RESEARCH OPPORTUNITIES

Report from the NEI/FDA Ophthalmic Clinical Trial Design and Endpoints Symposium*

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The National Eye Institute (NEI) of the National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA) held an open symposium on November 28–29, 2006, in Washington, DC, where representatives from both federal agencies, the Center for Medicare and Medicaid Services (CMS), university scientists and clinicians, and others conferred on endpoints and clinical trial strategies for evaluating new treatments for age-related macular degeneration (AMD), diabetic retinopathy, and other retinal disorders. The symposium was organized as a forum for discussion by the Association for Research in Vision and Ophthalmology (ARVO). Co-hosts of the symposium were Janice M. Soreth, MD, Director of the Division of Epidemiology and Clinical Research (NEI), and Karl G. Csaky, MD, PhD, NEI Senior Investigator.

The symposium evolved from a series of meetings between members of the eye and vision research community and CDER. The research community is looking to the FDA for information that will help with obtaining timely approval of new products arising from ophthalmic clinical research. The National Alliance for Eye and Vision Research (NAEVR) was the host of the initial meetings. NAEVR is a nonprofit advocacy organization working on behalf of professional, consumer, and industry organizations involved in eye and vision research. Stephen J. Ryan, MD, NAEVR Board President and President of the Doheny Eye Institute of the University of Southern California, in his keynote speech to symposium attendees, noted that the need for more efficient and cost-effective clinical trials “...is especially important in ophthalmology where new technologies are enabling better quantitative measurements of outcomes, which subsequently expedites the translation of clinical trials into improved practice patterns.”

The format of the NEI/FDA Ophthalmic Clinical Trial Design and Endpoints Symposium was a roundtable discussion moderated by Dr. Csaky. Presenters and discussants sat before an auditorium of approximately 250 observers. Audience members, mainly from industry, federal agencies, academia, and vision advocacy groups, had the opportunity to submit questions to the symposium organizers before the discussion.

In essence, the symposium addressed developing standards for clinical trials in ophthalmology and focused largely on the type and duration of clinical trials or post-surveillance studies in addition to the clinical importance of the endpoints used in vision research clinical trials. The discussion consisted of five sections for which speakers and discussants addressed questions they had received in advance. The five sections were as follows:

1. Visual acuity parameters as outcomes measures
2. Endpoints in diabetic retinopathy
3. Design and endpoints for neovascular AMD
4. Design and endpoints for geographic atrophy
5. Postmarketing drug surveillance

We continue this report with additional background on the topic of clinical endpoints in ophthalmology followed by an overview of the discussions in each of the five sections.

OVERVIEW

Sophisticated new technologies (e.g., Fourier domain optical coherence tomography [OCT]) are gaining the attention of ophthalmic researchers and clinicians worldwide for the beautifully detailed topographic and anatomic scans they provide of cross sections of the retina. The newest devices are capable of generating three-dimensional (3-D) reconstructions, topographic analyses, and macular thickness measurements. They reveal retinal disease and generate new data points not previously accessible. In addition to providing clinical information to physicians, they have the potential to serve as endpoints in clinical trials. However, changes that are seen and measured by OCT do not always correlate with visual function. The changes can be used as indicators of a treatment effect, but it is not clear how and when OCT findings can be used as a surrogate outcome for visual function.

The FDA currently recommends that clinical study sponsors use change in visual function as a primary endpoint in measuring the effect of a new compound for treating a disorder of the eye and also considers anatomic markers such as retinal detachment and the extent of spread of geographic atrophy (GA), which can indicate progression of an eye disorder. The new technologies, unlike functional tests and gross anatomic markers, have the potential to identify onset or progression of disease (e.g., nonproliferative diabetic retinopathy to proliferative disease) before symptoms occur, which could lead to earlier therapeutic interventions and better visual outcomes for patients.

New endpoints, biomarkers, and outcomes for clinical trials are being discussed in other fields besides ophthalmology, including Huntington’s disease. A recently published article argues succinctly in favor of using change in MRI-detected striatal volume as a biomarker of preclinical Huntington’s disease. 4 For purposes of clarification we will borrow definitions from this well-presented article and from elsewhere for this publication.
A biomarker, as defined by the Biomarkers Definitions Working Group, is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” Biomarkers are of greatest value if they can serve as surrogate endpoints in clinical trials.

A surrogate endpoint, according to the FDA, is a biomarker that is “reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence to predict clinical benefit.” The best surrogate endpoint is a biomarker that changes along with clinical endpoints. CD4 cell count in AIDS is a classic example: It was discovered that as patients’ clinical status improves in response to treatments, their CD4 cell count also increases, thereby making CD4 cell count a surrogate endpoint.

The Biomarkers Definitions Working Group defines clinical endpoint as “a characteristic or variable that reflects how a patient feels, functions, or survives.”

The FDA considers that a patient-reported outcome (PRO) is “any report coming directly from patients (i.e., study subjects) about a health condition and its treatment.”

A primary endpoint is defined as the main result that is measured at the end of a study to see if a given treatment works. The primary endpoint is chosen before a clinical trial begins.

An anatomic endpoint is an anatomic feature that is measured at the end of a study to assess whether a given treatment works.

As part of his introductory remarks, Dr. Ryan pointed out that Fourier domain OCT is opening a new frontier for patients with retinal disorders. Just over the horizon he sees software that can quantify the extent of drusen; follow the progression of GA; and measure the area of choroidal neovascularization, submacular leakage, hemorrhage, and so on, which would allow researchers to identify subgroups of patients for clinical studies and help clinicians make treatment decisions based on characteristics of an individual patient’s retinal pathologic profile.

