CME ACTIVITY

Updates on The Management of AMD and RVO:
An Evidence-based Approach

Richard S. Kaiser, MD
Moderator

Brandon G. Busbee, MD

Baruch D. Kuppermann, MD, PhD

Carl D. Regillo, MD

Jointly sponsored by The Dulaney Foundation and Retina Today
Supported by an unrestricted educational grant from Regeneron
Neovascular age-related macular degeneration (AMD) is characterized by a loss of vision in the center of the visual field and typically affects older people. Considered the most severe form of AMD, it has been designated as 1 of the leading causes of vision loss on a global scale.\(^1,4\)

Ranibizumab (Lucentis, Genentech) was approved by the US Food and Drug Administration (FDA) in 2006, and has been shown to stabilize or improve vision in those with neovascular AMD.\(^6,6\) but a common complaint is that dosing must be monthly for the effects to be maintained. The PrONT0 study evaluated patients treated with 3 monthly injections of ranibizumab, and then dosing on an as-needed (prn) basis. The preliminary results suggested patients maintained visual acuity gains, and were able to halve their monthly dosing schedule.\(^7\)

Some retina specialists have used bevacizumab (Avastin, Genentech), which is a full-length recombinant humanized monoclonal antibody directed against VEGF first approved for the treatment of metastatic colorectal cancer, off-label as a compounded ophthalmic preparation, for the treatment of neovascular AMD. There have been questions, however, as to how safe and effective off-label use of bevacizumab is compared with ranibizumab. A recent analysis of Part B Medicare expenditures suggests that this off-label use is prevalent.\(^8\)

To address the questions of efficacy and safety of this off-label use in comparison with the on-label treatment of wet AMD with ranibizumab, the National Eye Institute funded a large multicenter study to compare the 2 treatments. The results of the Comparison of AMD Treatments Trial (CATT), which were recently made available, demonstrated noninferiority of intravitreally injected bevacizumab in comparison to ranibizumab for the treatment of wet AMD.\(^9\) The study authors noted, however, that differences in rates of serious systemic adverse events require further study.

Afibercept (Eylea, Regeneron) is the most recent addition to available treatments for wet AMD. Afibercept was approved for the treatment of AMD by the FDA in 2011. VIEW 1 and 2 were parallel phase 3 clinical trials evaluating the efficacy of afibercept for the treatment of wet AMD.\(^10,11\) VIEW 1 and 2 results included the Comparison of AMD Treatments Trial (CATT), which were recently made available, demonstrated noninferiority of intravitreally injected bevacizumab in comparison to ranibizumab for the treatment of wet AMD.\(^10\) The study authors noted, however, that differences in rates of serious systemic adverse events require further study.

Afibercept (Eylea, Regeneron) is the most recent addition to available treatments for wet AMD. Afibercept was approved for the treatment of AMD by the FDA in 2011. VIEW 1 and 2 were parallel phase 3 clinical trials evaluating the efficacy of afibercept for the treatment of wet AMD.\(^10,11\) VIEW 1 and 2 showed that afibercept dosed every other month after 3 loading doses was noninferior to ranibizumab. Most recently, data from the phase 3 HARBOR study were released. This trial evaluated the effects of a higher dose of ranibizumab, 2.0 mg, vs the FDA-approved dose of 0.5 mg in monthly and prn dosing formats. The results did not meet the efficacy endpoint for superiority of 2 mg ranibizumab monthly, nor did they meet the secondary endpoint of noninferiority in the prn arm.\(^12\)

Retinal vein occlusion (RVO) is a common ocular disease that remains poorly understood due to the multifactorial nature of its presentation and contributing systemic factors. Several associated systemic factors have been identified and continue to be studied for their impacts on RVO, including hypertension, diabetes, hypercholesterolemia, thyroid disorder, and ischemic heart disease. Increased intraocular pressure and axial length also play roles in this disease.\(^13,14\)

For many years, clinicians have followed the recommendations set forth by the Branch Vein Occlusion Study\(^15\) and the Central Vein Occlusion Study for managing branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), respectively.\(^16\) The former study demonstrated that grid laser photocoagulation leads to more improvement of visual acuity than natural history, but the latter showed that grid laser photocoagulation did not improve visual acuity even though the macular edema decreased.

The SCORE CRVO trial found that patients treated with intravitreal steroid experienced a substantial visual acuity gain of 3 or more lines that persisted for up to 2 years.\(^17\)

The dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) was approved by the FDA for the treatment of macular edema secondary to RVO in 2009. Treated patients in the GENEVA study had visual acuity gains and reduction in macular edema at 2 months that was not observed in those in the placebo arm of the study.\(^18\)

Ranibizumab was FDA-approved for macular edema following both BRVO and CRVO in 2010, based on the positive results of the BRAVO\(^19\) and CRUISE\(^20\) studies. Afibercept was approved by the FDA in 2012 for the treatment of macular edema secondary to CRVO. The COPERNICUS study evaluated afibercept for the treatment of macular edema secondary to CRVO and found that patients in the treatment arms gained a significantly higher number of letters of vision than those receiving placebo.\(^21\)
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation and Retina Today. The Dulaney Foundation is accredited by the ACCME to provide continuing education for physicians. The Dulaney Foundation designates this enduring material for a maximum of 1 AMA PRA Category 1 Credit. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

After reviewing the material, please complete the self-assessment test, which consists of a series of multiple-choice questions. To answer these questions online and receive realtime results, please visit http://www.dulaneyfoundation.org and click “Online Courses.” Upon completing the activity and achieving a passing score of over 70% on the self-assessment test, you may print out a CME credit letter awarding 1 AMA PRA Category 1 Credit.” The estimated time to complete this activity is 1 hour.

Dr. Regillo states that he receives grant research support from Genentech and Regeneron Pharmaceuticals, Inc.; is a consultant to Synergetics, Genentech, Regeneron Pharmaceuticals, Inc., and Thrombogenics; is a speaker for Genentech, Regeneron Pharmaceuticals, Inc., and Thrombogenics; and receives royalty payments from Akorn.

Dr. Kaiser states that he receives grants/research support from Wills Eye Research Fund and J Arch McNamara Research Fund; is a consultant to Pan Optica and Regeneron Pharmaceuticals, Inc.; and is a stock/shareholder in Optotex.

