a focus on the early stages of the disease may be increasingly important in future clinical trial designs and endpoints. Given recent advances in DR treatment, trends in better systemic clinical management of diabetes, improved patient education, and the high prevalence of diabetes worldwide, it would be reasonable to project an increasing trend in the number of patients with mild DR in the coming decades. Recent reports of improvements in blood glucose control in small numbers of type 1 diabetes patients who received a bionic pancreas bode well for the future treatment of diabetes-related complications, including DR. Further, technological advances in retinal imaging, such as adaptive optics scanning laser ophthalmoscopy and optical coherence tomography angiography, which are currently largely used as research tools, could potentially allow earlier detection of DR and intervention to minimize or prevent the risk of vision loss. Other advances have already reached clinics: Telemedicine programs currently allow the remote detection and diagnosis of DR for patients in the United States Veterans Health Administration and Indian Health Service (IHS), the United Kingdom, and other countries. The Joslin Vision Network, a telemedicine arm of the Beetham Eye Institute, together with the IHS, deploys 94 health care facilities across 25 U.S. states to perform annual screening of more than 16,000 patients. In the IHS, the use of advanced screening tools such as scanning laser ophthalmoscope (SLO)-based nonmydriatic ultrawide-field imaging in 12 sites and three states resulted in a decrease of the number of ungradable images by 92% per patient and led to a 2-fold increase in the identification of any or referable DR. Some regional and national screening programs for DR both in the United States and in Europe now use automated retinal image grading systems to supplement their teleophthalmology efforts.

Despite the widely recognized therapeutic gains of anti-VEGF drugs, only approximately 50% of treated patients with DME have a gain of 10 or more letters of visual acuity, suggesting the need for further optimization of ocular-specific treatments for substantial numbers of patients. Dozens of ongoing DR clinical trials are exploring an array of agents that act through various molecular pathways. To ease the burden on patients and physicians of the current regimen of frequent, often monthly anti-VEGF treatments, a range of alternative sustained-release drug delivery systems are currently being explored or in development, including encapsulated cell techniques, drug conjugation in biodegradable vehicles, hydrogel contact lenses, and refillable port delivery systems, to name a few examples. Despite the low frequency of adverse events, such as vision-threatening endophthalmitis associated with intravitreal injections, the need for noninvasive drug delivery, such as topical application, exists. Further, individualized treatments tailored to the intravitreal biochemistry of patients is currently being explored, and preliminary studies of intravitreal biomarkers in animal models suggest a potential role for the synergistic effects of combined therapeutic agents in improving certain anatomic endpoints.

Dr. Sun noted that the coming decades are likely to witness improved understanding of disease biology, development of novel drugs and delivery systems, development of precise tools to classify patients based on risk profiles, and further improvements in systemic control of patients' blood glucose levels. Hence, Dr. Sun urged the gathering to engage in a discussion centered on evaluating potential treatments and outcome measures for early-stage DR while continuing to pursue improved treatments for advanced DR. She also emphasized the need to define, update, and clarify anatomic and functional outcomes in clinical trials that the FDA would deem acceptable and to identify and validate biomarkers that would enable analysis of the natural history of DR progression.

Highlights

Though anti-VEGF drugs have led to significant gains in DR treatment, only around 50% of treated patients with DME have a gain of 10 or more letters of visual acuity, suggesting that additional effective ocular treatments are needed and that specific treatment regimens must be further optimized for many patients.

Several clinical trials of novel drug delivery systems are currently being tested to ease the burden of monthly injections of anti-VEGF drugs for DR.

The need to evaluate potential treatments and outcome measures for early-stage DR is as pressing as the need to pursue improved treatments for advanced DR. Thus, biomarkers, endpoints, and trial designs must be explored to better understand the natural history of DR progression.

DR. EVA RORER

Dr. Rorer, MD, Chief Ophthalmic Medical Officer of the FDA's Division of Ophthalmic and Ear, Nose, and Throat Devices within the Center for Devices and Radiological Health, Office of Device Evaluation, provided the FDA's perspectives on evaluating the performance of diagnostic medical devices used in clinical trials of DR, including those used to measure trial outcomes. In FDA's guidance document "Design Considerations for Pivotal Clinical Investigations for Medical Devices: Guidance for Industry, Clinical Investigators, Institutional Review Boards and Food and Drug Administration Staff," issued on November 7, 2013, diagnostic devices are defined as those used to provide results that are used alone or with other

information to evaluate a subject's "target condition." The term "target condition" refers to an identifiable state, such as a state of health or a stage of disease, in a subject that prompts clinical action. Examples of diagnostic devices are imaging systems, nonimaging *in vivo* diagnostic devices, devices that provide anatomic measures, devices that measure subject function, or algorithms that yield a composite, subject-specific output. Based on their potential risk to patients, devices are grouped into and regulated by the FDA as three classes. Class I devices have a simple design, pose low risk to patients, and are subject to the lowest level of regulation, such as general controls (e.g., medical device listing with the FDA), with most being exempt from premarket submission for review. Class II devices have a more complex design, pose a greater potential risk to patients, must meet a higher standard, such as special controls (e.g., specific performance standards) in addition to general controls, and often require premarket notification, also known as "510(k) clearance," which depends on demonstrating substantial equivalence to a legally marketed predicate device. Clearance does not imply that the FDA has reviewed clinical evidence supporting all potential clinical uses of the device. Class III devices have a complex design, pose the highest level of risk, are subject to the highest level of regulation, and hence require premarket approval through the premarket approval (PMA) application process.

