CME SUPPLEMENT TO

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Advances in the Treatment of Wet Age-Related Macular Degeneration

Proceedings From a Roundtable Discussion

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After successfully completing this activity, you will have improved your ability to:

- Demonstrate the implications of the CATT results for monthly and PRN dosing and management of currently used anti-VEGF agents in various subsets of patients
- Compare and contrast the anti-VEGF agents with respect to mechanisms of action and binding affinities
- Discuss the results of the latest clinical trials and how anti-VEGF and other therapies may be used in patients with wet AMD
- Discuss the advantages and drawbacks of various treatments and combinations in their ability to reduce treatment burden and safety risks
- Employ current best practice use of OCT in guiding treatment
- Apply results from the latest clinical trials to AMD patient case scenarios

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Introduction
The paradigms for both the evaluation and the management of neovascular age-related macular degeneration (AMD) have evolved significantly in the past few years and continue to do so. New imaging technologies have been introduced that have greatly enhanced our ability to visualize the disease process at the tissue level. We are now in the era of vascular endothelial growth factor (VEGF) inhibition, and novel drugs continue to enter the marketplace. Clinicians face the daily clinical challenge of integrating new research findings, new technology, and new drugs into their practice patterns. We have assembled a panel of expert retina specialists to discuss the advances in the treatment of wet AMD and its evolving treatment paradigm. Our goal is to bring some clarity to the evaluation and management of wet AMD.

—Peter K. Kaiser, MD

Imaging the AMD Patient

Dr Kaiser: Dr Dugel, consider a treatment-naïve patient referred to your practice for evaluation of neovascular AMD. (Figure 1) What is your approach when evaluating this patient?

Dr Dugel: I have different approaches for treatment-naïve and for previously treated patients. For a treatment-naïve patient, I always obtain a fluorescein angiogram (FA) and routinely obtain optical coherence tomography (OCT) as well. (Figures 2 and 3) If the clinical examination suggests the possibility of polypoidal choroidal vasculopathy (PCV), I will also obtain dynamic indocyanine green (ICG) angiography.

Dr Kaiser: Please explain what you mean by dynamic ICG.

Dr Dugel: In static ICG, single images are obtained. In dynamic ICG, a video is captured throughout the test. Dynamic ICG can reveal high-flow abnormalities in the early seconds after dye injection that can be missed with static ICG. These high-flow lesions can represent PCV or other important lesions.

Dr Kaiser: What features on examination might make you suspicious of PCV and prompt you to obtain dynamic ICG?

Dr Dugel: A pigment epithelial detachment (PED) raises my suspicion. A reddish appearance beneath a PED is also suggestive of PCV. I also routinely obtain ICG on my non-white AMD patients.

Dr Kaiser: Does anyone else on the panel have a different approach for treatment-naïve patients?

Dr Ho: Fluorescein angiography and OCT imaging are standard for my new patients with wet AMD. I do not utilize ICG imaging quite as often as Dr Dugel does, but I will use it for the initial evaluation in a clinical setting suspicious for PCV (hemorrhagic PED, nodular orange macular or peripapillary lesions, non-white race).

Dr Kaiser: I agree with Dr Dugel on the imaging techniques used for a treatment-naïve patient. ICG is important to rule out PCV and other masquerade syndromes such as chronic central serous...
chorioretinopathy. For patients already receiving treatment, I find that FA and ICG are less relevant. There is a tendency to overcall leakage from choroidal neovascularization (CNV) on FA, so it may mislead you in terms of assessing response to therapy. To date, there have been no studies comparing FA with OCT to determine the best way to follow patients after anti-VEGF therapy, but my impression is that OCT is more useful for guiding therapy decisions once therapy has been initiated. Dr Puliafito, you have been instrumental in the development of OCT. Tell us what you look for on OCT scans in wet AMD patients.

Dr Puliafito: OCT is now the core diagnostic technology for management of wet AMD. Reading an OCT involves the inspection of various spaces. We look at the subretinal space. We look under the pigment epithelial layer. We look very closely for cystic changes within the retina. Those are the 3 primary structural end points in which we are interested. (Figure 4)

Dr Kaiser: Is there a role for other imaging modalities, such as wide field angiography or autofluorescence, in wet AMD?

Dr Puliafito: Wide field angiography may have a role in patients who have eccentric CNV.

Dr Dugel: There is definitely a role for autofluorescence, which can be very helpful in distinguishing AMD from other macular diseases, such as the various macular dystrophies.

Impact of Lesion Morphology and Location on Choice of Therapy

Dr Kaiser: Dr Martin, in the past much was made of lesion morphology, for example, classic versus occult. Should we still be classifying AMD lesions as minimally classic, predominantly classic, or occult with no classic?

Dr Martin: No. Lesion type was an important consideration when we relied on photodynamic therapy (PDT). But anti-VEGF therapy is so much more potent that it appears to overwhelm whatever differences in response existed on the basis of lesion morphology. In MARINA, ANCHOR, HARBOR, and CATT, the therapeutic response appeared to be about the same, no matter what lesion type was present at the initiation of therapy.

Dr Kaiser: Dr Dugel, does the location of the lesion have an effect on your management choice?

Dr Dugel: Lesion location matters in the sense that those rare patients with an extrafoveal classic lesion can be very effectively treated with thermal laser photocoagulation.