Dr. Kuppermann states that he is a consultant to Alimera Sciences; Allegro Ophthalmics; Allergan, Inc.; Fovea Pharmaceuticals; Glaukos Corporation; Neurotech Pharmaceuticals; Novagali Pharma; Novartis Pharmaceuticals; OptoTech, Regeneron Pharmaceuticals, Inc.; Santen; Second Sight; Teva Pharmaceuticals; and Thrombogenics.

Dr. Regillo states that he receives grant research support from Allergan, Inc.; Genentech; GlaxoSmithKline; Ophthotech; and Regeneron Pharmaceuticals, Inc. and that he is a consultant to Genentech; GlaxoSmithKline; and Regeneron Pharmaceuticals, Inc.

All of those involved in the planning, editing, and peer review of this educational activity report no relevant financial relationships.
Updates on the Management of AMD and CRVO: an Evidence-based Approach

Recently, a panel of experts was assembled to discuss the most recent treatment modalities for age-related macular degeneration (AMD) and retinal vein occlusion (RVO), 2 common conditions we see in our practices. Our goal is to discuss the epidemiology of both diseases, review the level 1 clinical trial data available, and identify unmet needs and the differential diagnoses for each condition. We will also delve into the practical issues of the management of AMD and central retinal vein occlusion (CRVO).

—Richard S. Kaiser, MD

Epidemiology of AMD and CRVO

Dr. Kaiser: Dr. Regillo, can you begin with providing some background on the epidemiology of AMD and CRVO?

Carl D. Regillo, MD: AMD and CRVO are conditions that we commonly see in the clinic. The most current reports state that more than 8 million people in the United States have been diagnosed with AMD and approximately 1.7 million of these have advanced, or neovascular, AMD. In the population of those who are older than 46 years in age, it is estimated that approximately 1.47% have either neovascular AMD or advanced geographic atrophy (GA). For those who are 65 years of age, the estimates of the incidence of AMD are 2.5%; for those 70 years of age, 6.7%; and for those 75 years of age, 10.8%. Because estimates are that the US population will increase by 50% between 2005 and 2025, along with increasing life expectancies, we can also expect an expansion in the elderly population.1-3

The numbers of people in the United States who present with RVO are not nearly as high as with AMD, but this remains a relatively common indication for the retina specialist. These patients have an average onset of disease at 65 years of age, which is younger than the average age of presentation of AMD (70 years of age). Most of the cases of RVO that we see are branch retinal vein occlusion (BRVO), but we also see many patients with CRVO.4

Dr. Kaiser: Are we going to be able to handle the treatment burden associated with AMD and RVO?

Dr. Regillo: This question leads directly to unmet needs for these diseases. Particularly with wet AMD, we are not curing the condition; rather, we are controlling the growth and development of the neovascular complex. Currently, there is no end in sight with the therapies that we currently have available to us, which leads to increasing numbers of patients that we are managing.

In my practice, we are compensating for increased patient volume by hiring 2 new retina specialists this year because we are maxed out in the clinic. In the long-term, I am hopeful that we can find better ways to control these diseases with a lower treatment burden.

Dr. Kaiser: Do you think that our treatment success is limited more by the number of retina specialists in a practice to handle increased patient volumes or the access to treatments themselves?

Baruch D. Kuppermann, MD, PhD: This issue is multifactorial. To a certain extent, some of our patients have dropped out of the system because of the intensity of monthly injections. Decreasing the treatment burden and having more sustainable therapies will help us to recapture these patients. The timeframe in which this will happen, however, is probably more than 5 years out, because even an older drug in a new delivery system is seen as a new drug by the US Food and Drug Administration (FDA) and must undergo the same level of scrutiny, essentially starting from scratch.

Dr. Kaiser: With current injection therapy, we have basically had to restructure our practice. Ten years ago, patients would come into our office, receive testing with angiography, and then maybe receive laser and counseling. Now we have more front desk employees to handle...
the increased numbers of patients and added injection lanes. Has the panel had the same experience?

Brandon G. Busbee, MD: We have had to change the structure of our practice—but first, I have to say that, despite the challenges to our practices, we are in a great situation. Ten years ago we did not have much available to help AMD and CRVO patients. Now we have agents that are highly successful for treating patients, and, in many cases, at improving vision. The treatment burden, however, falls squarely on the frequency with which patients must receive these injections. The burden of increasing our efficiency, hiring new staff, and initiating changes to our practice infrastructure to facilitate increased patient volume is probably easier on us than is the frequency of treatment on our patients.

CLINICAL TRIALS FOR AMD

Dr. Kaiser: Dr. Busbee, can you review some of the level 1 clinical trial data that we have to date? There are several clinical trials establishing anti-VEGF agents as viable treatments for both AMD and CRVO.

Dr. Busbee: Of course, MARINA and ANCHOR provided a great deal of information about ranibizumab (Lucentis, Genentech) for AMD. During the time of those pivotal trials, we had very little information regarding bevacizumab (Avastin, Genentech) other than small-scale investigator-sponsored trials (ISTS) and anecdotal reports. With the HARBOR trial, which evaluated high-dose ranibizumab vs standard-dose ranibizumab; CATT and IVAN studies, which evaluated bevacizumab vs ranibizumab; and VIEW 1 and VIEW 2, which evaluated aflibercept (Eylea, Regeneron Pharmaceuticals, Inc.) vs ranibizumab, we gained new perspective on how ranibizumab compares with these other 2 anti-VEGF agents, both in terms of efficacy and dosing.

Dr. Kaiser: What are the top-line data from HARBOR, CATT, and IVAN that are most useful to us in clinical practice?

Dr. Busbee: We found from HARBOR that standard-dose ranibizumab is at the top of the dose response curve. We also learned less than monthly dosing gives clinically meaningful visual gains over 2 years using standard-dose ranibizumab. We have found from both CATT and IVAN that ranibizumab appears to be better at drying the retina. We also have learned that an alternative dosing pattern of less frequent injections and monthly dosing seems to be viable for both ranibizumab and bevacizumab.

MARINA

The MARINA study, published in the New England Journal of Medicine, was a 2-year study of 716 patients with neovascular AMD. Participants were divided into 3 treatment arms: (1) 0.3 mg ranibizumab monthly, (2) 0.5 mg ranibizumab monthly, and (3) sham injections. The primary endpoint was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months.