In 2006, when the FDA and NEI convened to discuss clinical trial endpoints for DR, visual acuity charts and fundus cameras were the main diagnostic devices used in DR therapeutic trials. Around the same time, optical coherence tomography (OCT) and electronic visual acuity charts were put forth as promising diagnostic devices for measuring structural and functional outcomes, respectively, in future DR trials. Also available around this time were devices such as contrast sensitivity charts, perimeters, color vision testers, SLO, electroretinograms, and visual-evoked potentials. To be useful in early therapeutic intervention trials for DR, a diagnostic device must be capable of detecting changes that occur early in the natural history of DR. Diagnostic device performance should support such an indication for use. Technological advances since 2006 have led to a number of methods to "improve" images obtained using available diagnostic device technologies, including wide-field imaging, ultrawide-field imaging, and adaptive optics, a technique that adjusts for wavefront distortions in optical imaging systems. Other advances to assess blood flow, perfusion, and oxygenation in the retina include Doppler, stroboscopic fundus cameras, optical coherence angiography, and retinal oximeters, the latter two of which had not been FDA cleared or approved at the time of the workshop. Metabolic imaging, which measures changes in reflectance or fluorescence elicited by light stimulation during disease-related metabolic stress, is another technique on the horizon that might help detect metabolic changes prior to the onset of irreversible cell damage in DR; retinal metabolic imaging had not been cleared or approved by the FDA as of the workshop.

Many health-related mobile applications are now available on the market. The majority of these applications do not meet the definition of a medical device, and thus the FDA does not regulate them. Some mobile applications (apps), however, may meet the definition of medical devices, but owing to their low potential risk to patients, the FDA will not enforce requirements under the Federal Food, Drug, and Cosmetics Act for such devices. The FDA exercises regulatory authority over only those mobile apps that are medical devices and whose function could pose safety risks to patients. The February 2015 FDA guidance document on mobile medical applications (MMAs) elaborates these considerations.¹⁶ In general, the FDA considers a mobile app a medical device when the app meets the

definition of a medical device, which is any device whose intended use is for diagnosis, cure, mitigation, treatment, or prevention of a disease or condition, or is intended to have structural or functional effects in humans—or if the app is intended as an accessory to a regulated medical device or used to create a regulated medical device from a mobile platform. The FDA has a Web page dedicated to MMAs.¹⁷

Next, Dr. Rorer described paths to bringing diagnostic devices for DR to the market. The 510(k) clearance pathway requires manufacturers to show substantial equivalence of the new device to a similar "predicate" device legally marketed in the United States. Substantial equivalence depends on comparing the intended use and indications for use, technological characteristics, and performance measures of the devices.

When assessing the clinical performance of a diagnostic device for a particular indication for use, it is important for the device to be studied in the same context of that use—for the same purpose, on the intended patient population, by similar users, in the same type of clinical setting.

Dr. Rorer noted other considerations when designing studies for assessing the performance of diagnostic devices, using the case of imaging devices for illustration. When the device output includes qualitative output such as images, masked graders using preestablished criteria should assess the images obtained with the predicate and new devices in the same retinal location and in the same eye using equivalent parameters. Numerous pairs of images from subjects across the intended population should be assessed, including subjects with various forms of pathology and those who are disease free. Assessments should include image quality as well as the identification of relevant pathology. Devices that provide quantitative measurements should be evaluated for agreement, defined by how one device model's output compares with another's (agreement is distinct from accuracy except when the device is compared with a gold standard); bias, defined as the estimate of systematic measurement error (defined as the mean difference between the measured value and the reference value and expressed as difference in measurement units or percent difference); and precision, defined as an estimate of random measurement error and reflecting the closeness between repeated, independent measurements on the same eye under the specified testing conditions. (Variability related to devices, operators, settings, and patient alignment can affect precision. Repeatability and reproducibility are precision measures that vary with testing conditions, which must be clearly described.)

Dr. Rorer noted that agreement, bias, and precision measures can be either constant or variable across the measurement range of the device. Further, these measures of device performance may not be identical for healthy subjects and those with pathology. These measures can also vary with image quality. Thus, appropriate measurement validation studies should be carried out. Clinical decision limits, which allow discrimination between different health states of subjects, must be established before conducting pivotal diagnostic clinical performance studies.¹⁸ Cross-sectional studies of known normal and diseased subjects with disease of varying severity can reveal preliminary information about potential decision limits. Once the limits are established, a pivotal diagnostic clinical performance study may be performed. Such a study compares the reported diagnosis or referral decision with the clinical reference standard, that is, the best available method for establishing the true status of a subject with respect to a target condition, and uses a different population of subjects than that used to determine clinical decision limits. Clinical reference standards may be individual methods or combinations of methods, can evolve over time, and are typically established by evidence of current practice

from medical and regulatory communities. Therefore, any report of diagnostic device performance should always include the definition of the clinical reference standard used.

Finally, Dr. Rorer encouraged the gathering to solicit input and feedback from the FDA on proposed preclinical testing and clinical trial design through the presubmission program prior to embarking on studies and during early stages of device development. This program provides investigators and manufacturers an opportunity to meet with the FDA. Dr. Rorer concluded the talk with a call to action, highlighting the need for well-characterized diagnostic devices with low bias and imprecision for detecting early-stage DR. She added that diagnostic device performance must be carefully considered when the devices are incorporated into therapeutic trials, especially for evaluating endpoints.