Dr Kaiser: I agree that there are still the rare well-defined extrafoveal and peripapillary lesions that respond well to laser therapy. For the most part, the anti-VEGF trials evaluated mainly subfoveal lesions. In contrast, the CATT trial differed in terms of inclusion criteria regarding lesion location. Dr Martin, can you explain the rationale for this methodological difference?

Dr Martin: Previous studies required the CNV to be under the geometric center of the fovea. In clinical practice, however, many clinicians use anti-VEGF therapy for juxtafoveal and extrafoveal lesions as well. In addition, almost all retinal angiomatous proliferation (RAP) lesions have a hot spot that is juxtafoveal, but also have a PED or fluid that involves the center of the fovea. By design then, all previous studies have excluded RAP lesions because they required CNV under the center. We thought these patients were very important because they make up 10% to 20% of the population we see with wet AMD.

Figure 4. OCT identifies VEGF-induced exudation.

Figure Courtesy of Carmen A. Puliafito, MD
AMD, and the questions of relative efficacy of ranibizumab and bevacizumab are just as important for these patients as for any other.

So in CATT, we did not require the CNV to be under the fovea. However, the center was required to be involved by some aspect of wet disease, such as PED, subretinal fluid, blood, or the CNV itself. We also lowered the visual acuity requirement to 20/25, and if I had it to do over, I would have eliminated a lower boundary altogether. Previous studies did not allow patients who were better than 20/40 to participate, and yet in clinical practice, patients with these very good levels of vision and CNV are usually treated because of the relatively poor natural history if not treated. The CATT entry criteria allowed us to enroll a much more representative sample of what we actually treat in clinical practice than did previous trials.

**Counseling the Patient Regarding Therapy**

**Dr Kaiser:** Let's assume that the treatment-naïve patient has now been fully evaluated, the diagnosis is wet AMD, and treatment is indicated. How do you counsel patients regarding the course of treatment and follow-up regimen?

**Dr Dugel:** The first thing I tell my patients is that this is a chronic disease, very much like diabetes. It is a disease for a lifetime. It is fundamentally important that patients understand this from the start. The second thing I tell them is that current therapies can help us manage, but not cure, the disease. The third point I make is that there is substantial new research ongoing, and that I am convinced that we will soon have therapies that are better than those we have today. Regarding follow-up, I tell my patients that we will see them monthly until their lesion is dry. Once we've achieved this therapeutic goal, I tell them that the data support continuous monthly therapy for the absolute best results, but that such a regimen may be too burdensome for them. At that point, patients will have input on whether we continue monthly therapy or attempt to transition to a treat-and-extend approach.

**Dr Ho:** I agree that it is fundamentally important that we distinguish between treatment and cure. Patients’ perception of AMD therapy has changed considerably. Before anti-VEGF therapy, there were treatments, but they merely slowed the decline of vision rather than stabilized or improved vision. Patients did not always view these historic therapies as meaningful treatment. Modern anti-VEGF therapy offers stability to the vast majority of patients, and significant visual improvements in up to one-third of them. There is often an expectation of improvement, and because two-thirds of patients treated with bevacizumab or ranibizumab do not experience improvement, we have to manage these expectations up front.

**Dr Kaiser:** Are there any other counseling pearls?

**Dr Ho:** I routinely show my patients their imaging studies. They are very useful for patient education. I use the images to help illustrate the disease process.

**New Data From Clinical Trials CATT**

**Dr Kaiser:** In the past year, the results of several large randomized clinical trials concerning the treatment of wet AMD were reported. We are fortunate to have key personnel from each of those studies on the panel. Beginning with Dr Martin, let’s review the rationale behind and findings from the CATT study.

**Dr Martin:** Our first look at the ranibizumab MARINA data was in July 2005 at the American Society of Retina Specialists annual meeting in Montreal, Canada. We were all incredibly impressed with this paradigm-changing drug. On the same day, a case report describing the use of intravitreal bevacizumab in a patient with neovascular AMD detailed a remarkable therapeutic effect that looked similar to what was being described for ranibizumab. Many clinicians went home and began using bevacizumab as a surrogate for ranibizumab because it was available for off-label use, had a target specificity similar to that of ranibizumab, and was inexpensive.

By the time ranibizumab was approved by the US Food and Drug Administration (FDA), bevacizumab had become the standard of care for the treatment of neovascular AMD, despite the lack of any randomized clinical trial data confirming its efficacy. In addition, there was uncertainty about how bevacizumab, or for that matter ranibizumab, should be dosed. When we began using bevacizumab, little was known about its safety. Therefore, most retina specialists administered it on an as-needed (PRN) basis as opposed to the fixed monthly dosing that was employed in MARINA and ANCHOR. What we learned was that there were some patients who could achieve an excellent visual result with less frequent dosing. Once ranibizumab was FDA approved, PRN dosing was adopted for it too; a treatment algorithm had never been studied in a large clinical trial. So by the end of 2006, the vast majority of patients (>95%) were being treated with either a drug or a treatment regimen that had never been validated in a randomized clinical trial.