Visual Acuity Parameters as Outcomes Measures

Speakers in this session were Frederick Ferris, Rhea Lloyd, Maureen Maguire, and Ross Brechner.

Discussants were Lloyd Aiello, Roy Beck, William Boyd, Ross Brechner, Neil Bressler, Wiley Chambers, Karl Csaky, Matthew Davis, Frederick Ferris, Ronald Klein, Anne Lindblad, Rhea Lloyd, Maureen Maguire, and Martin Nevitt.

Two main questions were the focus of the discussion:

1. Are there measures of visual acuity other than the proportion of patients with either a 3-line gain or a 3-line loss that can be used as primary study outcomes?
2. How do we assure that statistically significant differences in visual function outcomes are clinically important?

Dr. Frederick Ferris

Dr. Ferris opened the session with a look at a new approach to measuring visual acuity, combining established eye charts and advanced technology. As he pointed out, “We are all thinking about how we are going to use the evolution of technology and information in clinical trials.” He added that the Snellen Eye Chart has been effective for the clinical assessment of visual acuity in patients for more than 100 years and remains a very useful clinical tool; but, for clinical trials, it lacks the strict standardization that is necessary for detecting differences in new treatments for retinal disorders.

Dr. Rhea Lloyd

Rhea Lloyd of the FDA, in answer to Ferris’ question about the acceptability of a smaller degree of change in visual acuity, responded with a statement that her colleagues repeated during the 2 days of meetings: “Smaller degrees of change might be considered acceptable, but the degree of risk must be correspondingly small.” An example of this position in an earlier case was the FDA’s approval of dorzolamide (Trusopt; A newer visual acuity chart was adopted for the Early Treatment Diabetic Retinopathy Study (ETDRS). The ETDRS chart has a logarithmic progression of letter size, and chart lighting and seating distance from the chart are standardized. A goal of its NEI developers is the standardization of visual acuity measurement in research studies and a “calculated visual acuity score” that can be used as a continuous variable for statistical analysis purposes. An electronic visual acuity (EVA) testing device has recently been developed for recording a person’s visual acuity. The patient views one letter at a time on a screen while a technician records a simple yes or no depending on whether the patient identifies the letter correctly or not. This device has been shown to provide visual acuity results comparable to the ETDRS visual acuity protocol and has the advantages of speed and reducing technician variability in the measurement process.

For the detection of treatment differences in clinical studies, the responses can be used for calculating mean visual acuity or mean change in visual acuity. Dr. Ferris raised a question for additional consideration: Would a 2-line rather than a 3-line gain or loss in visual acuity be acceptable as a primary study outcome? Can we identify a mean change in visual acuity smaller than 15 letters that would be considered clinically significant?
Merck, Whitehouse Station, NJ), which, when compared to timolol ophthalmic solution for reducing intraocular pressure, was less efficacious but posed a smaller risk to patients. Dr. Lloyd added that trial sponsors can always pursue different endpoints (e.g., 3 lines vs. 2 lines); the responsibility of the sponsor is to justify the clinical relevance of the new endpoints. An FDA argument in favor of a 3-line difference is that visual acuity changes of less than 3 lines often occur when there has been no change in treatment.

The FDA currently considers multiple measures of visual function as acceptable primary endpoints for clinical trials that evaluate the safety and effectiveness of drugs, including but not limited to:

1. **Visual acuity**, using charts at 4 or more distance with an equal number of letters on each line and equal spacing of lines. A 3-line (15-letter) change represents clinical significance. A between-group difference in mean visual acuity of 15 letters or more is also considered clinically significant.

2. **Visual fields**, provided a between-group difference in field progression is demonstrated.

3. **Contrast sensitivity**, provided there are clinically and statistically significant differences in multiple spatial frequencies.

4. **Color vision**, provided the amount of change is shown to be statistically significant by a validated scoring system, such as the Farnsworth-Munsell 100-hue test.

**Dr. Maureen Maguire**

Statistician Dr. Maureen Maguire addressed the method of comparing new treatments. In other words, does the mean reveal whether a new treatment—compared with a placebo or with the old treatment—shifts the distribution of change toward improvement? The simple answer in her opinion was yes. Visual acuity letter scores are continuous data. Therefore, the mean is the natural and most efficient summary measure. Determining whether a treatment difference meets the criteria to be clinically meaningful requires evaluating point estimates and confidence intervals as well as safety and efficacy data.

She added that the visual acuity scores from ETDRS charts and electronic EVA machines are highly reproducible, which gives the mean additional power. Requiring a 3-line difference can pose problems, especially when studying therapies for disorders that progress very slowly (e.g., retinitis pigmentosa) or when using the new anti-VEGF agents when only 5% of patients lose as much as 3 lines of vision within 1 year. In other words, a difference between treatment groups when a 3-line loss in visual acuity is the primary endpoint may be unachievable in many trials, and it may be necessary to identify other endpoints based on the disease and on the intervention.

**Dr. Ross Brechner**

Dr. Ross Brechner of CMS emphasized the increasing importance of strict standardization as researchers look for smaller treatment differences. Until recently, ophthalmic researchers have sought differences between treatment and no-treatment conditions. Now, they are looking at the effects of different treatments, where the variation in outcome is generally smaller.