Highlights

Prior to conducting a pivotal clinical trial to support the approval of a new therapeutic intervention for DR, it would be prudent to ensure that the performance of any diagnostic device planned for use during the course of the trial (e.g., assess enrollment criteria and outcomes) has been sufficiently evaluated in the same context as planned for its use during the therapeutic trial and that the performance is adequate to support that use.

In order to develop and market new medical products for the earlier treatment of DR, well-characterized diagnostic devices with low bias and imprecision for detecting early-stage DR are needed.

PANEL DISCUSSION: CLINICAL TRIAL DESIGNS FOR NPDR, PDR, AND DME

Dr. Ferris opened the panel discussion with a query regarding approaches to develop personalized treatments for DR, given the current federal focus on precision medicine and the fact that almost half of patients treated with anti-VEGF drugs for DR do not respond to the treatment. (To put this finding in perspective, Dr. Ferris observed that almost all patients with AMD who are treated with anti-VEGF drugs respond to the drugs but require long-term treatment.) Dr. Aiello acknowledged the query as an important one, underscoring the fact that current research efforts in the post-VEGF era would potentially allow researchers to use biomarkers to identify responders and nonresponders to anti-VEGF drugs among patients. Though the need for such studies is clear, methods to operationalize biomarker tracking remain to be established. In particular, the small numbers of nonresponders in past clinical trials of anti-VEGF drugs would render clinical studies of treatment response challenging. That said, Dr. Chambers noted that in the absence of additional treatment options for patients, personalizing treatment for small groups of patients poses a circular challenge, at least from an FDA labeling perspective. Next, Dr. Jampol raised a question regarding the FDA's views of the use of OCT as a tool to measure endpoints in clinical studies of DR, and Dr. Chambers responded that OCT measurements of retinal thickness changes are currently not approved endpoints because of insufficient data on retinal thickness changes and their effects on visual function; the extent and time period of clinically relevant changes in DR have not been established conclusively.

Given that DME can be seen as the final outcome of a number of cellular pathways, Dr. Ferris noted the need for clinical studies to identify biomarkers in early stages of the natural history of DR. Dr. Chambers noted that a preliminary clinical study to identify responders might conceivably precede

the actual trial of a therapeutic agent for the predefined responder population for which labeling is being sought. On a related note, Dr. Helen Nickerson raised the idea of exploring the future use of patients' electronic medical records to collect information on potential prognostic biomarkers in early stages of NPDR. Dr. Sun raised a question regarding the conditions under which the FDA would accept secondary, as opposed to primary, outcomes in trials; and Dr. Chambers responded that even if an outcome measure is not predefined, an evaluation of whether the outcome is a true, clinically meaningful result or due to chance would underlie the FDA's decision on approval of the drug treatment. Dr. Jampol asked under what conditions recent techniques such as wide-field fluorescein angiography, which can provide information about the retinal periphery, would be accepted for use in monitoring treatment response in therapeutic clinical studies. Dr. Chambers responded that the wide availability of a technique is a factor considered in the FDA approval of the technique for measuring any given endpoint in drug trials, but that a more important factor is the clinical relevance of the endpoint measured by the technique as deemed by a majority of ophthalmologists. Dr. Sun also raised the question of using incremental changes in measures such as visual acuity to monitor progression in early stages of the disease, but Dr. Chambers emphatically noted that given the future goal of balkanization of patient populations based on treatment response, the use of substantial changes in small populations of patients is more likely to be approved in future trials rather than the use of incremental changes in large numbers of patients.

DR. RONALD DANIS AND DR. GLEN JAFFE

Dr. Danis, MD, discussed alternate outcome variables in DR clinical trials. He noted that anatomic endpoints can be used to stratify patients according to disease severity and monitor disease progression and treatment response. They can serve as surrogate outcomes if validated in clinical studies. To develop anatomic endpoints for eventual clinical use, proof-of-concept studies, single-center pilot studies, and large clinical trials must be carried out. These endpoints must show a strong, specific, and sensitive association with the outcome of interest; must be longitudinally studied in multiple populations; must be capable of being repeatable and reproducibly measured; and must generate normative data for future trials. Currently, there are no FDA-approved surrogate anatomic endpoints for DME. Hence the need for alternate endpoints.

Dr. Jaffe, MD, presented an example of a color fundus photo of a patient with NPDR and DME who improved following treatment as demonstrated by fundus photos and eye charts. The goal would be to use OCT to measure a corresponding resolution of DME and restoration of macular anatomy through changes in retinal thickness per volume as a surrogate endpoint in a trial. Given that OCT is noninvasive, rapid, widely available, and quantitative, and allows cross-sectional and topographic evaluations over time, it would be an ideal technique to measure such an anatomic endpoint. In past clinical trials, OCT has been used as a secondary endpoint to demonstrate a biological effect of drugs and has been correlated with visual function. Dr. Jaffe presented an example of a 2006 trial of laser photocoagulation and the intravitreal steroid drug triamcinolone for DME in 69 eyes that were followed for 2 years; OCT measurements of decreases in retinal thickness demonstrated the drug's biological effect.¹⁹ Similar findings have been reported from the VIVID/VISTA trials. Together, these findings suggest that OCT is a valuable tool for the measurement of alternate anatomic endpoints in trials.

