Anti-VEGF Therapies: Ocular and Systemic Impact

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Efficacy endpoint for superiority of 2 mg ranibizumab monthly, and as-needed dosing formats. The results did not meet the secondary endpoint of noninferiority in the as-needed arm. RVO is a common ocular disease that remains poorly understood due to the multifactorial nature of the presentation and contributing systemic factors. Several associated systemic factors have been identified and continue to be studied for their impact on RVO, including hypertension, diabetes, hypercholesterolemia, thyroid disorder, and ischemic heart disease. Increased intraocular pressure and axial length are other factors that play roles in this disease. For many years, clinicians have followed the recommendations set forth by the Branch Vein Occlusion Study and the Central Vein Occlusion Study. The former study demonstrated that grid laser photocoagulation led to a higher improvement of VA than natural history, but the latter showed grid laser photocoagulation did not improve VA even though the macular edema decreased. The SCORE CRVO trial found that patients treated with intravitreal steroids experienced a substantial visual gain of 3 or more lines that persisted up to 2 years. Continued understanding of this landscape of available anti-VEGF therapies and their ocular and systemic effects is a process of putting recent clinical trials data in the proper context with longer term patient outcomes. As the complexity of treatment options also involves the cost and timing of repeated patient treatments, ophthalmologists using anti-VEGF treatments for common retinal diseases need to update their knowledge in order to provide their patients with the best understanding of treatment expectations and minimization of risks.

**STATEMENT OF NEED**

The increasing number of patients presenting to retina specialists and ophthalmologists for treatment of retinal diseases such as age-related macular degeneration (AMD), retinal vein occlusion (RVO), and diabetic macular edema (DME) escalates the discussion of long-term ocular and systemic effects of the multiple treatment options now available and under study. As with any medical therapy, the importance of patient education about treatment options and expected disease impact along with potential short- versus long-term risks is inherent to the process of determining and delivering appropriate treatment.

Especially in the rapidly developing environment of retinal disease therapy with antivascular endothelial growth factor (anti-VEGF) agents, there is a continual burden placed on retinal specialists and ophthalmologists using these agents to remain current on the latest clinical study results. In addition, due to the larger population that has now received treatment in the past, new and ongoing evaluations of long-term ocular and systemic effects of intravitreal anti-VEGF agents need to be considered when initiating new treatment or changing therapeutic strategies for undergoing therapy.

The process of ocular and systemic effects of anti-VEGF therapies is further complicated as patients progress in age and may develop additional unrelated health issues that require drug therapy. Thus, interpreting the analysis of ocular and systemic VEGF load before and during anti-VEGF therapy is more complex than ever.

Additionally important to the discussion of short- and long-term effects from anti-VEGF agents is the understanding of past and current testing assays available to determine ocular and systemic potency and drug clearance. Due to the long path of development and completion of large-scale clinical studies, new methods of evaluating the effects of therapies used in pivotal studies may not have been available during original protocol development. Understanding the utility of established and new testing assays can provide some further understanding of the key differences between available therapies, as well as new treatment regimens under study. As biological testing and imaging methods continue to develop, it is important to keep the interpretation of results in the proper context given similar, but often unique study designs.

To address the questions of safety and efficacy of this off-label use in comparison to 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 intravitreal bevacizumab in comparison to ranibizumab for the treatment of wet AMD. The study authors noted, however, that differences in rates of serious system adverse events require further study.

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 versus the FDA-approved dose of 0.5 mg in monthly and as-needed dosing formats. The results did not meet efficacy endpoint for superiority of 2 mg ranibizumab monthly, nor did it meet the secondary endpoint of noninferiority in the as-needed arm.
TARGET AUDIENCE
This certified CME activity is designed for retina specialists and general ophthalmologists involved in the management of patients with retinal disease.