CATT was designed as a head-to-head comparison of monthly treatment or PRN treatment of either ranibizumab or bevacizumab. At 1 year, ranibizumab
and bevacizumab produced equivalent, nearly identical, visual results when each drug was given at the same dosing regimen. PRN dosing of either drug also produced an excellent visual outcome, but resulted in, on average, 2 letters less than monthly treatment. Patients on PRN dosing received 4 to 5 fewer injections over 1 year than their monthly counterparts, but patients who were assigned to bevacizumab PRN received a mean of 0.8 more injections than did ranibizumab PRN patients. Structural outcomes were also evaluated. Ranibizumab appeared to dry the macula significantly more effectively than did bevacizumab, with more ranibizumab-treated eyes dry at the 12-month mark versus bevacizumab-treated eyes. The minority of eyes in either group were completely dry at 1 year, however; the eyes that were still wet had a small amount of fluid (mean of 10 microns). (Figure 5)

From an adverse event standpoint, there were no major differences in death, myocardial infarction, or stroke between the groups. However, total serious adverse events (SAEs) were higher in the bevacizumab group than in the ranibizumab group (24% vs 19%, P=.04). Most of these events were hospitalizations, and the importance of this information is not clear. At a mean age of 79, patients in CATT were admitted to the hospital for many different reasons. In the more than 10 years of study on intravenous bevacizumab in which patients receive 500 times greater doses than were given in our study, the vast majority of reasons for hospitalization has never been associated with the use of anti-VEGF drugs. Most of the imbalance in SAEs were in those events unrelated to anti-VEGF therapy. In addition, the highest rate of SAEs was in the group that received the least amount of drug.

There are several possible explanations for this finding. It could be a chance finding. It could be attributable to differences in the risk profiles of subjects at baseline—for instance, the bevacizumab group was, on average, 1 year older than the ranibizumab group. Or, it could be that the increased risk may be real and related to the treatment itself. We hope that this safety finding at year 1 will be clarified in year 2 of CATT and in the other 5 ongoing trials in Europe comparing ranibizumab and bevacizumab.

**Dr Ho:** There are theoretical reasons why the differences in SAEs could be real. Bevacizumab has a longer serum half-life than ranibizumab has. It is not unreasonable to hypothesize that a drug with a longer systemic half-life could potentially have more serious systemic safety events.

**Dr Puliafito:** Of the commercially available anti-VEGF agents, bevacizumab has a longer intravitreal half-life than either ranibizumab or the newest agent, aflibercept (VEGF Trap-Eye). However, ranibizumab has a higher binding affinity than bevacizumab, and aflibercept has the highest binding affinity of all agents. The relative importance of intravitreal half-life and binding affinity is not known. Our initial clinical results with aflibercept, however, indicate that having a high affinity may present a significant clinical advantage in eyes with chronic subretinal fluid and macular edema even when well treated with other agents.

**Dr Martin:** I very much look forward to the additional systemic VEGF data from IVAN. But the puzzle here is that if the risk is real and we think the imbalance is related to the half-life and the presence of an Fc fragment on bevacizumab, why don’t we see the same imbalance in SAEs with aflibercept? It, too, has a longer serum half-life than ranibizumab, has an Fc fragment, but has an even higher binding affinity for VEGF than does bevacizumab. By this logic, one would think there would have been an even bigger problem in VIEW1/VIEW2 and yet there was not. The whole thing doesn’t make sense.

**Dr Kaiser:** An increase in SAE rates from 2% to 3% represents a relative increase of 50%. The CATT study was not powered to discover a 50% relative increase in SAE rates. To discover such an increase, a study may need more than 10,000 patients. To achieve such numbers, there have been 2 recent reports based on the Medicare claims database, both evaluating systemic safety of anti-VEGF therapy in AMD. It would be helpful to review those findings in the context of the CATT findings.
Dr Dugel: The paper by Gower and colleagues was presented at the 2011 The Association for Research in Vision and Ophthalmology (ARVO) meeting (Gower EW et al. ARVO E-Abstract 6644, 2011). The researchers evaluated nearly 78,000 Medicare beneficiaries with neovascular AMD. They found an 11% higher risk of overall mortality and a 57% higher risk of hemorrhagic stroke in patients treated with bevacizumab compared with those treated with ranibizumab. Both of these findings were statistically significant. However, it is worth noting that the stroke rate in the bevacizumab group was approximately 4%, which is the normal background rate for people this age, while the stroke rate in the ranibizumab group was approximately 2.6%. Unless we believe that ranibizumab is protective of stroke, it is more likely that the reported values represent a statistical chance finding.

The paper by Curtis and colleagues evaluated differences in adverse events between anti-VEGF therapy and PDT in a 5% sample of the Medicare database. Overall, there was no difference between these 2 groups in the safety outcomes investigated. However, death rates differed among the treatment groups: death occurred in 4.1% of PDT patients, 4.1% of ranibizumab patients, 4.4% of bevacizumab patients, and in 4.8% of pegaptanib patients (P=.001). These results can be misleading, as some patients may have received more than 1 anti-VEGF agent throughout the course of treatment. When the data were reanalyzed to include only those patients who consistently received the same drug throughout treatment, the death incidence rates were statistically equivalent (4.7% for ranibizumab vs 4.3% for bevacizumab). Curtis concluded, and I agree, that there is no statistical safety difference between these 2 drugs. This conclusion was recently borne out in a major review of safety with all the anti-VEGF agents for AMD, in which it was noted that all were safe and had similar safety profiles overall.