**Session Discussion**

Discussion included comments that contrast sensitivity, visual fields, and color vision were, in most cases, more valuable for supporting visual acuity outcomes than as primary endpoints in clinical trials evaluating the safety and efficacy of drugs for retinal conditions. It was acknowledged that a 1-letter difference in tests of visual acuity (as was observed and found to be statistically significant in the Complication of AMD Prevention Trial [(CAPT))]3 would not be clinically important, but some individuals on the panel expressed that at least a 5- or 6-letter mean difference, again under certain circumstances and with appropriate comparable safety considerations, would be.

**Endpoints in Diabetic Retinopathy**

Speakers in the second session of the first day were Lloyd Aiello, William Boyd, Glenn Jaffe, Thomas Gardner, and Ronald Klein.

Discussants were Lloyd Aiello, Frederick Ferris, Roy Beck, William Boyd, Neil Bressler, Wiley Chambers, Emily Chew, Karl Csaky, Matthew Davis, Frederick Ferris, Thomas Gardner, Glenn Jaffe, Ronald Klein, Rhea Lloyd, and Martin Nevitt.

Two main questions were the focus of the discussion:

1. Are there clinical trials of diabetic retinopathy that do not require a 3-year follow-up period?
2. What is the role of anatomic endpoints in diabetes trials?

**Dr. Lloyd Aiello**

Dr. Aiello addressed the second question of using anatomic endpoints for clinical trials in proliferative diabetic retinopathy and diabetic macular edema. In clinical trials of diabetic retinopathy, severe loss of visual acuity, moderate loss of visual acuity, and 2- or 3-step worsening of retinopathy have traditionally been used as endpoints. He suggested that newer clinical trials may benefit from the establishment of anatomic endpoints, such as onset of proliferative diabetic retinopathy or changes in the thickness of the center of the macula, as demonstrated by OCT. The onset of proliferative diabetic retinopathy can be photographed and compared with identical regions in earlier photographs to confirm that the neovascularization is new or different from baseline. The development of neovascularization has been shown to be associated with eventual vision loss and reduction in color vision and dark adaptation. Trials in which the development of neovascularization is the primary endpoint would be potentially less costly and require fewer patients than studies in which change in visual acuity is the endpoint.

Similarly, he suggested new anatomic endpoints for diabetic macular edema that rely on thickness of the macula at its center. He presented data showing a significant correlation between retinal thickening in the center of the macula and increased risk to patients of sustained moderate visual loss. Conversely, patients with no central macular involvement had a more moderate visual loss over time. A deficit in color vision, another possible endpoint in clinical trials of new treatments for diabetic macular edema, is also associated with macular edema, particularly when the center of the macula is involved. Dr. Aiello suggested that central macular thickening quantified by OCT may be considered an outcome variable because it is generally an indicator for focal laser photocoagulation.

**Dr. William Boyd**

Dr. Boyd reported the endpoints that the FDA recommends for clinical trials of diabetic retinopathy and introduced another endpoint the FDA would accept.

The well-known recommended endpoints are as follows:

1. Statistically and clinically relevant differences in visual function at more than one time point.
2. Alternatively, a statistically significant difference in the percentage of patients at 3 years with a ≥3-step change on the ETDRS retinopathy scale.
3. The agency recommends that trials be continued for at least 36 months. Efficacy data for the primary endpoint would be accepted at 36 months or more. Past trials have demonstrated that findings from earlier than 36 months in diseases such as diabetic retinopathy are not always predictive of later findings. Drug products have shown different results at 6, 12, and 18 months compared with 36 months and longer. This finding is demonstrated in Figure 1, from the Diabetes Control and Complications Trial (DCCT), showing years of study on the x-axis and the percentage of patients experiencing a 3-step change in ETDRS retinopathy scale on the y-axis.

It was not until well into the second year that it became obvious that intensive therapy was superior to conventional therapy for preventing the 3-step change on the ETDRS retinopathy scale. At less than 1 year, in fact, conventional therapy appeared better.

Dr. Boyd also used the session to talk about a newer FDA-recommended endpoint, saying that clinical evidence of effectiveness in 3-year trials could be demonstrated either by a single time-point evaluation at 3 years or longer or two time-point comparisons with “wins” on both comparisons. There would have to be a clinically and statistically superior difference from the original baseline. The comparisons could be between baseline and 18 or 24 months and between 18 months and a later time point, such as 24 months or longer. This comparison would have to be numerically noninferior when the 18-month time point is used as a baseline. For each of these two comparisons, the same 24-month evaluation could be used as the final endpoint, or different evaluation time points could be used, as long as they are prespecified. The trial should continue to collect safety information for at least three full years. See Figure 2 for a summary of the FDA-recommended endpoints.

With respect to whether anatomic endpoints can be used as clinically relevant primary endpoints in diabetes trials, the FDA agrees that anatomic endpoints are potentially useful provided they can be validated as the ETDRS retinopathy scale was validated, showing that the anatomic change is predictive of a clinically important visual function change such as a 3-line change in visual acuity.

Dr. Glenn Jaffe

Dr. Jaffe discussed OCT for clinical trials of diabetic macular edema. OCT reveals cross-sectional and topographic morphology of the macula and can quantify macular thickness and other characteristics at baseline and at follow-up. OCT is noninvasive and fast. It can be used to calculate macular thickness in prescribed regions. Its capacity to reveal cystic changes and subretinal fluid (Fig. 3) could make it particularly valuable for studies of the effect of drugs. Dr. Jaffe presented evidence showing ways that OCT can reveal anatomic endpoints (e.g., decreased central macular thickness) that would act as surrogates for the commonly used functional endpoints. He suggested that OCT could be used to predict positive responders for different treatments and to guide retreatment with intravitreous injections for reducing macular thickness.