LEARNING OBJECTIVES
Upon completion of this activity, participants should be able to:
• Understand the most recent monotherapy and combination therapy clinical study evidence using available anti-VEGF therapies for common retinal diseases, including AMD, RVO, and DME
• Appreciate the relevance of key assay methods to determine ocular and systemic effects of anti-VEGF therapies and how to educate patients on appropriate expectations
• Develop plans to initiate treatment for conditions such as AMD, RVO, and DME using anti-VEGF agents, as well as better understand when to change therapeutic strategies

METHOD OF INSTRUCTION
Participants should read the CME activity in its entirety. 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 real-time 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.

ACCREDITATION AND DESIGNATION
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Anti-VEGF Therapies: Ocular and Systemic Impact

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The introduction of the antivascular endothelial growth factor (VEGF) intravitreal drugs has forever changed the way retina physicians treat diseases such as neovascular age-related macular degeneration (AMD), retinal vein occlusion (RVO), and diabetic macular edema (DME). Although there are 3 approved anti-VEGF drugs (pegaptanib, ranibizumab, and aflibercept), only the last 2 are consistently used, along with off-label bevacizumab. The molecular structures of these drugs may have an effect on their safety and efficacy. In particular, the molecular differences may lead to variable systemic effects.

This supplement to Retina Today features a discussion in which panel members detail the factors and diagnostics they use to determine treatment patterns in wet AMD, DME, and RVO.

—Peter K. Kaiser, MD

TESTING PREFERENCES

Peter K. Kaiser, MD: When a new patient with unilateral age-related macular degeneration (AMD) walks into your office, what imaging tests do you perform?

Thomas Albini, MD: I would get at least an optical coherence tomography (OCT) examination, and more often than not I get a fluorescein angiogram if it is a first time patient, as I may be concerned about alternative diagnoses such as central serous chorioretinopathy. More importantly, this is the key time to let patients know they have a chronic condition that is going to require treatment perhaps for the rest of their lives. Many patients are under the misperception that they will only need 3 to 4 intravitreal injections for AMD and then they are done.

Dr. Berrocal: I do not perform a fluorescein on the first visit. If I see treatment is needed, fluorescein is not going to change my treatment. If I see something on OCT, I get an autofluorescence and a color photo, and that is sufficient for me.

Dr. Kaiser: Are you looking for anything in particular on the fluorescein angiogram or OCT that would guide your treatment decision?

Dr. Albini: No. I am just confirming the presence or absence of choroidal neovascularization (CNV).

Dr. Kaiser: Is there any advantage to doing fluorescein angiography (FA) on the first visit?

Dr. Wykoff: Yes. Most importantly, it provides a baseline benchmark of the choroidal neovascular complex for comparison at future visits when I may change management strategies.

Dr. Berrocal: But does it matter? Will changes in the fluorescein pattern change your management?

Dr. Wykoff: Yes. Most importantly, it provides a baseline benchmark of the choroidal neovascular complex for comparison at future visits when I may change management strategies.

Dr. Berrocal: But how does that compare to what you are seeing on OCT? The reality is that FA will not change your management. I think that if a patient is not getting better and you are not seeing improvement in either vision or OCT, then an FA may be useful.

Dr. Wykoff: OCT will give you anatomic data. In contrast, FA provides physiologic information, showing you where there is active CNV; OCT just illustrates where the fluid is as a result.

Dr. Kaiser: Sometimes there is nothing on OCT but something on fluorescein, and that baseline image is the only way you will know what is new, old, improving, or deteriorating.

Dr. Berrocal: How many FAs would you take in a new AMD patient that you are following for 5 years?

Dr. Moshfeghi: One.

Dr. Lakhanpal: One. If I am using a 12-week dosing interval over the course of 2 years, I might have 3 FAs.
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Dr. Moshfeghi: Another reason to perform FA is because some of our referring physicians also have spectral domain OCT and are expecting additional diagnostics to be performed to provide a more complete assessment. So, I generally employ FA at baseline.

Dr. Berrocal: Which machine do you use?

Dr. Moshfeghi: Optos or Heidelberg.