Dr Kaiser: Despite methodological problems, both these reports demonstrated the same thing in contrast to the safety results of the CATT study. Do we think there is any systemic risk to the anti-VEGF drug class?

Dr Dugel: I am concerned about the occurrence of stroke in patients with AMD. There is a higher incidence of stroke in patients with AMD compared with those without AMD. Also, the SAILOR trial suggested that prior stroke patients are at particular risk of having another stroke following anti-VEGF therapy for AMD. In these patients, I may consider the 0.3-mg dose, which had a better safety profile in this subset of patients with very little efficacy cost.

Dr Kaiser: SAILOR identified prior stroke, cardiac arrhythmias, and a history of congestive heart failure as risk factors for stroke while receiving anti-VEGF therapy. Aside from these, is there any other patient profile or genetic factors that would influence your choice of anti-VEGF agents?

Dr Martin: We have collected DNA from all the CATT patients and hope to have some information pertaining to this situation in the future. Also, the DAWN study (presented at the American Academy of Ophthalmology meeting, October 2011, San Francisco, California, by Ianchuley I et al) sought to explore the relationship between patient profile and anti-VEGF therapy. DAWN is a substudy to HORIZON, which, in turn, was the long-term extension study of MARINA, ANCHOR, and FOCUS patients. DAWN sought to explain differential response to ranibizumab therapy based on genotype. In fact, there was a particular allele that accounted for a nearly 2-fold difference in visual gains depending on which allele the patient had. It is challenging to put this observation into clinical practice at this time, but future work may provide insight and guidance into the selection of therapy based on genotype.

Dr Kaiser: Before we move on to the other important clinical trials from this past year, what do you think we can look forward to in the second year of CATT?

Dr Dugel: The switch from TD-OCT to SD-OCT will provide us with a better representation of treatment efficacy. We will likely see more fluid, and the question will be: How aggressive should we be in eliminating this residual fluid? I am also interested to see if the PRN groups maintain vision through the second year.

Dr Ho: I am curious to know whether the statistically significant difference between systemic serious adverse events in year 1 will hold up through the second year or not. My prediction is that they will not hold up and that the rates of SAEs will equalize.

Dr Kaiser: I, like Dr Dugel, am eager to see how the monthly groups do in the second year when they are randomized to remain monthly or to switch to PRN therapy.

HARBOR

Dr Kaiser: There is no question that monthly therapy provides the best chance for visual gains, but this regimen imposes a huge burden on patients, their families, physicians, and the health care system. CATT indicated that PRN ranibizumab was equal to monthly therapy with monthly follow-up and aggressive PRN treatment guidelines. CATT-like PRN therapy reduces
the number of injections, but not the burden of visits. Some physicians have postulated that increasing the dose of ranibizumab, or even performing injections every 2 weeks, could improve outcomes. Dr Ho, please describe the rationale and findings of the HARBOR trial.

**Dr Ho:** HARBOR (presented at the American Academy of Ophthalmology meeting, October 2011, Orlando, Florida, by Ho AC and Busbee BG et al) was a Phase IV commitment by Genentech to the FDA to evaluate different doses and dosing regimens of ranibizumab. The HARBOR study enrolled 4 groups: the standard 0.5 mg monthly, a higher dose of 2 mg monthly, and each of those 2 doses in a PRN schedule, with PRN defined as 3 loading doses up front and then as-needed based on retreatment criteria that differed from prior studies because of the use of SD-OCT to guide retreatment. HARBOR confirmed that monthly dosing with 0.5 mg remains the optimal dosing regimen for ranibizumab. There was no added benefit to the higher dose, perhaps because 0.5 mg is at the top of the dose-response curve.

**Dr Kaiser:** It is nice to know that the 0.5-mg dose we already have appears to be the most effective, but HARBOR also showed us that in those rare cases in which we might need a higher dose or every-2-weeks dosing, it may be safe. I hope to see additional analysis from HARBOR since it is the first study to use SD-OCT. It will be interesting to see if there is a differential OCT response in the monthly versus PRN groups.

**Dr Ho:** That is an excellent point, that the HARBOR study safety findings revealed no new safety concerns for any dose investigated, specifically that the safety profile of 0.5-mg and 2.0-mg dosing was similar; this is important in light of prior ranibizumab trials that suggested possible dose-response safety concerns. As the only large neovascular AMD clinical trial to date that employed only SD-OCT imaging, it was not a complete surprise that the rates for “dry” OCT images at 1 year in HARBOR were on the order of only 6% to 12%, much lower than in other trials. We need to analyze these HARBOR SD-OCT results to determine what OCT parameters are visually meaningful, to help guide us in

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**Anti-VEGF Agents: Similar Effects, Distinct Mechanisms**

The 4 available anti-VEGF therapies for neovascular AMD share the common goal of suppressing VEGF activity. They all accomplish this goal by binding to the VEGF molecule and blocking its interaction with the VEGF receptors. Each molecule has distinct features that differentiate it from the others in this class.

- **Pegaptanib** is an aptamer, which is a single strand of RNA or DNA (RNA in the case of pegaptanib) that folds up in such a way that its shape meshes with the VEGF molecule like a lock and key. There are several isoforms of VEGF, all of which are active in the angiogenesis process. Pegaptanib selectively inhibits only the VEGF-165 isoform of VEGF, which may explain the relatively lower efficacy of this drug compared with others in the class.