At 1 year, 94.9% of patients given 0.3 mg ranibizumab and 94.6% of those given 0.5 mg lost fewer than 15 letters, as compared with 62.2% of patients receiving sham injections (P < .001). Visual acuity improved by 15 or more letters in 24.8% of the 0.3-mg group and 33.8% of the 0.5-mg group, as compared with 5.0% of the sham-injection group (P < .001). Mean increases in visual acuity were 6.5 letters in the 0.3-mg group and 7.2 letters in the 0.5-mg group, as compared with a decrease of 10.4 letters in the sham-injection group (P < .001). The benefit in visual acuity was maintained at 24 months. During the 24 months, presumed endophthalmitis was identified in 5 patients (1.0%), and serious uveitis was observed in 6 patients (1.3%) given ranibizumab.

The study authors concluded that intravitreal administration of ranibizumab for 2 years prevented vision loss and improved mean visual acuity, with low rates of serious adverse events, in patients with minimally classic or occult choroidal neovascularization secondary to AMD.


ANCHOR

The ANCHOR study, published in the New England Journal of Medicine, was a 2-year study of 423 patients with neovascular AMD. Participants were randomized into 3 treatment arms: (1) 0.3 mg ranibizumab monthly plus sham verteporfin therapy, (2) 0.5 mg ranibizumab monthly plus sham verteporfin therapy, and (3) monthly sham injections plus active verteporfin therapy. The primary endpoint was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months.

At 1 year, 94.3% of those given 0.3 mg ranibizumab and 96.4% of those given 0.5 mg ranibizumab lost fewer than 15 letters, as compared with 64.3% of those in the verteporfin group (P < .001). Visual acuity improved by 15 or more letters or in 35.7% of the 0.3-mg group and 40.3% of the 0.5-mg group, as compared with 5.6% of the verteporfin group (P < .001). Mean visual acuity increased by 8.5 letters in the 0.3-mg group and 11.3 letters in the 0.5-mg group, a decrease of 9.5 letters was observed in the verteporfin group (P < .001). Of the patients treated with 0.5 mg ranibizumab (n = 140), presumed endophthalmitis occurred in 2 patients (1.4%) and serious uveitis occurred in 1 patient (0.7%).

The study authors concluded that ranibizumab was superior to verteporfin for the treatment of predominantly classic neovascular AMD, with low rates of serious ocular adverse events, and that treatment improved visual acuity on average at 1 year.


The HARBOR study, published in *Ophthalmology*,1 was a 2-year study of 1098 patients with subfoveal neovascular AMD. Participants were randomized into 4 treatment arms: (1) 0.5 mg ranibizumab monthly, (2) 0.5 mg ranibizumab administered on an as-needed (prn) basis after 3 monthly loading doses, (3) 2.0 mg ranibizumab monthly, and (4) 2.0 mg ranibizumab administered on a prn basis after 3 monthly loading doses. The primary endpoint was the mean change from baseline in best-corrected visual acuity (BCVA) at month 12.

At month 12, the mean change from baseline in BCVA for the 4 groups was +10.1 letters (0.5 mg monthly), +8.2 letters (0.5 mg pm), +9.2 letters (2.0 mg monthly), and +8.6 letters (2.0 mg pm). The proportion of patients who gained ≥15 letters from baseline at month 12 in the 4 groups was 34.5%, 30.2%, 36.1%, and 33.0%, respectively. The mean change from baseline in central foveal thickness at month 12 in the 4 groups was −172.0 μm, −161.2 μm, −163.3 μm, and −172.4 μm, respectively. The mean number of injections was 7.7 and 6.9 for the 0.5-mg pm and 2.0-mg pm groups, respectively. The investigators found that ocular and systemic safety profiles were consistent with previous ranibizumab trials in AMD and comparable between groups.

In the HARBOR study, the monthly 2.0 mg ranibizumab group did not meet the prespecified superiority comparison, and the 0.5 mg ranibizumab and 2.0 mg pm groups did not meet the prespecified noninferiority comparisons. However, all treatment groups demonstrated clinically meaningful visual improvement (+8.2 to +10.1 letters) and improved anatomic outcomes, with the prn groups requiring approximately 4 fewer injections than the monthly groups. No new safety events were observed. The HARBOR study confirmed that 0.5 mg ranibizumab dosed monthly provided optimum results in patients with wet AMD, according to the authors.


**Dr. Regillo:** There are a few things we can take away from the CATT study. First, by year 1, the efficacy results were comparable with as-needed (prn) dosing and monthly dosing, but that breaks down eventually and, unfortunately, the effects of both ranibizumab and bevacizumab with prn dosing are not as sustainable at year 2; the results were inferior. In the first year, results comparable to monthly dosing were achieved with 7 to 8 injections of ranibizumab or bevacizumab. Second, it did not appear that bevacizumab lasts any longer than ranibizumab, which negates what had been suggested prior to the trial. In fact, the mean number of treatments was actually higher with bevacizumab.

Third, there were ocular and systemic safety issues that were potentially in play, but the meaning of these data remain unclear, and longer-term follow-up is necessary.

**Dr. Kaiser:** What did we learn from VIEW 1 and 2 in terms of how aflibercept compares with ranibizumab?

**Dr. Kuppermann:** We tend to pool these data from these 2 studies together, but VIEW 1 did have a different outcome from VIEW 2. VIEW 1 showed that the 2 mg dose of aflibercept injected every 4 weeks was statistically superior to the other dosing regimens, but this is rarely discussed. Overall, the pooled 52-week data from VIEW 1 and 2 showed noninferiority of aflibercept injected every 8 weeks following 3 monthly injections compared with ranibizumab injected every 4 weeks. These findings resulted in FDA labeling reflecting the regimen in the clinical trial, but I am not sure that all of us see aflibercept as being an every 8-week drug. I believe that many clinicians who have switched patients to aflibercept are still injecting with the same frequency as with ranibizumab.

**Dr. Regillo:** What I think is most informative about VIEW 1 and 2 is that not only was the noninferiority of all aflibercept regimens within 0.5 letters of the reference ranibizumab for mean change in BCVA. All aflibercept regimens also produced similar improvements in anatomic measures. Ocular and systemic adverse events were similar across treatment groups. The investigators concluded that intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab. The VIEW 1 and VIEW 2 studies demonstrated that aflibercept was effective for the treatment of AMD, with the every-2-month regimen offering the potential to reduce the risk from monthly intravitreal injections and the burden of monthly monitoring.