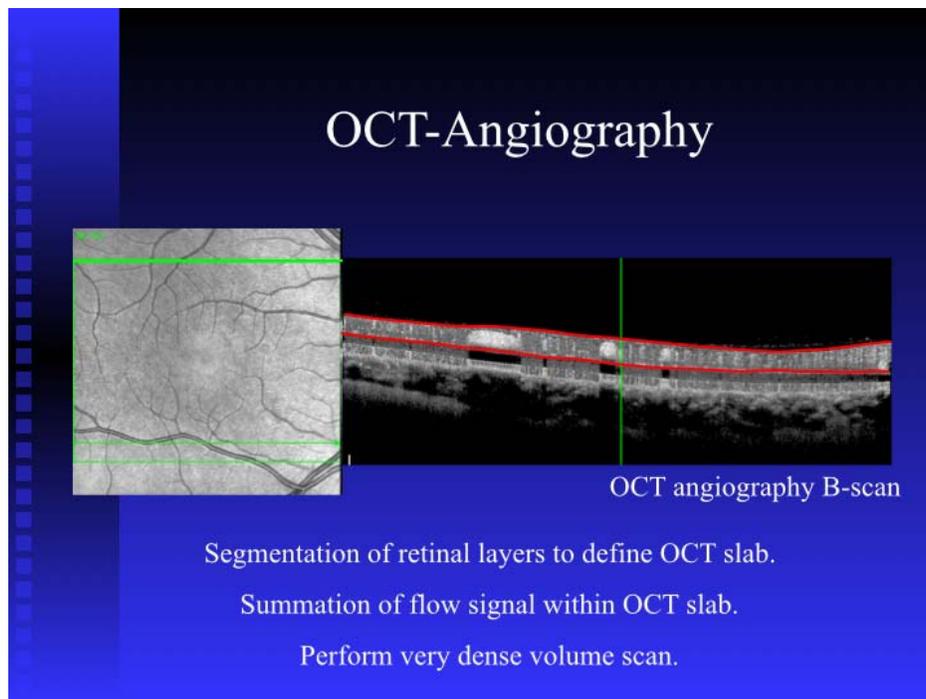


FIGURE 4. Open-label extension study of ranibizumab. Image courtesy of Jennifer Sun.

On a population level, cross-sectional studies and clinical trials have shown that OCT measures of retinal thickness are correlated with visual acuity. On a patient level, small studies have shown correlation between retinal thickness and visual acuity, but the correlation is far from perfect. Part of the problem, Dr. Jaffe noted, is the increasing resolution of OCT instruments, which have progressively revealed structural details previously hidden from view, posing a challenge for correlational studies. The development of software to perform automated segmentation of the different retinal layers allows the definition of boundaries between retinal layers for comparison as well as the quantification of multiple retinal layers and edema. Comparison of such automated segmentation with that performed by expert graders at reading centers has validated such software. Dr. Jaffe presented an example of OCT images from a patient with DME in a clinical trial who had been treated with a steroid drug. While the OCT images showed an improvement in DME over time, there was no corresponding improvement in visual acuity. Automated segmentation revealed disruptions in the fine structure of different retinal layers that could not be observed in the OCT images without segmentation. Further, studies have revealed correlation between visual acuity and disruptions in the outer retinal layers, namely, the photoreceptor external limiting membrane and ellipsoid zone, as well as disruptions in the inner retinal layers. Thus, by establishing a threshold of disrupted surface area for a given retinal microstructure, it would be possible to monitor worsening or improvement of the disruption over time using automated segmentation.

Next, Dr. Jaffe discussed the potential of OCT angiography, a focus of increasing attention among ophthalmologists. The technique involves the acquisition of a series of B scans at a fixed retinal location; and changes in the contrasts of the OCT images, such as hyperreflectivity, correspond to retinal blood flow. The retinal layers containing hyperreflective spots can be segmented to define OCT slabs, and dense-volume scans of the slabs can reveal deep structural details in layers of the vascular network at high resolution, including the perifoveal arcade,

superficial capillary plexus, deep capillary plexus, choriocapillaris, Sattler's layer, Haller's layer, and the choroid (Fig. 4).

Dr. Danis noted that retinal specialists often observe DR lesions outside the seven standard photographic fields used in the ETDRS grading of fundus photos in DR, and raised the question of the relevance of these peripheral lesions as prognostic biomarkers of DR (Fig. 5). Previous studies using ultrawide imaging have revealed substantial prevalence of such peripheral lesions and suggested that inclusion of these lesions may indicate increased severity on the ETDRS scale in some eyes. For example, one study of 121 eyes followed over more than 3 years using ultrawide imaging found that eyes with mostly peripheral lesions had a 5-fold increased risk of two-step DR progression over 3 years, and the absence of mostly peripheral lesions reduced the risk of DR worsening over 3 years by two-thirds (Silva PS, et al. *IOVS* 2014;55:ARVO E-Abstract 2278). He also noted that ultrawide-field imaging for DR severity is a widely available technique that remains to be widely adopted in clinical trials. A commercial SLO for ultrawide-field imaging from Optos, a United Kingdom-based manufacturer, is now available in hundreds of clinics worldwide, and the use of the device is being tested in ancillary projects to clinical trials. The SLO has a field of capture of up to 200° and a reasonable pixel resolution for microstructures, and previous studies have shown agreement between the grading performed using fundus photos and SLO images for DR severity. Thus, Dr. Danis mentioned that the pilot studies might allow refinement of the prognostic ability of the ETDRS grading scale using the peripheral lesion data. A 5-year study of DR severity that compares the standard seven-field fundus imaging and ultrawide-field imaging using Optos SLO is anticipated under the aegis of the DRCR Network.