Dr. Wykoff: Either Heidelberg or Optos.

Dr. Kaiser: Does anybody routinely perform indocyanine green (ICG) angiography at baseline?

Dr. Albini: One study has shown 15% to 20% of all wet AMD actually had a polypoidal component at least in Asian populations.¹

Dr. Moshfeghi: For patients with a polypoidal component, I do not see a role for photodynamic therapy (PDT) up front. I will start anti-VEGF treatment and add-in PDT for those with a suboptimal response to anti-VEGF mono-therapy. I do NOT see a pivotal role for FA assessing in vitelliform macular dystrophy patients—in whom there is generally no indication for anti-VEGF injections—and the fluorescein pattern will often mimic CNV, just further complicating matters. In my mind, patients with vitelliform have a very characteristic spectral domain-OCT appearance and I will generally just use OCT to follow them. I only consider anti-VEGF therapy in these patients when unequivocal signs of CNV (subretinal hemorrhage, intraretinal fluid adjacent to, but not, above, the vitelliform lesion) are observed.

Dr. Kaiser: Do you get an FA if you are switching treatment regimens?

Dr. Moshfeghi: I do not.

Dr. Kaiser: What do you tell patients who have no idea why they are sitting in your office, even though they were referred to you for retinal pigment epithelium (RPE) elevation on OCT?

Dr. Moshfeghi: I reassure them. I personally do not get an angiogram unless I am very suspicious.

Dr. Kaiser: What do you look for on OCT that would make you get an FA?

Dr. Moshfeghi: Some evidence of exudative activity. Without it, I will probably forego the angiogram unless the patient has noticed something in the past several weeks.

Dr. Berrocal: I will do an FA when I do not see much on OCT if the patient has either decreased vision or real complaints.

Dr. Moshfeghi: Most likely, you are going to see a predominantly classic, easy-to-identify lesion on the angiogram.

Dr. Kaiser: If a patient has a type 1 lesion, the so-called occult lesion, that only has mild RPE elevation on OCT and some nondescript leakage on FA, what do you do?

Dr. Lakhanpal: If the patient has symptoms and if there is evidence on testing, I start treating immediately. Obviously, we have a discussion on which drug we will use. There is an expectation by not just the patient but also the referring physician that we are going to treat the issue. And if we do not, someone else will. That perception does not change my management, but it is something we need to be cognizant about in the community.

Dr. Kaiser: If you do not treat the patient, do you send him or her home with instructions to use an Amsler grid or one of the home-monitoring devices?

Dr. Albini: I do not use home-monitoring devices yet but I am looking forward to incorporating that into my practice. I think they have potential for pre-exudative patients, but ultimately, it may also be something that we use in our patients with exudative AMD to help guide the injection rates.

Dr. Moshfeghi: The lack of reimbursement for the ForseeHome (Notal Vision) home-monitoring program has been an issue. I use the SightBook App (Digisight), which is basically a free app for my more tech-savvy patients.

Dr. Kaiser: How does that work?

Dr. Moshfeghi: We are not using it as a tracking app like it was set up. Instead, we use it as a more elegant way of doing an Amsler grid. I ask patients to call when they notice a change.

Dr. Berrocal: What percentage of patients come back and notice a change?

Dr. Moshfeghi: Somewhere around 10%.

Dr. Lakhanpal: I have had difficulty convincing patients to use it, but my patients may be older and less tech savvy. It is a great idea, but socioeconomics may not make it available for everyone. Add to that the question of how tech savvy a 90-year-old AMD patient is, and it becomes difficult to reproduce good feedback. Most of my older patients do
not know how to use a smartphone and are not interested. I use Amsler grids.

**Dr. Wykoff:** Ideally, we would have a home-monitoring device that is objective. We need a nonsubjective study, an OCT-based algorithm that will identify fluid. Until we have that, I think it is going to be less than what we all want.