Dr. Jaffe concluded that long-term studies would be needed to correlate visual function (e.g., visual acuity, dark adaptation, and microperimetry), macular thickness, and other morphologic characteristics. There is also a need for better algorithms to quantitate morphology and subretinal fluid volume. OCT may even be useful for evaluating photoreceptor cell health.

**Figure 1.** Results of the secondary intervention group from the DCCT demonstrating the two year lag before the effect of intensive therapy on the degree of diabetic retinopathy becomes evident. Reprinted with permission from The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977 to 986. © 1993 Massachusetts Medical Society. All rights reserved.

**Figure 2.** The FDA recommends several endpoints for clinical trials of diabetic retinopathy. A new endpoint was recently added.
and the amount of remaining retinal tissue. He suggested, too, studying what short-term changes in visual acuity, correlated with OCT measurements, means for the patient in the long term.

Dr. Ronald Klein

Dr. Klein pointed out the challenge that the current endpoint of a progress of a ≥3-step progression on the ETDRS retinopathy scale poses for clinical trials—in terms of the number of patients needed and the duration of the trial—when subjects at the outset have minimal or no retinopathy. Based on the Wisconsin Epidemiologic Study of Diabetic Retinopathy, he has calculated that to demonstrate a 25% reduction in the risk of a ≥3-step progression, a clinical trial would require 1836 subjects with type 1 diabetes or 2088 with type 2 diabetes for a period of 4 years.

He suggested instead that two surrogate endpoints be used in clinical trials: microaneurysm counts and 2-step progression on the ETDRS retinopathy scale. He and colleagues have shown that microaneurysm counts at the outset of a trial correlate with degree of progression to proliferative disease and clinically significant macular edema 4 years later. They have also shown that as few as 2 steps of progression along the ETDRS retinopathy scale over a 4-year period is associated with a similar increased risk of incidence of proliferative diabetic retinopathy or clinically significant macular edema over the following 6 years as a 3-step or greater progression.

Dr. Thomas Gardner

Dr. Gardner suggested that current endpoints for diabetic retinopathy, designed to assess macular edema and proliferative diabetic retinopathy, are focused on events too late in the continuum. To prevent vision impairment, it would be necessary to identify retinal dysfunction at a preclinical stage before signs and symptoms become apparent to the patient or clinician. This novel approach would require a new definition of diabetic retinopathy. The historical definition is that diabetic retinopathy begins when the ophthalmologist identifies microaneurysms in the fundus.

FIGURE 3. This Stratus OCT (Carl Zeiss Meditec, Inc., Dublin, CA) cross-sectional image reveals retinal thickening, intraretinal cysts, and subretinal fluid. (Courtesy of Glenn J. Jaffe, Duke University Eye Center, Durham, NC.)

FIGURE 4. The NEI’s Visual Functioning Questionnaire (VFQ-25) has revealed the impact that improved visual acuity has on quality of life in patients with exudative AMD. The patients participated in the ANCHOR study of the anti-VEGF compound ranibizumab. (Graph courtesy of Genentech, Inc., South San Francisco, CA.)

Mean Change in VFQ-25: Vision-Specific Subscales at Month 12 as a Function of Change in VA at Month 12

[Graph showing changes in various subscales related to visual functioning and vision acuity changes.]
Dr. Gardner proposed that a better definition of diabetic retinopathy would be when cells of the whole retina are not working properly, which he and his colleagues plan to assess by studying dark adaptation, scotopic sensitivity, contrast sensitivity, visual fields, and frequency-doubling perimetry in patients who have various degrees of disease severity. He pointed to a study showing that visual fields correlate better than visual acuity to the severity of diabetic retinopathy\(^{12}\) and to observations about delays in dark adaptation in patients with diabetic retinopathy.

For clinical trials, Gardner and his colleagues believe that a multipronged approach to retinal assessment stemming from their research could have the advantage of showing effects of new therapies in a smaller number of patients in a shorter amount of time.

**Session Discussion**

A point was made that a 3-year clinical trial to prove efficacy of a drug for proliferative diabetic retinopathy is a high hurdle compared to 2 years. (In AMD, by comparison, drug efficacy is usually measured at 1 year and assured out to 2 years.) With caveats for steroids and other drugs with known potential side effects, should a 2-year approach be applied to diabetic retinopathy? The answer from the FDA’s Dr. Wiley Chambers was that the agency is willing to look at 2-year data but only as defined by Dr. Boyd’s presentation. There was a lengthy discussion about 3-year trials for diabetic retinopathy and diabetic macular edema indications. Past trials submitted to the FDA have demonstrated that earlier findings in diseases such as diabetic retinopathy are not predictive of later findings (i.e., a drug product has shown different results at 6, 12, and 24 months versus 36 months and longer). It was noted, too, that 3-year trials in ophthalmology are not excessive in comparison to the trial durations required for similar diseases such as heart disease.

Dr. Chambers added that the development or remission of proliferative diabetic retinopathy is an acceptable anatomic endpoint. How the changes are captured and classified is very important, as is the criteria for clinical study enrollees.

Looking at regression of neovascularization as an endpoint, participants agreed that abolishing neovascularization is good; however, regression, when used as an endpoint, may be particularly difficult to document and quantitate. A clinical trial protocol that requires no proliferative disease at the outset of enrollment would be easier than the opposite.