- **Bevacizumab** is a full-length antibody that binds all isoforms of the VEGF-A family. It was developed as a systemic antineoplastic therapy but has been used off-label for neovascular AMD since 2005, first systemically and then intravitreally.

- **Ranibizumab** is an antibody fragment adapted from bevacizumab. Like its parent molecule, ranibizumab binds all isoforms of the VEGF-A family.

- **Afibercept,** also known as VEGF Trap-Eye, is a recombinant protein in which the binding domains of VEGF receptors 1 and 2 have been combined with the Fc portion of IgG. The molecule has a very high binding affinity for all VEGF-A isoforms as well as for the related molecules placental growth factor-1 and factor-2 and VEGF-B.
treatment decisions. Year 2 HARBOR data are forthcoming in the fall of 2012, and I am looking forward to the results.

**VIEW 1 and VIEW 2**

**Dr Kaiser:** The other comparison study that reported last year was the VIEW study with aflibercept versus ranibizumab.

**Dr Ho:** VIEW 1 (Nguyen QD. ARVO E-abstract 3073, 2011) enrolled North American subjects and VIEW 2 (Schmidt-Erfurth U. ARVO E-abstract 1650, 2011) enrolled international subjects with treatment-naïve neovascular AMD. Both trials randomized subjects to 4 arms: 0.5 mg monthly ranibizumab, 0.5 mg monthly aflibercept, 2 mg monthly aflibercept, and 2 mg aflibercept every 2 months. This dosing regimen was used for the first 12 months. For the second 12 months of the study, patients were examined monthly, but treated quarterly, unless they met pre-specified retreatment criteria, which triggered treatment earlier than quarterly. The 12-month integrated analysis pooled the data from both studies and demonstrated that when these 2 drugs were each administered monthly, their efficacy was similar. However, considering the 2 studies separately, VIEW 1 found that 2-mg monthly aflibercept was more efficacious than monthly ranibizumab, while VIEW 2 found just the opposite.

This difference in results may be related in part to differences in the 2 study samples. VIEW 1 was composed of predominantly white subjects, while VIEW 2 had a more ethnically diverse sample population. Also, dosing aflibercept every 2 months seemed to be as efficacious as either drug dosed monthly. Overall, subjects in all arms gained, on average, 8 to 10 letters (Figure 6), and the proportion gaining 3 or more lines of acuity was in the 30% to 35% range. Finally, no new safety concerns were identified for anti-VEGF therapies in the VIEW 1 and VIEW 2 studies.

**VIEW 1 and VIEW 2 Year 2 Results**

**DESIGN:** In year 2 of the VIEW studies, participants continued to receive the same drug and dose to which they were randomized in year 1, but all 4 treatment arms changed to a PRN dosing interval. Participants were evaluated monthly, and treated no more often than once monthly and no less often than every 3 months, based on retreatment criteria.

**EFFICACY:** All 4 groups suffered modest loss of best-corrected visual acuity in year 2 compared to the end of year 1, with mean losses ranging from 0.8 to 1.7 letters. As in year 1, approximately one-third of patients in all 4 groups maintained gains of 3 lines or more. Central retinal thickness improvements seen in year 1 were maintained through year 2 in all 4 groups as well.

**SAFETY:** Both aflibercept and ranibizumab demonstrated favorable safety profiles through year 2, with similar incidences of serious ocular adverse events among groups. As in year 1, the most common adverse events were typically associated with the injection, the underlying disease process, or the aging process.

**TREATMENT BURDEN:** Through 2 years, participants in the aflibercept 2 mg every-4-weeks group received an average of 16 injections, of which 4.2 occurred during the year 2 PRN dosing phase. In the aflibercept 2 mg every-8-weeks group, the corresponding numbers were 11.2 and 4.1 injections, and in the ranibizumab group, 16.5 and 4.7 injections.

Figure 6. 2-year VIEW 1 and VIEW 2 results.


**Dr Kaiser:** The 2-mg dose of aflibercept received FDA approval last month, so now we have an additional therapy in our anti-VEGF armamentarium. In which patients would you consider switching from your current anti-VEGF therapy to aflibercept?

**Dr Puliafito:** There are 2 categories of patients in whom I am using aflibercept therapy. The first group consists of those patients who have required monthly treatment with their current therapy for a long period of time and who lose ground whenever we try to extend the dosing interval. These patients seem to consume anti-VEGF drugs at a high rate. The second group is made up of those patients who still have anatomic changes consistent with wet AMD—including persistent subretinal fluid and/or persistent PED—after many months of conventional anti-VEGF therapy. Herein, an important issue arises in clinical practice. What is the definition of treatment failure, and what is the best way to manage patients who fail therapy with bevacizumab or ranibizumab?

**Dr Kaiser:** It is worth reiterating that with SD-OCT we are going to see residual fluid in many eyes that are responding well to therapy. The idea that most patients will have a dry OCT even with 1 year of monthly therapy was challenged by the CATT study. So, it is important to emphasize that the presence of residual fluid does not necessarily indicate treatment failure. Perhaps these patients would benefit from an alternate therapy such as aflibercept, but it is important to know that we lack data on its benefit in eyes that have failed ranibizumab or bevacizumab therapy. Over the next few months we will see how aflibercept therapy works in these difficult patients.