**VITAMIN SUPPLEMENTATION**

**Dr. Kaiser:** Do you discuss vitamin therapy with your patients?

**Dr. Moshfeghi:** We use AREDS 2, but honestly the data for AREDS 1 are just as good.

**Dr. Wykoff:** I recommend AREDS 2 over AREDS 1. I am concerned about the risks with beta-carotene. We can discuss the extra costs associated with lutein and zeaxanthin, but beta-carotene consistently carries a higher risk of cancer, particularly in smokers. How do we define a “non-smoker” in clinical practice? If you live with someone who smokes inside the house, are you a nonsmoker? I am not so sure. There is a very grey line in my mind about who is safe and who is not safe to be taking beta-carotene.

**Dr. Lakhanpal:** There is also a socioeconomic issue. Certain professions tend to have a lot of smokers, and others may not. And there are some patients who just do not tell you they smoke because of the social stigma associated with it.

**Dr. Berrocal:** A lot of my patients cannot afford the vitamins; other patients are on so many medications that they do not want another pill. Other diseases take precedence and they have to prioritize where they spend their medication money.

**Dr. Berrocal:** I tell my patients to eat well, but that little old Cuban lady in Miami? She is not going to take vitamins, she is going to keep eating her rice and beans and no vegetables. It is an issue with that population.

**FIRST-LINE TREATMENTS**

**Dr. Kaiser:** What is your first-line treatment for a newly diagnosed AMD patient?

**Dr. Albini:** We know that three of the intravitreal anti-VEGF agents available—Avastin (bevacizumab, Genentech), Lucentis (ranibizumab, Genentech) and Eylea (aflibercept, Regeneron)—are very similar in efficacy. That being said, Eylea has demonstrated reduced frequency of injection relative to Lucentis, while maintaining noninferiority in visual outcomes tips me to Eylea. Consequently, I mostly use Eylea if finances are not an issue, Avastin if finances are an issue.

**Dr. Moshfeghi:** I generally prefer anti-VEGF monotherapy using a TAE protocol. The ASRS Preferences & Trends Survey still shows the majority of retina specialists using Avastin as their primary treatment. Although I am very comfortable using Avastin, Lucentis, and Eylea for patients with a new diagnosis of neovascular AMD, in recent months I have been using Eylea for a greater proportion of these patients.

**Dr. Berrocal:** If cost is not an issue, Eylea. If it is an issue, Avastin.

**Dr. Lakhanpal:** If the patient has a pigment epithelial detachment (PED), I use Eylea. If cost is not an issue, I would probably use Eylea for other lesions as well.

**Dr. Kaiser:** We have numerous comparison studies showing that the efficacy of these drugs is similar.

**Dr. Wykoff:** If possible, I prefer to use an FDA-approved medication, Lucentis or Eylea. Unfortunately, in many circumstances this is not feasible and these obstacles to care for our patients are only increasing. Avastin, Lucentis, and Eylea have different molecular structures, so it is logical that they may have different effects inside the eye and in systemic circulation. Molecular structure drives function; because of the lack of an Fc domain compared to the other two agents, Lucentis poses potentially less systemic anti-VEGF exposure, a finding replicated in multiple clinical analyses. However, the clinical relevance of this is still unclear and needs to be further defined. For patients at higher risk of cardiovascular events such as older patients, diabetics and those with known cardiovascular disease, this is an issue I consider.

**Dr. Kaiser:** Most of us would chose aflibercept if cost were not an issue. However, would you start a patient on a less-expensive medication to see how they do before switching to a more expensive drug?

**Dr. Lakhanpal:** A good number of my patients know which drugs are FDA-approved. So if cost is not an issue, it is hard to justify not using an FDA-approved medication. That means the choice is really between ranibizumab and aflibercept. The VIEW data are incredibly compelling. I am seeing 60 to 80 patients a day, and if I can extend them out to 8 weeks and have a noninferior result, we are both happy. Fewer injections are better all around.