Participants continued with a discussion about central macular involvement as one of the key aspects of diabetic macular edema and the use of fundus photography and OCT for documenting macular thickening and for making decisions about treatment. Dr. Chambers expressed a concern that development or regression of macular edema might not be as absolute an endpoint as development of neovascularization because of its sometimes transient nature. “There are different grades of macular edema,” he said, “some of which come and go at different points in time and some of which cause irreversible harm. . . . The issue is knowing how thick before you call it macular edema and how frequently you need to be monitoring to be sure you wouldn’t miss edema that came and went.”

Questions were posed about how well OCT-derived measurements of macular thickness correlate at a given time point and over an extended period with various aspects of vision. The feeling was generally that the answer is not currently available, but will be in the near future.

In terms of prevention of diabetic eye disease, there is agreement that a biomarker that tells who is at risk for diabetic eye disease would be a major asset, one that would be predictive in the same way that cholesterol is predictive of cardiovascular events. This could mean that people at risk would be taking a drug for many years. A paramount interest of the FDA is that drugs available to the American people be safe and effective. Benefits must outweigh the risks, which can be a challenge when drugs are used for many years.

**Design and Endpoints for Neovascular AMD**

Speakers in this first session of day 2 were Neil Bressler, Karl Csaky, Wiley Chambers, Frederick Ferris, Jeffrey Heier, and Philip Rosenfeld.

The discussants were William Boyd, Ross Brechner, Neil Bressler, Wiley Chambers, Frederick Ferris, Karl Csaky, Jeffrey Heier, Glenn Jaffe, Jennifer Lim, Matthew Davis, Rhea Lloyd, Joan Miller, Martin Nevitt, and Philip Rosenfeld.

Three main questions were the focus of the discussion:

1. What primary outcome variables can be used for multi-agent clinical trials for neovascular AMD?
2. How should one use OCT as a tool for retreatment in neovascular AMD?
3. How can anatomic endpoints (development of CNV or changes in fundus examination as seen on fundus photography) be used in AMD trials?

**Dr. Wiley Chambers**

Dr. Chambers reminded meeting attendees that a reason the FDA sets a high bar for new drug approvals is that they are making predictions about these drugs 3 and 4 years into the future. A lower bar may be acceptable if the degree of risk to the patient is correspondingly smaller. He added that the FDA would consider different endpoints for clinical trials, but the trial sponsor would have to justify the clinical relevance of the new endpoints.

He explained the FDA standard for drugs where two products are used in combination (called combination products or multi-agent products):

1. A synergistic effect is not required.
2. Well-controlled studies must demonstrate the statistical and clinical superiority of the combination therapy, such that A + B > A, A + B > B, A not worse than placebo, and B not worse placebo. (A 3-line change in visual acuity is considered a relevant endpoint for demonstrating clinical superiority.)
3. The benefits of the combination therapy must outweigh the risks.
4. If the sponsor asserts improved compliance on the part of the patient, it must be proven. Furthermore, simply reducing the frequency of administration of another product is not considered beneficial unless the reduced frequency also lessens adverse consequences.

The FDA recommends 24-month trials of combined therapies for neovascular AMD, although primary efficacy data for the primary endpoint is acceptable at 12 months. To demonstrate equivalence, the 95% confidence interval (CI) should be within 10 percentage points for those subjects demonstrating less than 3 lines of ETDRS visual acuity loss at 1 year when compared with ranibizumab. Alternatively, to demonstrate equivalence, the 95% CI of the mean visual acuity should be within 3 letters on an ETDRS visual acuity chart.

Dr. Chambers thinks that OCT will be a useful tool for deciding on retreatment of AMD lesions but not until OCT findings have been validated against visual function. Multiple OCT measurements of retinal thickness over time are likely to be more valuable than single measurements for making decisions about treatment. For decrease in retinal thickness or change in any other anatomic feature to be used as an endpoint
in AMD trials, the trial sponsor must be able to demonstrate an associated change in visual function. The FDA “would welcome the submission of studies that validate anatomic endpoints compared to functional endpoints.”

Dr. Frederick Ferris

Dr. Ferris proposed four retinal lesions that could be identified on routine fundus photography and that did not require fluorescein angiography—retinal detachment (neurosensoric or hemorrhagic retinal detachment), hemorrhage (sub-retinal or sub-RPE), subretinal fibrosis, and central GA—as independent outcome variables for clinical trials of compounds for preventing advanced AMD in patients at risk. He demonstrated the association of the lesions in AMD to lowered visual acuity scores based on Age-Related Eye Disease Study (AREDS) data. He suggests that a combination of two of these lesions could be a useful indicator of development of advanced AMD.

Dr. Jeffrey Heier

Dr. Heier reminded attendees that the primary outcome for phase 3 trials in the treatment of exudative AMD has traditionally been the prevention of moderate vision loss, defined as loss of less than 15 letters on the ETDRS visual acuity chart at month 12 compared with baseline. Several studies have achieved this standard in recent years, including the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP)15 trial for photodynamic therapy and the VEGF Inhibition Study in Occular Neovascularization (VISION)14 trial for pegaptanib. He pointed out that although the endpoints are statistically significant and clinically meaningful, the gain for patients is less satisfying. After all, the outcome is less visual loss and not gains in visual function.