Based on previous studies that showed an association between the location and area of nonperfusion in the retinal periphery and DR severity and the risk of onset of PDR, Dr. Danis suggested that fluorescein angiography of the peripheral fundus might have prognostic value in clinical studies. Further, the RIDE/RISE trials revealed an improvement in retinal

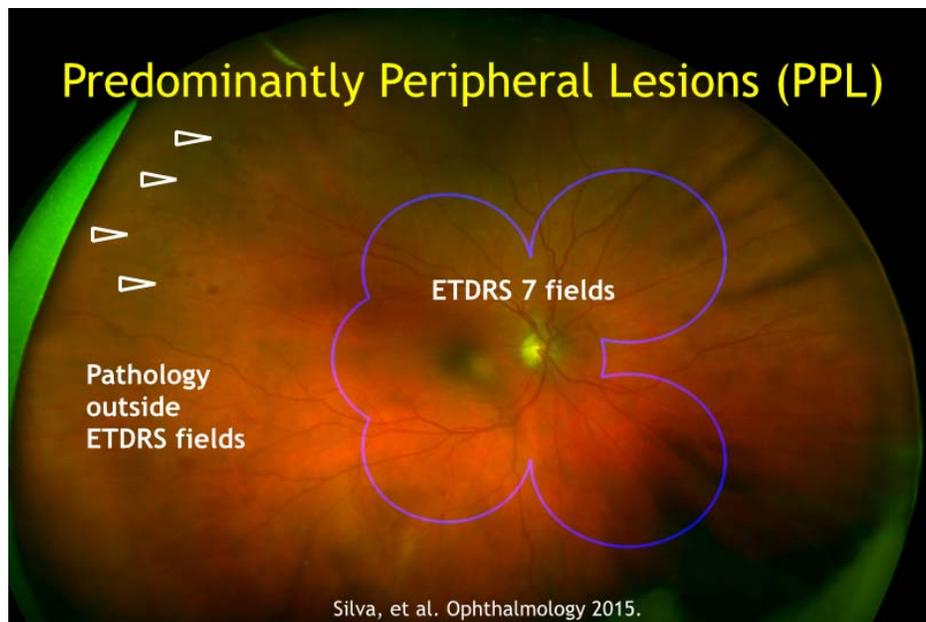


FIGURE 5. Automated segmentation and dense-volume scans can reveal fine structural details in retinal layers. Image courtesy of Glen Jaffe.

perfusion with anti-VEGF treatment, and other studies have documented improvement in peripheral nonperfusion with treatment of retinal vein occlusion and worsening of nonperfusion with increased risk of DME and onset of PDR. Parameters such as area of nonperfusion in the periphery could be reproducibly measured using segmentation programs and SLO, suggesting that vascular nonperfusion might serve as a potential clinical trial endpoint for DR.

Another potential endpoint-related technique is OCT angiography, which provides images of unparalleled resolution and contrast. Segmentation of digital images can help generate vascular density maps, and Doppler and phase signals can be used to measure blood flow, resulting in quantitative measures of vasculature using OCT angiography. One commercial instrument is currently available in around 300 clinics and must be validated in proof-of-concept studies before the technique can be considered for clinical trials. Another technique that might hold potential for use in clinical trials is adaptive optics SLO, a noninvasive technique to track erythrocyte aggregates in retinal blood capillaries.

In conclusion, Dr. Jaffe noted that in addition to ongoing collaborations between reading centers and the DRCR Network, there is a need for more partnerships with industry. The new imaging techniques must be tested in current and future prospective trials to establish structure-visual function correlations. Such trials might yield anatomic surrogates of visual function. The potentially superior prognostic value of such endpoints might help refine current DR severity scales.

Highlights

Validation of an anatomic endpoint requires concerted effort in multiple clinical trials to demonstrate a sensitive and specific association with functional outcomes.

Ultrawide-field fundus imaging holds promise to add additional prognostic information regarding DR progression, which may refine the sensitivity of the ETDRS scale in clinical trials.

Change in retinal capillary nonperfusion area over time as measured with ultrawide-field fluorescein angiography to quantitatively measure peripheral capillary nonperfusion is

another potential endpoint of high clinical relevance for clinical research because of its relationship with progression to PDR and possibly DME.

Applications of new technology such as OCT angiography and adaptive optics SLO imaging to the study of DR and DME are in early development but may provide useful metrics to monitor and predict disease progression.

DR. MICHAEL LARSEN

Dr. Larsen, MD, DMsc, discussed clinically significant measures of visual function that might predict long-term changes in visual acuity. Among the potential endpoints for DR clinical trials that are directly relevant to patients are best-corrected visual acuity, standard visual fields in photopic and scotopic modes, contrast sensitivity, glare sensitivity, color vision, dark adaptation, and practical tests such as maze navigation. The potential surrogate endpoints include electroretinograms, visual-evoked potentials, and frequency-doubling perimetry. Dr. Larsen noted that the long-term predictive value and robustness of several of these potential endpoints must be validated for use in DR clinical trials. He presented data from a Swedish study showing visual field deterioration over a 5-year period in patients with diabetes.²⁰ Other cross-sectional studies have shown that in diabetic patients, including those without retinopathy, duration of diabetes and glycemic control were associated with deficits in the retinal blue cone system. Still other studies have shown that diabetic patients with NPDR show abnormal frequency-doubling perimetry and poor sensitivity to dark adaptation. Dr. Larsen also presented evidence from an array of studies showing that glycemia can act as a confounder in studies of psychophysical measures such as ERG amplitude and dark adaptation. Studies involving insulin pump therapy for people with diabetes have shown a slow improvement in dark adaptation and ERG measures, and the duration of the glycemic history appears to influence the rate of improvement. Other confounders of visual field studies include lens aging and cataract surgery. In conclusion, Dr. Larsen proposed visual field studies as a strong candidate for a potential endpoint in clinical trials, given the known clinical

relevance of the endpoint and the different ways in which it can be refined.