The CATT study, published in the New England Journal of Medicine, was a 2-year study of 1208 patients with neovascular AMD. Participants were randomized into 4 treatment arms: (1) ranibizumab monthly, (2) ranibizumab prn, (3) bevacizumab monthly, and (4) bevacizumab prn. The primary endpoint was the mean change in visual acuity at 1 year, with a noninferiority limit of 5 letters. According to the 1-year CATT results, bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered prn was equivalent to ranibizumab prn, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was equivalent to monthly ranibizumab; however, the comparison between bevacizumab prn and monthly bevacizumab was inconclusive. Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab. The proportion of patients with serious systemic adverse events was higher with bevacizumab than with ranibizumab, with excess events broadly distributed in disease categories not identified in previous studies as areas of concern. The study authors concluded that, at 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same dosing schedule. Ranibizumab administered prn with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly.

In the 2-year analysis (n=1107) published in Ophthalmology, among patients following the same regimen for 2 years, mean gain in visual acuity was similar for both drugs. Mean gain was greater for monthly than for prn treatment. Switching from monthly to as-needed treatment resulted in greater mean decrease in vision during year 2 and a lower proportion of patients without fluid. Rates of death and arteriothrombotic events were similar for both drugs (P > .60). The proportion of patients with 1 or more systemic serious adverse events was higher with bevacizumab than ranibizumab. Based on these results, it was concluded that ranibizumab and bevacizumab had similar effects on visual acuity over a 2-year period, and prn treatment resulted in less gain in visual acuity. There were no differences between drugs in rates of death or arteriothrombotic events. The investigators noted that the interpretation of the persistence of higher rates of serious adverse events with bevacizumab was uncertain due to the lack of specificity to conditions associated with inhibition of VEGF.


The IVAN study, published in Ophthalmology, was a 2-year study of 610 patients with neovascular AMD. Participants were divided into 4 treatment arms: (1) ranibizumab monthly, (2) bevacizumab monthly, (3) ranibizumab prn, and (4) bevacizumab prn. The primary efficacy and safety outcome measures were distance visual acuity and arteriothrombotic events or heart failure. In the prespecified interim analysis, at 1 year after randomization, the comparison between bevacizumab and ranibizumab was inconclusive. Discontinuous treatment (ie, prn) was equivalent to continuous treatment. Foveal total thickness did not differ by drug but was 9% less with continuous treatment. Fewer participants receiving bevacizumab had an arteriothrombotic event or heart failure, but there was no difference between drugs in the proportion experiencing a serious systemic adverse event. Serum VEGF was lower with bevacizumab and higher with discontinuous treatment. Bevacizumab was less costly for both treatment regimens. The study authors found that, at 1 year, the comparison of visual acuity between bevacizumab and ranibizumab was inconclusive, and visual acuities with continuous and discontinuous treatment were equivalent. Other outcomes were reportedly consistent, with the drugs and treatment regimens having similar efficacy and safety.


**Clinical Trials for CRVO**

**Dr. Regillo:** There is a lag between our real-world clinical practices and what is done in the clinical studies. The vast majority of retina specialists, both in the United States and abroad, are not using the drugs the way they were used in the clinical trials.

**Dr. Kaiser:** What is the level 1 clinical trial data for CRVO?

**Dr. Busbee:** The first protocol for CRVO set forth by Genentech was for 6 monthly injections of ranibizumab, followed by prn injections. In the prn phase, patients could

afafibercept determined, but these 2 drugs were equivalent. After year 1, all arms in the VIEW studies went on to prn dosing with a minimum of quarterly injections. There was a trend observed that fewer injections were required in the aflibercept arms, implying longer duration of effect to some degree.

**Dr. Kuppermann:** The differences in injection frequency in the prn phase of the trials were not that large.

**Dr. Regillo:** It is clear, just from anecdotal experience and prn studies, which include HARBOR and CATT, that good results can be achieved dosing less frequently than monthly.

**Dr. Kaiser:** One of the limitations with clinical trials is the pre-established protocol, so there will always be questions that go unanswered.

**Dr. Regillo:** There is a lag between our real-world clinical practices and what is done in the clinical studies. The vast majority of retina specialists, both in the United States and abroad, are not using the drugs the way they were used in the clinical trials.
skip an injection if they lost fewer than 5 letters of vision and did not have an increase in optical coherence tomography (OCT) thickness. Approximately three-quarters of patients in CRUISE needed an injection at month 6.\(^{11}\)

In COPERNICUS, there was also a high percentage of patients who required injections in the prn phase of the trial, although, at approximately 50%, it was slightly lower than in CRUISE. It appeared that patients who required injections tended to have more ischemia.\(^{12}\)

**Dr. Kuppermann:** In the CRUISE and COPERNICUS studies, good results were achieved in the first 6 months of monthly injection of ranibizumab and every-2-month injection of aflibercept after the initial 3 monthly loading doses. For all these trials, the initial results were sustained in the 6-month prn phase. Although patients in the control arms who were placed on active treatment in the second 6 months did see a benefit, this was attenuated, and this group never caught up to the treatment groups.

This finding supports the rationale that therapy for RVO should not be deferred. The GENEVA trial for the dexamethasone intravitreal implant (Ozurdex, Allergan) showed similar responses. The patients in the control group who received the implant in the second 6 months experienced a clear benefit, but these patients did not achieve results equal to the initially treated patients at any time point.

**Dr. Kaiser:** Were there any differences in the clinical trials?
The GENEVA study, published in *Ophthalmology*, was a 1-year study of 1256 patients with macular edema secondary to BRVO or CRVO. Participants were randomized to 1 of 3 treatment arms: (1) 0.7 mg intravitreal dexamethasone implant (dexmethasone implant), (2) 0.35 mg dexamethasone implant, or (3) sham. At day 180, patients could receive the 0.7 mg dexamethasone implant if BCVA was less than 84 letters or retinal thickness was greater than 250 μm. The primary outcome for the open-label extension was safety, and BCVA was also evaluated.

At day 180, 997 patients received the open-label dexamethasone implant. The investigators found that, with the exception of cataract, the incidence of ocular adverse events was similar in patients who received their first or second dexamethasone implant. Over 12 months, cataract progression occurred in 90 of 302 phakic eyes (29.8%) that received 2 0.7-mg dexamethasone implant injections vs 5 of 88 sham-treated phakic eyes (5.7%). Cataract surgery was performed in 4 of 302 and 1 of 88 eyes, respectively. In the group receiving 2 0.7-mg dexamethasone implants, a ≥10-mm Hg IOP increase from baseline was observed in 12.6% after the first treatment and 15.4% after the second. A ≥15-letter improvement in BCVA from baseline was achieved by 30% and 32% of patients 60 days after the first and second dexamethasone implant, respectively.