This outcome has changed recently with anti-VEGF treatments such as ranibizumab that not only stabilize vision but also demonstrate a potential for improving vision. This potential introduces a secondary outcome for phase 3 trials in the treatment of exudative AMD—mean gain in vision—and the question of what constitutes a meaningful gain in vision to clinicians and patients. Three lines? Fewer? Dr. Heier suggested looking at PROs using the NEI-VFQ 25 to examine the correlation between vision gain and measures such as social functioning, role difficulties, vision-specific mental health, and dependency. Figure 4, from the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR)15 study, shows dramatic differences in NEI-VFQ 25 scores beginning with zero vision gain or loss.

Dr. Neil Bressler

In response to the questions of what primary outcome variable to use for multi-agent clinical trials for neovascular AMD, Dr. Bressler recommended using change in mean visual acuity because of its strength as a summary statistic when a continuous variable such as a letter score is used and its better ability than a dichotomous outcome to detect small differences between treatments with fewer subjects. He further proposed considering a 10-letter (−2-line) or greater change in visual acuity to be clinically relevant, for several reasons. First, published reports show that a ≥2-line change is clinically relevant in people with visual acuity better than 20/200, which is the case in most patients with AMD who initially present with neovascular AMD. Second, the criterion is supported by combining data from the ANCHOR and the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA)16 studies and comparing NEI-VFQ 25 scores between patients who had gained 10 or more letters and those who had lost 10 or more letters. No matter where patients started out in initial visual acuity (i.e., 20/50 or better, 20/63 to >20/100, 20/100 to >20/200, 20/200, or worse) the composite score for the NEI-VFQ 25 score went up by at least an amount judged clinically relevant by experts in this field (between 5 and 10 points) in the people who had gained at least 10 letters of vision and down by at least 5 to 10 points in those who had lost at least 10 letters of vision.

Dr. Philip Rosenfeld

Dr. Rosenfeld described 1-year data from the Prospective Open Label Exploratory Optical Coherence Tomography Study (PRONTO),17 in which OCT was used to guide the frequency of intravitreal injections of ranibizumab for treating neovascular AMD. The objective of the study was to identify a protocol facilitating treatment beyond the monthly dose regimen used in the MARINA and ANCHOR studies.

Knowing that macular cysts, subretinal fluid, and pigment epithelial detachment affect visual function, the investigators in PRONTO used OCT to examine the effect of as-needed dose regimens on macular anatomy and visual acuity and the anatomical changes that occur before retreatment. Patients with exudative AMD received ranibizumab injections at the outset of the study and again at 1 and 2 months, after which they were treated only if changes in OCT and visual acuity indicated that fluid was reaccumulating in and under the macula. Criteria for retreatment included an increase in central macular thickness of at least 100 μm, a loss in visual acuity of more than 5 letters, recurrent fluid on OCT, new hemorrhage, or conversion to a classic AMD lesion.

They found that the first mean “injection free” interval in the variable period was 4.5 months with a median of 3 months and a range of 2 to 10 months. The second injection-free interval tended to be shorter, and patients who needed injections more frequently continued in that pattern. The average number of injections at 1 year was 5.6, and visual acuity gains were better than in the MARINA study.

Dr. Rosenfeld recommended a retreatment protocol for ranibizumab injections that includes visual acuity as the primary endpoint, clinical examination, and OCT measurements. He proposed a new secondary endpoint for future clinical trials: fluid-free interval or injection-free interval. As for his current practice, he gives monthly injections until OCT shows that the macula is fluid-free and then reinjects at the first sign of macular fluid. The goal, he believes, should be to prolong the fluid-free interval.

Dr. Karl Csaky

Dr. Csaky asked attendees to consider the treatment burden imposed by frequent OCT, fluorescein angiogram, and intraocular injections. He used photodynamic therapy as a comparator. The burden for photodynamic therapy is about four to five treatments in the first year and perhaps the same number of office visits. There are fewer visits in subsequent years. For anti-VEGF treatments, in contrast, if one were to follow the ANCHOR and MARINA protocols, the burden would be 13 procedures/office visits in the first and second years and perhaps twice that number to monitor patients for adverse effects such as endophthalmitis. If a patient were to undergo 13 intraocular injections each year followed by an office visit to make sure there is no adverse reaction, he or she would be making twice-monthly doctor visits for a 2-year period. That is a large commitment for patients and physicians.

Dr. Csaky opined that it is important to weigh the treatment burden when developing treatment regimens for neovascular AMD. Treatment burden would include the cost of the procedure, cost of time spent by the patient and clinician, cost of...
Session Discussion

The first topic was proving noninferiority of a new drug when using ranibizumab for comparison. Dr. Chambers told attendees that in trials in which monthly injection of ranibizumab was compared with new drugs, drug combinations, or new treatment protocols, equivalency could be indicated by visual acuity within 3 to 4 letters of the outcome achieved with ranibizumab. Safety is also an important factor, indicated by Trusopt (Merck) and timolol for treating elevated intraocular pressure. Although Trusopt failed equivalency compared with timolol, it was approved because of its safety profile. “The issue for approval,” said Chambers, “is that you don’t have to be the best. You have to have your benefits outweigh the risks.”

The FDA would also consider treatment burden (to patient, family, and physician) and quality-of-life issues associated with a drug, provided the variables could be validated (confirming that what people report is accurate) and quantified. Another concern for the FDA would be the extent to which a drug could reduce the risk of endophthalmitis associated with intravitreal injections.

The FDA emphasizes the importance of the totality of the data. Studies examining anatomic endpoints are encouraged.