Highlights

Visual field examination, a method with accepted clinical relevance, is a promising candidate endpoint for early intervention studies in DR.

The method can be refined in multiple ways, including photopic/scotopic, blue-on-yellow, and frequency doubling technology, to serve as a suitable endpoint in studies.

Confounders of this endpoint that should be taken into account include glycemia, glycemic history, lens aging, and cataract surgery.

DR. ANTONIA JOUSSEN

Dr. Joussem, MD, PhD, described the need for endpoints that would help predict clinical outcomes at each stage in the development process, from preclinical models to patient-relevant endpoints. Hence, Dr. Joussem stressed the need to combine molecular, structural, and functional data in computational models and machine-based learning to develop patient-relevant endpoints for DR. Advances in imaging techniques have allowed a detailed characterization of retinal pathology in patients with DR. For example, wide-angle angiography has revealed ischemia in the retinal periphery in many patients; and the presence of hyperreflective spots in OCT, which may represent early markers of inflammation, has been reported in patients with diabetes before overt clinical signs of DR begin to appear. Further, activated microglial cells, nervous system cells that respond to inflammation, have been found in the retina of patients with diabetes. Optical coherence tomography and SLO have been used to determine the extent of macular edema in patients with DME and to characterize retinal blood vessels. Interframe analysis of OCT angiography data can provide useful information about retinal blood flow contrasts, and OCT angiography can be used to detect microaneurysms, improve capillary visualizations, and derive three-dimensional reconstructions of the microvasculature of the retina and the choroid. Doppler OCT can be used to visualize the pulsatile nature and dynamics of the bidirectional flow of blood in arteries and veins. Retinal oxymetry has been used to measure light absorbance and oxygen saturation in blood vessels of patients with PDR before and after treatment. Phase-variance OCT, which measures neuronal potentials, can be used to distinguish retinal and choroidal blood vessels from nerves. However, many of these endpoints and imaging modalities remain to be validated for clinical use in substantial studies.

Given that diabetes is a complex disease with several potential comorbidities such as stroke, cardiovascular disease, diabetic nephropathy, and diabetic neuropathy, Dr. Joussem emphasized the need to focus on common molecular pathways underlying DR and its frequent comorbidities. Advances in next-generation sequencing technology have facilitated an in-depth analysis of the genetic basis of diseases, and Dr. Joussem highlighted the need for such fine-grained information in efforts aimed at identifying biomarkers for early-stage DR. She also mentioned the need to have central repositories for all project data, including molecular and clinical data, as well as platforms for integrating the data using a systems biology approach. While such data capture, annotation, validation, analysis, processing, transfer, and integration efforts have been demonstrated for several conditions, Dr. Joussem urged the DR research community to conceive similar approaches to help reconfigure the chain of endpoint development for DR.

Highlights

Endpoint research requires head-to-head comparisons of current and new imaging devices and functional measures.

A systems medicine approach can help integrate endpoint data with a deep molecular analysis of patients.

Validation, analysis, processing, and computational modeling can help predict the appropriate treatment approach for individual patients and help reconfigure the chain of endpoint development for DR.

DR. PAUL LEE

Dr. Lee, MD, JD, addressed issues related to insurance coverage of treatments for DR, in particular the level of evidence necessary for reimbursement of specific clinical procedures and treatments by payers. Once a drug is approved by the FDA, payers consider a number of factors in deciding whether to cover it, including physicians' input, accepted medical practice, and evidence related to the drug's necessity. As a practical matter, inexpensive drugs prescribed by individual physicians for small groups of patients may be covered by payers without special review. However, not all FDA-approved drugs are automatically eligible for coverage by the Centers for Medicare and Medicaid Services (CMS). The statute that governs CMS coverage requires that the covered drugs be safe and effective, not be experimental or investigational, be appropriate with respect to duration and frequency of administration, and comply with accepted medical practice. In compliance with accepted practice, the CMS considers whether the drug or service, which must be ordered and furnished by qualified practitioners, meets but does not exceed the beneficiary's medical need.

In the United States, local entities in various states often determine eligibility for Medicare coverage. The determination of national coverage typically depends on whether specific questions related to the beneficiary's health outcome can be conclusively answered and on whether the item or service covered is reasonable, is medically necessary, and improves health outcomes. Clinical evidence presented to support coverage must be applicable to the qualifying population and must provide quantitative conclusions about the magnitude and direction of risks and benefits to that population.

Though most therapies seek coverage without conditions, certain items and services are covered with special conditions known as "coverage with appropriateness determination factors," such as restricted use of the drug or service for specific indications and by providers with specialized training or credentials; substantial likelihood of misuse of the item or service; and likelihood of change in the nature of management of patients using the item or service. Drugs and devices that do not meet the evidentiary standards for CMS Medicare coverage can sometimes be covered on the basis of additional data from individual studies showing a benefit to some Medicare recipients. Such coverage is termed "coverage with study participation factors."