According to the study authors, among patients with macular edema owing to BRVO or CRVO, single and repeated treatment with dexamethasone implant had a favorable safety profile over 12 months. In patients who qualified for 2 dexamethasone implant injections, the efficacy and safety of the 2 implants were similar with the exception of cataract progression.

The importance of enrollment criteria was highlighted by GENEVA, because the duration of macular edema affected how patients responded to dexamethasone. If patients had macular edema for less than 90 days prior to enrollment, the outcomes were better. CRUISE was heavily weighted with patients with a shorter duration of macular edema, compared with GENEVA, in which approximately 85% of patients had macular edema for longer than 90 days prior to enrollment. When Allergan looked at the subset of patients with a shorter duration of macular edema, the outcomes were far more similar to CRUISE. Allergan is currently conducting a BRAVO-style head-to-head trial in Europe titled COMO, in which patients are randomly assigned to the dexamethasone implant or ranibizumab. It will be interesting to see these outcomes.

**Dr. Busbee:** The CRUISE trial allowed for anti-VEGF or intraocular corticosteroid treatment as long as the patient had not had an injection in 3 months prior to study entry. The COPERNICUS study excluded patients who any intraocular injection prior to study screening. This difference most likely led the mean duration of diagnosis of CRVO in CRUISE (majority under 4 months) to be longer than mean duration of RVO in COPERNICUS (majority under 2 months). When comparing the results of the CRUISE and COPERNICUS studies, which had similar outcomes, these subtle factors certainly need to be considered.

**SCREENING AND DIAGNOSTICS FOR AMD AND RVO**

**Dr. Kaiser:** How do you screen for AMD and RVO?

**Dr. Regillo:** What we know is that the earlier we catch neovascular AMD and CRVO-related macular edema, the more effective our treatments are in improving patients’ final visual outcomes. Thus, early detection is important for both conditions, particularly for wet AMD, which is a more time-sensitive condition.

Education is critical for primary eye care providers and patients so that symptoms are recognized and patients are referred early for treatment. An easy method of screening for patients who we know have dry AMD is to give them an Amsler grid to self-test at home for any vision changes. The Foresee Home test (Notal Vision) is an intriguing way to potentially pick up on the transformation from dry to wet AMD at an earlier stage. There are some data scheduled for release in the next year or so that will indicate whether this method of testing improves the rates of patients getting earlier treatment and, thus, improves results over time.

**Dr. Busbee:** We need to improve our screening efforts for AMD. You can tell patients how to effectively use the Amsler grid, but how they use it at home cannot be controlled. We do use the Foresee Home in our practice, but it has limited applicability at this time because it is costly.

**Dr. Kaiser:** What diagnostics are you using for your initial evaluation and follow-up? In my opinion, fluorescein angiography (FA) remains the gold standard in picking up the subtleties of retinal disease.

**Dr. Regillo:** FA is a critical tool in diagnoses for retina disease for several reasons. First, we know that we can achieve the best results for patients when we catch disease early. For wet AMD, FA is the best tool to gauge the size of the choroidal neovascular (CNV) lesion. Additionally, in masquerade situations, such as nonvascularized serous retinal pigment epithelial detachment, central serous chorioretinopathy, drusenoid pigment epithelial detachment (PED), or pattern dystrophies, FA is a useful diagnostic tool. How many times do we have a situation where we wonder, “Is this really wet AMD?”
when nothing is happening with anti-VEGF injections? In RVO, the presence of gross macular ischemia can indicate that a patient’s vision may not improve significantly with treatment. You can also determine if that patient is at high risk for neovascular sequelae by looking at the degree of peripheral capillary nonperfusion. If you start with anti-VEGF and back off or stop treatment suddenly in a highly ischemic eye, iris neovascularization and neovascular glaucoma may emerge suddenly in CRVO cases.

**Dr. Busbee:** I agree that it is critical to get a baseline FA to establish a phenotype, as many diseases initially appear to be wet AMD. When we have suboptimal responders, it is beneficial to be able to compare a later FA to baseline to determine whether indocyanine green imaging is necessary.

**Dr. Kuppermann:** For RVO, the documentation of ischemia, particularly in the periphery, is important. The Optos widefield angiography device is useful in this regard, allowing us to examine in greater detail.

**Dr. Kaiser:** I also think that gonioscopy is useful in the diagnosis and management of RVO.

**Dr. Busbee:** One of the exclusion criteria in CRUISE was the presence of an afferent pupillary defect (APD). This was a clinical way to exclude patients with significant ischemia from CRVO. I have applied this to my practice by emphasizing to my technicians that it is important to look for an APD. If an APD is present, delayed rubeosis with any extension of the interval between anti-VEGF injections is a real possibility. I believe this is another important tool along with gonioscopy in recognizing potential neovascular complications in CRVO.

**Dr. Kuppermann:** For eyes that I have identified as having a potential risk, I mark this in the chart and have a fellow examine these patients prior to dilation to assess for an APD.

**Dr. Kaiser:** What does your follow-up examination include for AMD?

**Dr. Busbee:** If I have a patient with distinct visual disturbance in the form of central distortion, and I cannot find the cause, I will bring the patient back at a defined time, usually within 2 to 3 weeks, and repeat all my testing. If they pass the bar on OCT, fluorescein, and Snellen visual acuity, and they have no increase in their distortion, I feel much better about the prognosis. For patients who are newly diagnosed with wet AMD, I typically perform only an OCT and exam along with subsequent injections. I repeat the initial FA if I do not think I am getting an optimal response to consistent treatment.

**Dr. Kaiser:** When you have a patient you have diagnosed with wet AMD, do you treat that patient on the same day?

**Dr. Busbee:** I have evolved to a practice of treating the same day, which I believe has a couple of benefits. First, I do not have to fit the patient in my schedule in the next couple of days when I think he or she needs treatment. Second, treating the same day relieves the anxiety that a patient may have about an impending injection. I prefer to use either ranibizumab or aflibercept on label. I have samples of ranibizumab on hand to specifically address insurance barriers to same-day treatment, which helps in this regard.