Anatomic endpoints will also be useful in trials of nonexudative AMD. One obvious endpoint that the FDA is willing to accept is conversion from dry to wet AMD. Other anatomic endpoints could include—provided they are shown to correlate with risk of neovascular AMD—15-letter loss in visual acuity, disciform scars, hemorrhage, and drusen of a particular size. Changes in dark adaptation and biomarkers such as circulating endothelial cells in serum were also discussed as possible indicators of increased risk for conversion of dry to wet AMD.

Design and Endpoints for Geographic Atrophy

Speakers were Martin Nevitt, Michael Klein, Anne Lindblad, Maureen Maguire, and Janet Sunness.

Discussants were William Boyd, Wiley Chambers, Karl Csaky, Frederick Ferris, Michael Klein, Anne Lindblad, Rhea Lloyd, Maureen Maguire, Martin Nevitt, and Janet Sunness.

Two main questions were the focus of the discussion:

1. Does rate or extent of anatomic progression of atrophy represent a clinically important study outcome?
2. Do within-patient (between-eye) differences in the rate or extent of anatomic progression of GA represent a clinically significant study outcome?

GA is represented by a sharply demarcated depigmented area of the retina through which choroidal vessels are visible. As GA progresses, the retinal pigment epithelium, photoreceptors, and choroid are lost. Approximately 3.4% of people older than 75 years have GA, according to Dr. Michael Klein.

Dr. Martin Nevitt

Speaking on behalf of the FDA, Dr. Nevitt explained that there are several acceptable clinical endpoints for studies of GA: rate or extent of anatomic progression of GA in the functional (seeing) retina, visual acuity, visual fields, and reading speed. In all cases, the differences between treatments could represent a clinically important outcome, provided the differences are statistically and clinically significant.

The FDA is not yet convinced of the extent of correlation of disease progression between eyes, which complicates the use of the contralateral eye as the control.
Growth of GA between the right and left eye correlated highly over time, leading Dr. Lindblad to support considering, for clinical trials, comparisons of GA lesion size in treated and untreated eyes of the same patient.

Dr. Michael Klein

Dr. Klein added to the description of GA, saying that to develop and test treatments, scientists must understand how GA develops and progresses. He and colleagues studied photographs, retrospectively, of eyes of 95 patients from two AREDS clinical centers, reviewing and grading yearly characteristics from baseline to onset of GA, with the following results:

- In nearly all cases, very large, confluent drusen (> 250 μm) occurred at the site of future GA. The drusen were seen in baseline photos, which made it impossible to know how long they were present before GA was diagnosed. These patients were then observed for an average of 6.5 years.
- Hyperpigmentation of the region followed in most cases—on average, approximately 4 years before diagnosis of GA.
- Hyperpigmentation was the next step, occurring approximately 2.3 years before GA.
- Crystalline deposits appeared before GA in approximately 15% of patients. The deposits might be unphagocytosed material associated with regression of the drusen.
- Some patients had GA that was centrally located. Others had multiple areas of atrophy.
- GA appeared to represent the final stage in the drusen life cycle.

Dr. Klein also noted that, in the study, not all eyes that contained large drusen, hyperpigmentation, and hypopigmentation progressed to GA. Sometimes the drusen faded and left only mild atrophy or no atrophy at all. Some eyes progressed to neovascularized AMD. Twin studies indicate that genes play a role in deciding the course of the disease.

There is no proven treatment for GA. Proposed treatments include nutritional supplements, RPE cell transplantation, neuroprotective agents, and antioxidants, among others.

Session Discussion

There is agreement that GA grows slowly over time and has characteristics that are measurable and quantifiable. As GA grows larger, there is a commensurate decrease in visual acuity and reading speed. A goal of therapy would be to slow growth of GA, which could be studied by looking at rates of progression of anatomic features of the atrophy. Digitized fundus photography could be used to measure and grade changes in the borders of GA.

The FDA agrees that the evidence of a correlation between the size and extent of anatomic borders of GA and retinal function is strong. It would be necessary to provide more data about the relationship of GA to retinal function for the FDA to be convinced of progression of atrophy as an anatomic endpoint. Dr. Sunness described the areas of GA as quite distinct, like continents on the retina. She has further found that perimetry studies reliably correlate boundaries of the GA and retinal function. The FDA would require three different time points in any clinical study in which progression of GA is the primary endpoint.

Dr. Maguire noted that progression rates do not have to be identical between eyes in order for a between-eye design to be efficient. Even very modest correlation between progression rates between eyes is efficient in terms of number of patients required and study cost. However, the existence of crossover effects (e.g., medication administered to one eye has an effect on the contralateral eye) would be a reason not to use a between-eye design.

Selection of patients for clinical trials might depend on possible risk factors for GA such as changes in night vision, drusen size, and appearance of hyperpigmentation or hypopigmentation.

POSTMARKETING DRUG SURVEILLANCE

Speakers were Jonathan Javitt, Kevin Schulman, and Scott Cousins.

The discussants were William Boyd, Wiley Chambers, Karl Csaky, Scott Cousins, Jeffrey Heier, Jonathan Javitt, Jennifer Lim, Rhea Lloyd, Joan Miller, and Philip Rosenfeld.

One main question was the focus of the discussion:

1. What is the best mechanism for obtaining and substantiating data on drug-induced complications in patients receiving therapies for retinal disease postmarketing?

Dr. Jonathan Javitt

Dr. Javitt discussed the use of databases to ensure drug safety in ophthalmology. As new compounds for treating retinal diseases are approved and millions of people become candidates for treatment, the concern about systemic and other side effects grows. One adverse event in 10,000 becomes a large concern—and it is inherently impossible to detect these rare events in clinical trials with far fewer patients enrolled.