**Dr. Albini:** We all have anecdotal cases of partial responders to either bevacizumab or ranibizumab that seem to do better with aflibercept. There seems to be a group of patients that respond better to aflibercept than to ranibizumab, but these are anecdotal, not prospective, randomized data.

Dr. Albini: We know that three of the intravitreal anti-VEGF agents available—Avastin (bevacizumab, Genentech), Lucentis (ranibizumab, Genentech) and Eylea (aflibercept, Regeneron)—are very similar in efficacy. That being said, Eylea has demonstrated reduced frequency of injection relative to Lucentis, while maintaining noninferiority in visual outcomes tips me to Eylea. Consequently, I mostly use Eylea if finances are not an issue, Avastin if finances are an issue.
Dr. Wykoff: In my patient population, it is split into approximately thirds in terms of which medication I use, and I maintain a low threshold to switch between medications. There has never been a fair head-to-head comparison in which both FDA-approved pharmaceuticals are used in completely same way. From a payer perspective, at least in my part of the country, we have been cornered because of the package labeling for aflibercept. Yet there is good post-hoc analysis showing that persistently wet eyes do better with continued monthly aflibercept versus every-other-month aflibercept or monthly ranibizumab. I like to maintain a dry retina on SD-OCT, and in my clinic aflibercept is, on average, not dosed as an every-2-month drug. If you look at VIEW 1/VIEW 2 and the VIVID/VISTA DME trials, switching to every-other-month treatment can lead to recurrence of macular edema. Because of this, I tailor treatment to the individual needs of a given patient to minimize retinal fluid and maximize visual outcomes while minimizing treatment burden (Figure 1).

Dr. Berrocal: One of my patients had the biggest PED I have ever seen. She is a snowbird and had been treated in the Northeast with anti-VEGF, citing no improvement. I tried bevacizumab and nothing happened. Next, I decreased the interval to 2 weeks and still nothing happened. Switched to ranibizumab and the same outcome—nothing happened. Once aflibercept was approved, I tried it once and that lesion collapsed like magic. Not only that, but I can actually extend my treatments with aflibercept—something I could not do in the past with bevacizumab. I’m not really a ranibizumab user unless patients come in on ranibizumab and it is working.

**WHEN TO SCHEDULE VISITS**

Dr. Kaiser: After the initial injection, what type of treatment regimen do you follow?

Dr. Wykoff: I start out with monthly treatments until intraretinal and subretinal fluid have resolved and then typically transition to a TAE strategy. But, I often consider a single trial of initial as-needed (PRN) treatment after drying the macula completely, because approximately 10% of eyes...
may require no further treatment. The LUCAS trial provided good data in support of a TAE regimen,\textsuperscript{5} and we have an ongoing prospective trial of 60 patients with wet AMD who we are directly comparing monthly to TAE management.

**Dr. Lakhanpal:** I prefer to treat monthly until it is dry, and then it is a little dicier. If I am able to get this lesion dry, I will offer PRN more readily than TAE. But if the lesion has taken a while to dry out, I let the patient know he or she is likely to recur on a PRN regimen. I very gingerly treat the patient a couple of weeks at a time until I find that threshold.

**Dr. Kaiser:** Explain what you consider a dry lesion and when you would either extend treatment in TAE or not inject in PRN.

**Dr. Lakhanpal:** It is patient by patient. If they are asymptomatic, and there is nothing on the FA, I am likely to watch. If it is something I have been treating, and the patient is feeling better in terms of vision or metamorphopsia, then I would likely extend the treatment 2 weeks at a time until we reach 12 weeks. At that point, I do not extend further.

**Dr. Berrocal:** If I have a patient with a PED or drusen, the retina above looks normal, and if the patient has a VA of 20/25, I will follow. That to me is dry. As soon as that retina is cystic, there is evidence of intraretinal fluid, and the patient’s vision drops, then I consider that wet and treat.

**Dr. Wykoff:** In the PrONTO study, PED was not an indication for treatment, and here we are nearly a decade later talking about treating PEDs.\textsuperscript{6} I do not treat a PED in the absence of intraretinal or subretinal fluid.