**Dr. Kuppermann:** I also prefer to treat same day, staying on label with ranibizumab or aflibercept. Which drug I use is a fairly arbitrary decision, but I also pay attention to insurance barriers. If the patient has Medicare only, this can be a significant cost burden to the patient, so I may start out with off-label bevacizumab, enrolling the patient in a patient-assistance program for subsequent aflibercept or ranibizumab. Most of my patients end up receiving injections of these 2 on-label drugs.

**Dr. Regillo:** I also start treatment the same day, with a preference for the FDA-approved drugs. What Dr. Busbee noted about patient anxiety is a valid point. It is also important to consider the additional costs and burden for that extra office visit, both for the patient and for any accompanying family members or friends. Furthermore, if the patient gets lost for 1 or 2 weeks after the initial diagnosis, there may be a detrimental effect on vision.

**Dr. Kaiser:** After the patient has taken a deep breath after that first injection, 1 of the most common comments that I hear is, “That wasn’t so bad. How many of these injections am I going to need?”

**Dr. Busbee:** I tell patients that they will need frequent injections indefinitely until we find a therapy that can significantly extend the treatments.

**Dr. Kuppermann:** I tell patients that it depends, and that we will make this decision together at every visit based on their visual status and anatomic appearance on OCT.

**Dr. Regillo:** I tell patients that the injections will control the disease, not cure it, and so we will have to perform many injections over a long period of time. I also advise them that the injections will be frequent until we stabilize the condition, and the frequency of treatment thereafter will vary from patient to patient.

**Dr. Kaiser:** I quote the studies and tell the patient that the studies all were designed for monthly injec-
tions for 24 months and that most patients in these studies went on to get injections for 36 months. I add that, although this is not necessarily the program that we are going to use, and that the regimen will be based on a number of factors, these are the guidelines set forth by the FDA.

When would you schedule a follow-up exam after the first injection and what testing would you perform?

Dr. Busbee: I do not order an FA, but I examine the patient and perform another OCT. I dilate both eyes for examination, because I believe it is important in determining whether asymptomatic hemorrhages are present in the untreated eye.

With regard to treatment on the follow-up visit, I believe in the loading-dose theory based on the results of VIEW 1 and 2 and HARBOR. I think this strategy buys me some time to see what the progress of disease is in the early treatment period. Based on this strategy, I treat on the next monthly visit.

Dr. Kuppermann: I dilate every patient for OCT on the second visit, and both eyes if the patient will consent, because I am looking for early disease in the fellow eye. I do not administer 3 loading doses for every case; rather, I treat based on the OCT findings.

Dr. Regillo: I rarely obtain follow-up FAs unless I suspect that something else is going on. I perform a dilated ocular examination and obtain OCTs in both eyes. I treat monthly until I believe I have reached the patient’s best potential macular status and visual acuity.

Dr. Kaiser: Although I do not obtain an FA at every exam, I think that periodic FAs are helpful to detect lesion growth.

TREATMENT STRATEGIES FOR AMD AND CRVO

Dr. Kaiser: Are you administering monthly anti-VEGF injections (or bimonthly injections with aflibercept) in a treat-and-extend protocol or treat-and-observe protocol?

Dr. Busbee: I treat and extend. To clarify my earlier

By Carl D. Regillo, MD

Figure 1 shows a patient with new wet AMD who was 20/100 at baseline and had occult subfoveal choroidal neovascularization (CNV) with leakage and some blood in the center of the macula in the affected eye. The corresponding OCT showed subretinal fluid, macular edema, and a pigment epithelial detachment. The patient was started on monthly treatment with ranibizumab injections. One month after the second injection, the patient’s OCT showed no signs of exudation. I gave another injection of ranibizumab and extended the follow-up to 6 weeks. Six weeks later, the macula was still dry. I gave an injection and extended the follow-up to 8 weeks. Everything looked good at 8 weeks, so an injection was given and the follow-up in turn extended to 10 weeks. At 10 weeks, there were signs of recurrent CNV activity with edema on OCT and some decreased visual acuity. I treated at that visit and reduced the follow-up to 8 weeks. When the patient returned, the macula was dry and stable, and I rechallenged the patient by re-extending the follow-up/treatment interval to 10 weeks (Figure 2). This time I was successful and was able to extend a bit more out to 12 weeks. I maintain the macula dry thereafter with treatments every 12 weeks over the next 2 years with visual acuity remaining very good at 20/30 (Figure 3).

Figure 1. Baseline presentation.

Figure 2. Treatment intervals of up to 10 weeks.

Figure 3. Treatment intervals of up to 12 weeks.
statement, I do not automatically give 3 loading doses. Most patients have 1 area of improvement, whether it is visual acuity or drying of the macula, which has resulted from their first few injections, and that compels me to treat again. Although sometimes it seems that I am giving monthly injections, my ultimate goal is to treat and extend.

Dr. Kuppermann: I prefer the prn approach. It allows more flexibility for my patients and allows me to administer the least number of injections necessary to provide a maximum benefit with the minimum risk. Because there is a possibility that the expression of VEGF may be of some benefit to patients, I try to counterbalance forces.

Dr. Kaiser: How do you rationalize this strategy against the clinical trials, which have shown that monthly treatment is superior to prn dosing?

Dr. Kupperman: My prn regiment is aggressive. Although I do not use loading doses, I treat at the first sign of any blood or fluid. I am not looking for reasons not to inject; I prefer to inject, but if I can avoid it, I will.

Dr. Kaiser: How do reconcile when the patient looks good to you on OCT but is not reading the Snellen chart as well as he or she should be?

Dr. Kupperman: I listen to what the patient has to say, perform the exam, and look at the OCT. In my opinion this provides enough guidance. I have an electronic medical record, making it easy for me to view progression.

Dr. Regillo: I use a treat-and-extend approach, which is a continuous, but variable, individualized treatment regimen. I only stop treatment when I have been giving injections for a long time and nothing is happening, or in patients who have end-stage disease.

Dr. Kaiser: How will you manage a patient you have just diagnosed with nonischemic CRVO?