The presence of residual fluid with SD-OCT does not necessarily indicate treatment failure.

**Dr Dugel:** Another component of failure is often found in the patient who does not come back as often as required for reevaluation and retreatment. A treatment that significantly reduces the number of injections needed per year would be valuable in my practice, because it would reduce the treatment burden in many patients. It would save a lot of injections and a lot of visits.

**The Evolving Therapeutic Regimen**

**Dr Kaiser:** So far I have heard that in this group aflibercept has a place as second-line therapy in patients who have failed ranibizumab or bevacizumab therapy. Is there a role for aflibercept as first-line therapy? Assume a newly diagnosed, treatment-naive patient presents to your office. What is your treatment strategy now that aflibercept is available?

**Dr. Martin:** After many years of good experience with bevacizumab and ranibizumab, I am likely to start with these drugs first. Since the CATT results became available, I use much more bevacizumab than ranibizumab. It is inexpensive and effective. I will occasionally start with ranibizumab if, after our discussion, that is the patient’s preference. I look forward to gaining experience with aflibercept and am certain that I will use it more in the future. I can imagine using it in patients who require monthly therapy and who would like to reduce their treatment burden, or in patients who fail to achieve a dry macula with bevacizumab.

**Dr Puliafito:** I agree that for treatment-naive patients with no other concerns, bevacizumab is the appropriate first-line therapy. Patients who clearly cannot maintain a monthly visit schedule are good candidates for aflibercept therapy. There is a substantial pool of patients, however, who have not responded well to conventional therapy and still have potential to respond to effective therapy. These patients are also appropriate candidates for aflibercept therapy.

**Dr Ho:** To summarize, there does not appear to be a distinctive difference in efficacy among these 3 drugs, and I am comfortable starting treatment-naive patients with any one. Initially, only a handful of retina specialists—primarily those involved in the VIEW trials—have had significant experience with aflibercept, but the number is growing as we have witnessed the successful launch of this new treatment option. There may be some first-line indications, particularly in patients who struggle with monthly follow-up, but for the most part, aflibercept is likely to be used primarily as a second-line drug until clinicians become more familiar with it. Having more treatment options is better for us as well as better for patients because some patients may respond better to one agent than to another.

**Dr Martin:** On balance, ranibizumab given every 2 months might have done just as well as aflibercept every 2 months. That was not an arm of the VIEW studies. Neither ranibizumab nor bevacizumab dosed every 2 months has ever been studied in a clinical trial.

**Dr Dugel:** The assumption that aflibercept can reduce the burden of follow-up should be carefully examined. Keep in mind that in both VIEW 1 and VIEW 2, all patients were seen every month, not every 2 months. The label for this drug states that after the 3-dose loading phase, patients can be reevaluated every 2 months. But we cannot be certain that there will be no differences in outcomes with follow-up that is monthly versus follow-up every other month.
Dr Martin: That is a very fair point. In VIEW1 and VIEW 2 there were no treatment decisions being made in the months when sham injections were given. In the real world, we make treatment decisions every time we see the patient. Seeing the patient monthly increases the probability of observing a relapse event earlier. Seeing the patient only every 2 months reduces the opportunities to detect a relapse. And also, with a 2-month follow-up schedule, the consequences of a missed visit—and therefore a 4-month window between evaluations—become more significant.

Dr Kaiser: Whether to see patients every month or every 2 months when using aflibercept is an important clinical question. I suspect that until retina specialists get comfortable with the typical clinical response to aflibercept therapy, they will continue to follow patients monthly. They won’t necessarily retreat on a monthly basis, but I believe they will continue to evaluate monthly until they can appreciate the duration of effect for themselves.

Dr Martin: It will not surprise me to see clinicians begin to use aflibercept monthly and then transition to a treat-and-extend regimen. This is likely how I will initially incorporate aflibercept into my practice.

Dr Kaiser: I agree fully and use this regimen myself. Dr Martin, please describe what you mean by a treat-and-extend regimen.

Dr Martin: Treat-and-extend begins with monthly treatment until the macula is dry. Then the follow-up interval is extended to 6 weeks, 8 weeks, 10 weeks, and so on, treating at each visit to maintain a dry macula. If there is disease relapse (usually fluid or blood), say at 10 weeks, then the inter-visit interval would be shortened again. Depending on the severity of the relapse, the patient would be seen again at 8 weeks (2 weeks less than the previous maximum time between visits) or on a monthly basis until dry again. This algorithm is, of course, different from PRN dosing, in which patients are followed monthly but only retreated if there is evidence of recurrence of fluid.

Dr Ho: The treat-and-extend regimen accommodates the reality of treatment burden. It is my treatment pattern no matter which anti-VEGF agent I use.

Dr Dugel: The PRN regimen does not reduce treatment burden. You must still see the patient on a monthly basis. Treat-and-extend does reduce the treatment burden by reducing the frequency of visits. Both treat-and-extend and PRN dosing reduce the number of injections, which is likely to reduce the rate of catastrophic events such as endophthalmitis.