Dr. Javitt suggested using existing databases as an inexpensive and effective way to monitor drug safety. He cited his experience with Medicare databases when he was looking for onset of glaucoma in patients treated with intravitreous steroids for AMD. He and colleagues used the data to compare patients treated with PDT, no treatment, or intravitreous steroid injections. They found that patients treated with intravitreous injections were substantially more prone to the development of glaucoma over the ensuing several years.

He also recommended helping to ensure drug safety through a system that identifies questionable medical treatment by studying, for example, hospital databases, and then prompts physicians with information about drug treatments and appropriate surveillance of side effects. A prompt might say, “You have a patient on X drug. Liver function testing is essential for Y reason.”

Finally, he reported on the success observed in a study in which doctors of 20,000 patients were prompted by a mailing to be alert to patient compliance and drug safety. The patients whose doctors received these mailings were selected based on having had one physician visit and one pharmacy claim in the preceding 12 months. They were compared to an equal number of similarly identified patients whose doctors received no mailing. The researchers saw a 6% reduction in the cost of medical care in people who had been part of the intervention group, leading the researchers to support the use of sentinel systems that would identify at-risk patients through insurance records and then send reminders to physicians about drug use and complications. Sentinel systems are being deployed by more and more large health plans who find that the costs are more than offset by savings in healthcare.

Dr. Kevin Schulman

Dr. Schulman spoke about assuring drug safety from his prospective as an internist, health services researcher, and clinical trialist. He suggests that safety should not be regarded as the “absence of findings.” There should be a deliberate effort to prove safety. In terms of postmarketing, the mandate should be to look for moderate- and low-frequency events (1/500, 1/1000, or 1/10,000) by asking questions that are specific to each new product and population of patients.
For a macular degeneration drug, questions might be about interactions with other medications and about specific effects on the heart, liver, kidneys, or central nervous system. In older patients, does the drug have an effect on progression of Alzheimer's disease? The challenge to epidemiology is distinguishing the adverse drug effects from events that occur because of independent risk factors.

Data to answer the questions are available or becoming available in unprecedented quantities. Medicare, for example, has very large datasets and BlueCross-BlueShield has announced its plans to build a 100-million-person data warehouse. Cardiovascular disease has approximately 700,000 patients in its National Registry of Myocardial Infarction. The Society of Thoracic Surgery has a database with records on approximately 70% of inpatient surgical cases. Web-based collection of clinical data from people taking newly approved products is also being considered.

Dr. Schulman envisions the FDA and the Centers for Medicare and Medicaid Services working together when newly approved products are released to build postapproval datasets for tracking administrative and clinical data related to new drugs. For enhancing vigilance among physicians, he pointed to a program used in the United Kingdom in which physicians are warned when the safety profile of a new product is not yet fully developed.

**Dr. Scott Cousins**

Dr. Cousins described a novel initiative at Duke University for postmarketing drug surveillance for retinal therapies, particularly for the new anti-VEGF therapies. An important question concerns adverse effects once they have entered the systemic circulation. We know at least some anti-VEGFs circulate; Avastin (Genentech, South San Francisco, CA) injected in one eye can cause a response in the fellow eye. Although no differences in rate of adverse effects appeared in studies comparing treated patients with control subjects, it is possible that a subset of patients with AMD is at risk. Dr. Cousins opined that anti-VEGF trials are not sufficiently powered to identify small but clinically relevant rates of adverse effects.

Are retinal physicians good sources of information about adverse drug effects? Probably not, for several reasons. One, patients who feel ill are not likely to contact an eye doctor. They go a family physician or emergency room instead. Two, surveys show that retina specialists tend not to ask patients why they have missed their appointments. Three, according to an informal survey by the American Society of Retina Specialists, their members do not have a tradition of reporting adverse events to the FDA's MedWatch.

At Duke, a pilot program is being established that would use a three-pronged approach to adverse-effects reporting: CMS claims analysis, to identify all codes for neovascular AMD, with and without treatment; a Web-based patient registry in which physicians would enroll patients who agree to be contacted about symptoms; and chart audits to validate patient-reported events. The intention is to publish positive and negative findings as a way to provide postmarketing drug surveillance for the community of physicians and patients.

**Session Discussion**

Ophthalmologists and the FDA are growing concerned about drug safety, given that the new intravitreous drugs they use to treat retinal disorders have the potential to enter the systemic circulation and cause drug-induced complications. They are also concerned that complications do not come to their attention. They are looking for better ways to address drug safety.

One approach would be to conduct large safety studies in the postmarketing period. Another would be to trawl existing databases looking for adverse effects in patients who have received the drugs by intravitreous injections. Also suggested were ad hoc registries to which doctors and patients could report adverse effects. With regard to using the Duke system for postmarketing drug surveillance, there was concern expressed about access to the data by the larger scientific community. Everyone would have to be assured access to the data collected, its distribution, and its interpretation.

The FDA carefully reviews all reports about possible drug-induced complications that come into their MedWatch system. The system is voluntary, however, and is only as good as the reports it receives. A proactive approach was discussed in which patients and physicians would be cued to submit information about drug side effects. Another idea was to build awareness by notifying physicians regularly and more aggressively about concerns related to drug safety.

**Acknowledgments**

The authors thank the program participants and speakers for scientific contributions to the conference and contributions to the panel discussions; the staff of ARVO for professional support of the conference; the members of the organizing committee and session chairs for valuable contributions; and Richman Associates, LLC, of Baltimore, Maryland, for providing writing and editorial support.

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