Dr. Kuppermann: The clinical trials evaluating anti-VEGF agents for CRVO have changed the way that we manage these patients. Historically, we employed a watchful waiting strategy for a period of time prior to initiating any treatment with laser, the only treatment available. This treatment regimen was based on the CVOS study, which is more than 10 years old. Now that we have anti-VEGF agents that are FDA approved for CRVO, I tend to inject patients immediately—maybe not the first day, but soon after I first diagnose CRVO. From the CRUISE and COPERNICUS studies evaluating ranibizumab and aflibercept, respectively, we have learned that delays in treatment result in decreased outcomes.

Dr. Regillo: Compared with wet AMD, CRVO is a condition in which the intraocular VEGF levels on average are higher and, therefore, more intensive treatment may be needed. That being said, I do not treat every patient with CRVO the same day if the edema is very mild and visual acuity relatively good, eg 20/25. However, if there is moderate edema, decreased vision, or if there is a history of the condition worsening, I treat with anti-VEGF therapy on the first visit.

Dr. Kaiser: What if there is no macular edema, but hemorrhages are present on the macula and the visual acuity is poor? Would you treat this patient?

Dr. Regillo: In this scenario, the visual acuity is decreased for 1 of 2 reasons—either the macula is ischemic or there is blood on the fovea (or both). I would observe rather than treat.

Dr. Kuppermann: Going back to the patient with nonischemic CRVO, I would most likely treat unless the symptoms are very mild. Unlike AMD, the treatment for CRVO is usually not ongoing and the risk of harm from 1 initial injection of an anti-VEGF agent is low. After an initial injection, I see the patient a month later and then treat prn.

If there is no edema, just occlusion or poor vision because of potential ischemia vs presence of blood on the fovea, I do not inject.

Dr. Busbee: I am quick to treat a patient with symptomatic CRVO and macular edema. I routinely extend treatment after stabilizing the disease with monthly treatment. Patients with CRVO are different from patients with diabetes or AMD in that they can tell you the exact day when they noticed that the drug effect has dwindled to nontherapeutic levels.

Dr. Kaiser: I am biased toward early treatment, even for patients with ischemia and hemorrhages. It may take longer to see results, and patients may not do as well as their nonischemic counterparts, but I have had success with anti-VEGF treatment for ischemia.

Dr. Kaiser: If you treated a patient on the first visit, when will you have them come back for follow-up?

Dr. Regillo: I have the patient come back monthly until the macula is dry.

Dr. Kaiser: If there was no macular edema and hemorrhage in the macula but vision was decreased, and you
decided not to treat at the initial visit, when will you see a patient back and when will you treat him or her?

**Dr. Regillo:** It would be rare for a patient to have no macular edema and decreased vision. Even when there is blood present, edema tends to coexist. I would see such a patient back in 1 month to check for edema.

**Dr. Kaiser:** Once you begin to treat a patient, what must happen in order to change your frequency of follow-up?

**Dr. Regillo:** Once the macula is dry I switch to a treat-and-extend strategy. In general, most of my patients for whom CRVO does not spontaneously resolve will receive treatment every 4 to 8 weeks.

**Dr. Kaiser:** I have a group of patients with RVO who are 50 to 60 years old and who are “addicted” to anti-VEGF therapy, regardless of specific drug. They function at a high level when the drug is working, and when a drop-off of effect occurs it is so dramatic that these patients know they need another injection. Individualization of treatment for these types of patients is critical.

**Dr. Regillo:** I agree. These patients recover well from macular edema, and even if it recurs, usually no ground is lost unlike with wet AMD, in which CNV lesion size can increase. In general, patients with RVO have more tolerance for recurrence, even if the recurrent edema is relatively severe. That being said, it is probably better to reduce these macular edema recurrences in the long run.

**Dr. Kaiser:** In terms of drug response, I have noticed in my practice that patients with AMD have more options because they generally respond to any anti-VEGF agent. There is a subset of patients with RVO, however, in whom I see a dramatic drug-specific response, either to ranibizumab or aflibercept, and a stronger response overall to these on-label drugs than to bevacizumab.

**Dr. Kuppermann:** I always start patients with CRVO on anti-VEGF injections, but when confronted with a situation in which they have not responded after 3 injections, I consider steroids. I favor the dexamethasone intravitreal implant because of its sustained release and lower rate of cataract formation as compared with other steroids.

**Dr. Kaiser:** Do you use steroids in conjunction with anti-VEGF, or do you switch to steroids as monotherapy?

**Dr. Kuppermann:** I have found that patients who do not respond to anti-VEGF therapy respond well to monotherapy with the dexamethasone intravitreal implant.

**Dr. Regillo:** I also occasionally use steroids for RVO in conjunction with anti-VEGF injections, usually when I cannot extend treatment beyond 4 or 5 weeks.

**Dr. Busbee:** If macular edema persists after several injections (Figure 2). The OCTs show that, although some fluid remained, the patient had a good response. After 4 injections of aflibercept, the patient’s insurance carrier refused to pay for more aflibercept injections, so she had to be switched back to bevacizumab. Figure 3 shows the sequence of 4 injections of bevacizumab. The subretinal fluid is again more prominent in both eyes. However, after 4 injections, the patient switched insurance and was able to resume aflibercept injections; Figure 4 shows the 1-month improvement after the patient received injections of aflibercept. At last follow-up, the vision was stable in both eyes at 20/50, which was the same as baseline.
monthly injections with an anti-VEGF agent, I have the patient come back 2 weeks after the last injection so I can gauge the response at that time point with an interim OCT. If the macula is dry at 2 weeks, I will try preservative-free triamcinolone (Triesence, Alcon) and have the patient return for follow-up 4 weeks later. In many cases, I do not reinject at that 4-week visit.

SAFETY ISSUES WITH ANTI-VEGF AGENTS

Dr. Busbee: The data on systemic safety in CATT were somewhat confusing and caused me to have some concerns that I did not have with bevacizumab prior to the publication of the results. Coupled with the IVAN results, which found significantly lower serum VEGF levels with bevacizumab during the trial compared with ranibizumab, the increase in systemic serious adverse events is a notable finding in the CATT trial. I discuss this with my patients who receive bevacizumab.

The take-home message from both CATT and IVAN is that we do not have to treat all patients monthly—some treatments can be individualized to the patient. Regarding safety, what it really comes down to is that everyone should evaluate the safety data and come to their own conclusions.

Dr. Kaiser: The CATT trial showed a statistically significant difference in hospitalizations in patients in the bevacizumab compared with the ranibizumab treatment arms, and you alluded to the fact that this is confusing because there was no real explanation. Dr. Kuppermann, what can we say about this?