Combination Therapy

Dr Kaiser: We now have several distinct monotherapy treatment modalities for managing neovascular AMD. Assuming a typical AMD lesion without evidence of PCV, is there any role for combination therapy and which treatments might you combine?

Dr Dugel: Ultimately, combination therapy will be an important part of disease management. Our current approach is tremendously better than what we’ve had in the past, but still far short of the ideal. Combination therapy may help us achieve better outcomes, but just as importantly, it may help us reduce treatment burden. Currently, I am unconvinced that there are any potential combinations of available drugs that have any data to support their use for wet AMD. It is an area of great unmet need.

Dr Kaiser: So are you saying there is currently no role for combination therapy?

Dr Dugel: There is 1 clinical scenario at present in which I would consider combination therapy. This is when the patient informs me ahead of time that he or she does not wish to return for ongoing evaluation and therapy. In that setting, we are faced with the choice of simply surrendering to the natural history of the disease or offering a treatment that, while not ideal, combines the best possible efficacy with the best possible duration given the limitations of no follow-up. In my thinking, the patient described would be one in whom I would combine anti-VEGF therapy with PDT. That would be the only time that I would use combination therapy with the currently available treatments.

Dr Ho: Why do not you use this approach more frequently to reduce treatment burden?

Dr Dugel: Because most of the time patients don’t announce their intention to stop coming back. They just stop coming without giving me the opportunity to use this strategy.

Dr Ho: What is the rationale for this combination in patients who do not intend to come back?

Dr Kaiser: Two studies—DENALI14 and MONT BLANC15—evaluated the combination of ranibizumab with verteporfin PDT. The results have been presented, but not yet published. In these studies, subjects received PDT at baseline, as well as ranibizumab at baseline, and at months 1 and 2. Thereafter, retreatments with either modality were on a PRN basis. We can draw some support for Dr Dugel’s approach from these studies because approximately 30% of patients required no PRN retreatment with either modality during the 12 months
of the study. These results suggest that in some patients who elect not to continue treatment or follow-up, perhaps the best we can do is to offer them a treatment that will afford an approximately 30% chance for stability over the ensuing year. If the patient is adamant about not returning, this certainly is a reasonable course of action.

The studies also showed that the combination therapy was safe, and no evidence of acute severe vision loss that has been described with PDT monotherapy in larger lesions was reported.

**Dr Ho:** The Phase II RADICAL study (presented at the American Academy of Ophthalmology Retina Subspecialty Day meeting, October 2009, San Francisco, California, by Ho AC) also suggested that combination therapy—in this case ranibizumab, low-fluence PDT, and dexamethasone—produces comparable 12-month results with fewer retreatments than does ranibizumab alone. So there is converging evidence that combination therapy may reduce the treatment burden, as Dr Dugel noted. But we probably haven’t found the ideal combination regimen yet.

**Dr Kaiser:** We should point out the obvious exception—patients with PCV. The EVEREST study showed that combination therapy with ranibizumab and PDT was superior to PDT and ranibizumab-alone in causing complete polyp regression and improving visual acuity. Thus, in patients with PCV, my treatment of choice is standard fluence PDT combined with anti-VEGF therapy.

**The Future**

**Dr Kaiser:** What breakthroughs can we expect in the near future in terms of therapy for neovascular AMD?

**Dr Dugel:** Monotherapy with anti-VEGF therapy is so effective that new therapies will be hard pressed to outperform the established efficacy threshold. Studies of combination therapies will clarify the regimens that offer the best in terms of optimizing efficacy and treatment burden. One aspect of clinical management that we need to address is identifying the correct patients for each new regimen that emerges. I suspect the algorithm will start with anti-VEGF monotherapy for treatment-naïve patients, this being the clinical standard today. Those who do well and can bear the treatment burden will continue with monotherapy. Those who do not enjoy the efficacy benefit we expect from this regimen, or who cannot bear the associated treatment burden, may be candidates for emerging combination therapies.

In terms of novel treatments, there are a few potential therapies that may emerge soon. One is radiation, which may be a useful adjunct to anti-VEGF therapy. This therapy recently failed to meet its primary end point in a 2-year trial combined with ranibizumab therapy in treatment-naïve patients (presented at the Angiogenesis, Exudation and Degeneration meeting, February 2012, Coral Gables, Florida, by Dugel P et al). But radiation may find application in other subsets of patients, such as those who fail to respond adequately to primary anti-VEGF therapy. Another novel treatment is platelet-derived growth factor (PDGF) inhibition. Anti-PDGF therapy is very promising and may have a role as primary therapy.

**Dr Kaiser:** What is the status of sustained-release therapies to reduce treatment burden?

**Dr Ho:** Reducing treatment burden via sustained-release therapy is a huge unmet need. There are several technologies to be introduced relatively soon that may reduce the treatment burden for patients requiring frequent anti-VEGF injections, and these technologies may even raise the bar in terms of efficacy.

**Dr Kaiser:** What is the status of gene therapy?

**Dr Dugel:** I tend to think of this concept as a drug delivery issue, with the virus that delivers the gene being the delivery device. There is a study ongoing, but it is early and there are no results to discuss yet.