In the United States, each private insurer may offer many insurance plans, each with its own set of criteria for coverage eligibility, including peer-reviewed journal studies, randomized controlled trials, and evidence-based consensus statements, though most insurers generally consider the proven benefit, excluding experimental or investigational treatments, and medical necessity of treatments for coverage. Private insurers often rely on a range of sources, such as contract organizations, Cochrane reviews, internal assessments, and professional societies, to perform technology assessments to decide coverage eligibility. Surveys have revealed that influential source material for comparative effectiveness studies includes

that from the National Institutes of Health, Agency for Healthcare Research and Quality, and Cochrane reviews, among others. Studies have also revealed that while health technology assessment organizations provide credible, rigorous, and expert reviews that are largely independent of external influences, many private insurers lament the lack of nonclinical factors in such reviews, such as cost-effectiveness studies, information on the barriers to adoption of services, and the lack of timeliness in delivery of services.

Private insurers determine the precise amounts of reimbursement based on an array of criteria, such as the number of lives saved and number of uses of a given item or service. On the other hand, Medicare payment amounts are governed by statute, and CMS has final authority on payment amounts. Dr. Lee highlighted the issue regarding patient pricing; that is, for some covered items and services, costs to patients might still be extremely high. Further, one study found that the top 1% of patients in ophthalmology consumed approximately 21% of the costs in a recent survey of annual eye-related charges incurred by a private insurer.

Dr. Lee concluded the talk by observing that large provider organizations, not physicians, have increasingly become customers for payers. Further, given the increasing focus on early intervention to forestall disease, some health systems are now beginning to use quality-of-life measures in determining coverage eligibility. Hence, there is a continuing need for comparative effectiveness research, additional functional endpoints relevant to patients' health, and policy decisions on levels of reimbursement and pricing.

Highlights

Private insurers determine the precise amounts of reimbursement based on criteria such as the number of lives saved and number of uses of a given item or service. In contrast, Medicare payment amounts are governed by statute, and CMS has final authority on payment amounts.

There is a continuing need for comparative effectiveness research, additional functional endpoints relevant to patients' health, and policy decisions on levels of reimbursement and pricing.

ADAM GLASSMAN

Mr. Glassman reviewed findings from previous clinical trials to provide a perspective on future trial design for DME with reduced visual acuity using anti-VEGF treatment as the new standard of care. He began with considerations of appropriate control groups for future trials. Most recent trials of anti-VEGF agents for DME with reduced vision, such as the DRCR Network protocol I, RIDE/RISE trials, and VIVID/VISTA trials, used laser or sham treatment as the control, but in the post-anti-VEGF era, the anti-VEGF agents might be the new control. Using sham or laser as control confers advantages, such as the ability to demonstrate efficacy of the agent using a smaller sample size than would be needed if anti-VEGF drugs were the control, as well as the ease of blinding the trial. However, the continued use of laser or sham treatment as controls carries disadvantages, such as the ethical dilemma of withholding anti-VEGF treatment in favor of a placebo, the lack of efficacy data compared to the standard of care, issues related to consensus over suitable controls, noncompliance by patients, and crossover of treatments that can confound and derail trials.

Though evidence from past trials offers a rational basis for the use of anti-VEGF agents as controls in future trials, Mr. Glassman noted that the choice of therapeutic agent depends on efficacy, safety, cost, accessibility, and clinical applicability

considerations. Once an agent is chosen, patient eligibility must be considered. Given that anti-VEGF treatments are effective in improving visual acuity for many patients, and that few patients receiving them show worsening of visual acuity, the issue of a potential ceiling effect might arise while evaluating efficacy in trials for which visual acuity is a primary outcome, if the patients have moderately good visual acuity at the beginning of the trial. Such a ceiling effect would render comparison of effectiveness challenging and minimize the chances of detecting substantial improvements in visual acuity with an experimental agent. Demonstrating superiority of treatment over anti-VEGF drugs might thus require large cohorts of patients.

Nevertheless, such trials might provide clinically useful information if the experimental agent is cheaper, safer, and easier to administer and enables patient compliance and widens the choice of treatments in the marketplace. For such experimental agents, a noninferiority trial may be designed to show that the candidate does not lead to a worsening of the outcome by an acceptable margin, compared with an active control. However, such trials also pose challenges, including the determination of acceptable margins of noninferiority, elimination of bias in interpretation of findings, and analysis of secondary outcomes. Mr. Glassman noted that the determination of an acceptable margin must be grounded in clinical judgment, not merely in statistical considerations. The statisticians' input, however, is crucial in distinguishing between improvements in visual acuity for individual patients and average/mean improvements for groups of patients.

Next, Mr. Glassman discussed the choice of appropriate outcome measures for future trials. While mean change, area under the curve, and three-line improvement in visual acuity have been commonly used as outcome measures in past trials, taking a binary approach to evaluate outcomes on continuous variables might lead to loss of important clinical information, necessitate large sample sizes in trials, create ceiling effects, and lead to misclassification of outcomes. Thus, Mr. Glassman recommended that most clinical trials use comparison of mean changes as the primary outcome and report binary variables as secondary outcomes.

Based on an analysis of rates of visual acuity improvements over time in past clinical trials, Mr. Glassman suggested that a year-long trial might be reasonable when anti-VEGF treatment is chosen as a control, yet the trial may need to be lengthened depending on the rate of emergence of safety data and the efficacy of the comparator treatment used.

Finally, Mr. Glassman highlighted the increased cost associated with using anti-VEGF treatments as a control in future clinical trials. Depending on the choice of anti-VEGF drug, a clinical trial of 200 participants might cost between \$2.2 million and \$7.6 million, according to some estimates. In addition, the need for laser treatment as a control in future clinical trials of DME remains unclear.