Dr. Kuppermann: There was a statistically higher incidence of serious systemic adverse events in the bevacizumab arms compared with the ranibizumab arms. One of the interesting findings to which Dr. Busbee also alluded was that in IVAN, the serum VEGF levels after 12 months of therapy with bevacizumab were lower (lowered by approximately 70%) vs ranibizumab (lowered by approximately 10%), a dramatic difference. There was a clinical correlation to this finding in CATT. When you look at the Kaplan-Meier curves for risk of fellow eye CNV for the first 52 weeks, the bevacizumab and ranibizumab curves are directly on top of each other. Then, after 12 to 15 months they diverge, with the bevacizumab arm showing a lower rate of fellow eye CNV than the ranibizumab arm through the end of the study. This suggests that the lower serum VEGF levels caused by intravitreal bevacizumab (as seen in IVAN) decreased the risk of fellow eye CNV, indicating that the drop in VEGF levels requires some time to manifest.

Dr. Kaiser: Some anecdotal reports suggest that frequent injections of anti-VEGF drug may cause increased

GA. Is this something you consider important to anti-VEGF therapy?

Dr. Kuppermann: This is a controversial topic because there are 2 equally compelling explanations. One explanation is that we are administering anti-VEGF on a chronic basis, which may be causing cell death and promoting GA because the VEGF molecule, in addition to having angiogenic and vascular permeability effects, also has an important role in neuroprotection. The counter argument is that, when treating wet AMD with anti-VEGF agents, we are not addressing the underlying dry AMD, so its natural course is to progress to GA. Before this progression was hidden from us, other than in the formation of disciform scars.

Dr. Busbee: The connection between anti-VEGF agents and progression to GA, in my opinion, must be demonstrated with better diagnostic tools to produce more solid evidence. Unfortunately, we did not have the science at the time of protocol development for all of our recent AMD clinical research to treat pre-treatment fundus autofluorescence. I do not think that current reports can lead to any definitive conclusions about increasing areas of GA, particularly because GA can easily be missed or masked in a patient with treatment-naive wet AMD.

Dr. Regillo: I think that these reports support the theory that the least amount of treatment to achieve the best result is favorable, regardless of whether anti-VEGF injections promote the progression of GA. I believe that treating in a cookbook fashion rather than individualizing treatment is a practice that comes with added burden and cost and also with greater potential safety issues.

1. Which is true about the data from the CATT and IVAN studies?
   a. ranibizumab is superior to bevacizumab for the treatment of wet AMD
   b. ranibizumab appears to be better at drying the retina than bevacizumab
   c. ranibizumab and bevacizumab had equivalent efficacy for the treatment of wet AMD
   d. B and C
   e. none of the above

2. VIEW 1 and 2 findings included:
   a. that aflibercept monthly is noninferior to ranibizumab.
   b. that aflibercept every 8 weeks after 3 monthly doses is noninferior to ranibizumab
   c. that aflibercept prn is noninferior to ranibizumab
   d. A and B
   e. none of the above

3. HARBOR confirmed that monthly dosing of ranibizumab 0.5 mg produces optimal results for patients with wet AMD.
   a. true
   b. false

4. How is fluorescein angiography important in testing for a diagnosis of wet AMD and/or CRVO?
   a. in establishing a baseline for follow-up for both AMD and CRVO
   b. to help identify diseases masquerading as AMD
   c. to evaluate choroidal neovascularization lesion size in AMD and presence of gross macular ischemia in CRVO
   d. none of the above
   e. all of the above

5. At 6 months, ___% of patients in the 0.3 mg ranibizumab monthly group and ___% in the 0.5 mg ranibizumab monthly group in CRUISE gained ≥15 letters at 6 months, as compared with ___% of patients in the 2 mg aflibercept group in COPERNICUS.
   a. 56.1%; 61.5%; 46.2%
   b. 52.3%; 47.7%; 56.1%
   c. 46.2%; 47.7%; 56.1%
   d. 36.4%; 56.1%; 46.2%
   e. none of the above

6. Key patient and care delivery challenges involving AMD and RVO include which of the following:
   a. patient dropout due to injection frequency
   b. patient access to retina specialists in rural locations
   c. increasing patient load for existing retina specialists
   d. aging population demographics for these diseases
   e. all of the above

7. Anecdotal findings of increased GA following frequent injections of anti-VEGF drug may be due to which of the following:
   a. a compromised neuroprotection role of the VEGF molecule
   b. progression of underlying dry AMD during web AMD treatments
   c. both A and B

8. In the COPERNICUS study, the 56.1% of protocol treated eyes at week 24 that gained ≥15 letters from baseline was:
   a. significantly higher than sham, but the same as sham at week 52
   b. significantly higher than sham and remained higher than sham at week 52
   c. the same as sham, but significantly higher than sham at week 52
   d. significantly lower than sham and remained lower than sham at week 52

Did the program meet the following educational objectives?

Recognize various forms of macular edema and inflammation, using the latest developments in the medical literature and new insights from case-based learning

Understand the new data available on treatments for AMD and RVO and how to apply this information in monotherapy and combination therapy treatment schemes

Treat various forms of macular edema and inflammation, based on assessment of patient need, latest developments in the medical literature and insights from case-based learning

<table>
<thead>
<tr>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Jointly Sponsored by The Dulaney Foundation and Retina Today

Supported by an unrestricted educational grant from Regeneron
Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME). Please complete the following course evaluation and return it via fax to FAX # 610-771-4443.

Name and email ____________________________________________________________________________________

Do you feel the program was educationally sound and commercially balanced?  □ Yes  □ No

Comments regarding commercial bias:
______________________________________________________________________________________________
______________________________________________________________________________________________
______________________________________________________________________________________________

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low ______

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low ______

Would you recommend this program to a colleague?  □ Yes  □ No

Do you feel the information presented will change your patient care?  □ Yes  □ No
If yes, please specify. We will contact you by email in 1 to 2 months to see if you have made this change.
______________________________________________________________________________________________
______________________________________________________________________________________________
______________________________________________________________________________________________

If no, please identify the barriers to change.
______________________________________________________________________________________________
______________________________________________________________________________________________
______________________________________________________________________________________________

Please list any additional topics you would like to have covered in future Dulaney Foundation CME activities or other suggestions or comments.
______________________________________________________________________________________________
______________________________________________________________________________________________
______________________________________________________________________________________________