**Dr Kaiser:** Any other thoughts on what the future holds?

**Dr Puliafito:** The average patient in my practice now sees me more often than he or she sees a primary care physician. Retina specialists have taken a front-line role in disease management with an increasingly growing segment of the population. But I think we are simply in a holding pattern, waiting for technology to catch up to reality. Neovascular AMD will inevitably and necessarily evolve into a disease managed by surgical implantation of a sustained-release drug delivery device.
References


CME POST TEST
 Advances in the Treatment of Wet Age-Related Macular Degeneration

To obtain AMA PRA Category 1 Credit™ for this activity, you must complete the CME Post Test by writing the best answer to each question in the Answer Box located on the Activity Evaluation/Credit Request form on the following page.

1. Which of the following is/are false regarding the use of optical coherence tomography (OCT) in the evaluation of neovascular AMD?
   a. TD-OCT offers higher resolution than SD-OCT
   b. Eyes that appeared fluid-free with TD-OCT may show residual fluid with SD-OCT
   c. Both A and B are false

2. Which of the following is/are commonly used tests in the evaluation of a newly diagnosed patient with neovascular AMD?
   a. OCT
   b. Fluorescein angiography
   c. Both A and B

3. Which of the following correctly describes the molecular structure of the anti-VEGF molecules?
   a. Pegaptanib is an antibody fragment
   b. Bevacizumab is an antibody
   c. Aflibercept is an aptamer

4. Which of the following was not a finding in CATT?
   a. When each was dosed monthly, ranibizumab and bevacizumab produced comparable visual acuity outcomes
   b. When each was dosed PRN, ranibizumab and bevacizumab produced comparable visual acuity outcomes
   c. Monthly therapy was clearly superior to PRN therapy with each drug

5. Which of the following is/are a valid conclusion regarding the VIEW studies of aflibercept?
   a. Both View 1 and View 2 demonstrated that monthly aflibercept was more effective than monthly ranibizumab
   b. Aflibercept dosed every 2 months was as effective as either aflibercept or ranibizumab dosed every month
   c. Both A and B are true

6. Which of the following most accurately describes the safety of anti-VEGF therapy?
   a. Patients with AMD have fewer strokes overall than patients without AMD
   b. Anti-VEGF therapy clearly increases the risk of stroke
   c. Neither A nor B is true

7. Which of the following most accurately describes the burden of therapy associated with anti-VEGF treatment for neovascular AMD?
   a. The need for monthly evaluation and therapy is extremely costly to the health care system
   b. Risks of catastrophic complications such as endophthalmitis are cumulative with each additional injection
   c. Both A and B are true

8. Which of the following is/are indications for switching to an alternate therapy?
   a. Stability with monthly injections, but loss of acuity when the dosing interval is extended
   b. Persistent subretinal fluid despite multiple monthly injections of current therapy
   c. Both A and B

9. Which of the following is a reasonable approach to the neovascular AMD patient who desires to discontinue follow-up?
   a. Inject a double dose of anti-VEGF therapy on the last visit
   b. Combine anti-VEGF therapy with PDT to extend the therapeutic benefit
   c. Neither A nor B is a reasonable approach

10. Which of the following is/are true regarding combination therapy?
    a. Combination therapy produces superior visual acuity outcomes to monotherapy
    b. Combination therapy can often increase the dosing interval
    c. Both A and B are true
**ACTIVITY EVALUATION/CREDIT REQUEST**

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**OUTCOMES MEASUREMENT**

☑ Yes  ☐ No  Did you perceive any commercial bias in any part of this activity? **IMPORTANT! If you answered “Yes,” we urge you to be specific about where the bias occurred so we can address the perceived bias with the contributor and/or in the subject matter in future activities.**

Circle the number that best reflects your opinion on the degree to which the following learning objectives were met:

- 5 = Strongly Agree  4 = Agree  3 = Neutral  2 = Disagree  1 = Strongly Disagree

After successfully completing this activity, I have improved my ability to:

- Demonstrate the implications of the CATT results for monthly and PRN dosing and monitoring of currently used anti-VEGF agents in various subsets of patients
- Compare and contrast the anti-VEGF agents with respect to mechanism of action and binding affinities
- Discuss the results of the latest clinical trials and how anti-VEGF and other therapies may be used in patients with wet AMD
- Discuss the advantages and drawbacks of various treatments and combinations in their ability to reduce treatment burden and safety risks
- Employ current best practice use of OCT in guiding treatment
- Apply results from the latest clinical trials to AMD patient case scenarios

1. Please list one or more things, if any, you learned from participating in this educational activity that you did not already know.

2. As a result of the knowledge gained in this educational activity, how likely are you to implement changes in your practice? 4 = definitely will implement changes  3 = likely will implement changes  2 = likely will not implement any changes  1 = definitely will not make any changes

Please describe the change(s) you plan to make:

3. Related to what you learned in this activity, what barriers to implementing these changes or achieving better patient outcomes do you face?

4. Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced for you through participation in this activity.  ☑ Patient Care  ☑ The New York Eye and Ear Infirmary—ICME  ☑ Professionalism  ☑ Practice-Based Learning and Improvement  ☑ Interpersonal and Communication Skills  ☑ Systems-Based Practice

5. What other topics would you like to see covered in future CME programs?

**ADDITIONAL COMMENTS**

**POST TEST ANSWER BOX**

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Advances in the Treatment of

Wet Age-Related Macular Degeneration

Proceedings From a Roundtable Discussion