Highlights

Given results from several phase III randomized trials, because of ethical issues, equipoise, and applicability to clinical practice there is strong rationale for the use of anti-VEGF treatment as the control group in most cases in a study evaluating novel treatments of eyes with decreased visual acuity from DME.

The selection of anti-VEGF agent to use as a control in future trials should be based on efficacy, safety, cost, accessibility, and clinical applicability considerations.

If consistent with the objectives of the study, a continuous outcome like mean change in visual acuity should be used as the primary outcome in most DME-related clinical trials because other outcomes, such as a binary outcome, might

lead to loss of important clinical information, necessitate larger sample sizes in trials, create ceiling effects, and lead to misclassification of outcomes.

DR. PETER SCANLON

Dr. Scanlon, MD, briefly discussed alternative outcome variables that might serve as potential endpoints in DR trials. He underscored the distinction between two- or three-step changes at different levels of the ETDRS scale; for example, a three-step change from 10/10 to 35/<35 is a markedly different change of severity than a three-step change from 47/47 to 61/<61. Further, Dr. Scanlon cited results from a study of the drug candesartan to delay the onset of DR in type 1 diabetes patients, showing an 18% reduction in two-step progression of DR that was of marginal statistical significance and 35% reduction in three-step progression of DR in a post hoc analysis.²¹ He also cited studies showing microaneurysm counts as a potential outcome variable in early stages of DR²² (though in later stages the counts can drop due to ischemia), and noted that a 15-letter loss or gain of visual acuity is a poor measure in early stages of DR but relatively good for later stages once the macula is involved. The thickness of the center of the macula might also be a useful endpoint in later stages of maculopathy.²³ The NEI-Visual Functioning Questionnaire, a 25-item list of questions to assess visual function deficits and their impact on daily functioning, is another quality-of-life outcome variable that may be useful in trials; analysis of past trial data shows that the questionnaire was correlated most closely with a weighted visual acuity score of 0.75 in the better eye and 0.25 in the worse eye, or 0.6 in the better eye and 0.4 in the worse eye.²⁴ Dr. Scanlon also mentioned an ongoing European trial of implicit time in multifocal ERG as a potential primary outcome variable for DR. Further, he raised general considerations regarding past and future clinical trials. The choice of treatment-naïve or -refractory patients may be crucial in trial design; past trials have largely included only patients with reasonable hemoglobin A1c levels, though many treated patients in clinics do not have well-controlled hemoglobin A1c levels; and older patients with concurrent illnesses are often not included in trials. Dr. Scanlon emphasized the importance of centralized assessment of endpoints with independent validation, including lab assays and the reading of OCTs, color fundus photos, and fluorescein angiograms, and the need for harmonized quality assurance methods across study centers over the entire course of studies.

Highlights

Standardization of measurements between the different grading sites needs to be assured by within- and between-site variation in grading, including over time. One approach for quality control might include putting masked images into the grading to ascertain any drift.

Centralized training using the same equipment and protocols and user certification are also needed for such standardization.

The more precise the measure, the smaller the sample size of the study needed.

PANEL DISCUSSION: ALTERNATIVE OUTCOME VARIABLES AS RELEVANT ENDPOINTS

Dr. Barbara Klein, MD, MPH, began the discussion by highlighting potential challenges tied to the harmonization of data from multicenter clinical trials, such as differences in

funding and trial procedures between centers. She mentioned efforts such as CONCERT, a consortium aimed at integrating and harmonizing clinical trial data from multiple centers for a range of trials, including DR trials. She also emphasized the importance of testing scientifically relevant interventions in trials rather than choosing interventions based primarily on monetary considerations of drug manufacturers. Next, an audience member raised a question regarding the choice of anti-VEGF agent that clinicians and the FDA might consider appropriate for use as a control in future trials. Dr. Chambers responded that the FDA does not always require the demonstration of superiority over another drug for labeling a given indication, and that the labeling is often based on more than one trial. Mr. Glassman added that despite the safety and efficacy data obtained from past clinical trials, the choice of anti-VEGF agent as a potential control for future trials remains an open question, dependent on cost and clinical applicability considerations, among others. Dr. Larsen next raised a question regarding the potential routes of administration for any future systemic drugs for DR. He wondered whether clinicians and regulatory authorities would weigh the frequency of drug administration against the relative gain of visual acuity in determining whether or not to approve and/or prescribe such systemic drugs. Dr. Aiello added that although the move toward systemic therapies for DR is a plausible one, clinical trials must explore safety, off-target effects, prescription choices, and compliance issues before any systemic agents for DR can be considered for regulatory approval.

CONCLUDING REMARKS: DR. THOMAS GARDNER

Dr. Gardner invoked the well-known successes in prevention and treatment of cardiovascular disease achieved through clinical monitoring and management of blood pressure and cholesterol as a reminder of the significance of early intervention in forestalling diseases with a progressive toll. Similarly, screening and intervention for premalignant lesions have also led to remarkable changes in clinical care of skin, colon, and breast cancer for many patients. In the same vein, physicians have long known that dynamic changes in intraocular pressure, creatinine levels, and ejection fraction can predict loss of visual, kidney, and cardiac function in patients, respectively. Hence, Dr. Gardner emphasized the need to pursue similar approaches to design clinical trials and generate clinically relevant, multiple, practicable endpoints for subsets of patients that would ultimately help reduce the worldwide disease burden tied to DR. Toward that end, he underscored the need to focus on prevention of DR from an epidemiologic standpoint.

On a broader level, he also argued that it is essential for the National Institutes of Health and other diabetes research funding organizations to continue to lead the development of better approaches to the ocular complications of diabetes.

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