**Dr. Kaiser:** Do you use TAE in a patient with a disciform scar in his or her fellow eye? Let us say the second eye develops a CNV 2 years after the first, with 20/200 vision and the scar is predominantly fibrotic.

**Dr. Moshfeghi:** I do not change my protocol, and basically keep treating.

**Dr. Albini:** I would treat more frequently.

**Dr. Berrocal:** I would also watch closer, too. Age matters—if the patient is aged 60 years with a disciform scar in the untreated eye, it may be a different treatment than if he or she is aged 80 years with a disciform scar in the other eye.

**Dr. Wykoff:** I agree, and I also look out strongly for smoking in those patients, especially young ones. And I push to get them to quit.

**Dr. Kaiser:** Does it work?

**Dr. Wykoff:** Sometimes. I believe that choroidal neovascular membranes can be more active in the setting of an active smoker.

**Dr. Moshfeghi:** Do you ever have patients who ask you to treat them monthly? I have had 10 or 12 patients who request that.

**Dr. Berrocal:** I have had patients request treatment in the other eye that has no indication of disease.

**Dr. Moshfeghi:** They want treatment as a preventive measure against AMD.

**Dr. Lakhanpal:** These are the patients who are convinced that monthly treatment is the way to go. It can be hard to say no.

**Dr. Kaiser:** If you have a patient you are treating TAE who is out to about 12 weeks, at what point do you stop injecting that patient? Or, do you keep extending?

**Dr. Lakhanpal:** You need to assess the other eye, because it all depends on the patients’ symptoms, too. If they are asymptomatic, I prefer PRN. If the fellow eye is fine, I prefer PRN. It seems after TAE, some patients regress and we need to start treating on a more regular schedule until they are dry and we can extend again.

**Dr. Berrocal:** If the eye was drier during that 12-week period, I may go another month or 6 weeks before I see the patient. If they are still dry, I’ll extend again. I have a few patients that I only inject once a year and they have stayed dry.

**Dr. Moshfeghi:** When you are not sure about whether to keep treating, I try to give patients the option, but treating PRN still means monthly visits.

**Dr. Wykoff:** Here is a great example of when a fluorescein angiogram can be valuable. If there is active CNV on FA, I keep treating. If there is not, I stop. If there is a little
leakage in the same location as the original CNV, I will continue with quarterly injections in hopes of preventing a recurrence of a significant leak that could set us back.

Dr. Lakhanpal: But if there is leakage, that means technically there is activity. The OCT tells you anatomically but not physiologically. So if you are on the fence about changing drugs or treatment patterns, I recommend an FA as well.

Dr. Berrocal: We have a capacity issue with the number of patients we see. I will do an FA when I feel I need more information in order to find the best treatment for that patient.

Dr. Albini: Unless the patient asks to stop, I will keep treating, probably 3 to 4 times a year. I do not think we have great data on long-term outcomes if we reduce or stop treatment altogether. I am concerned that the leakage will return, so there is an advantage to having some level of anti-VEGF on board.

Dr. Berrocal: Do we know if we can ever shut down neovascularization completely with anti-VEGF?

Dr. Wykoff: Based on the PRN strategy, wet AMD prospective trials that we have such as PrONTO and HARBOR, approximately 10% of cases will regress.6,7

Dr. Lakhanpal: There is not a lot of good evidence that shows controlled versus variable treatment is equal. Even in VIEW, those on the variable or PRN dosing did not fare as well.3

Dr. Moshfeghi: In the real world, people do not treat monthly for a year before moving over.

Dr. Wykoff: And we also have data from CATT,8 during which patients were treated monthly for 1 year and then half were switched to PRN. After switching to PRN retreatment, patients lost a statistically significant amount of vision, approximately 2.5 letters; so, to maintain the maximal visual benefit as obtained with monthly dosing, monthly dosing seems to be needed to be continued at least beyond 1 year.

Dr. Berrocal: If it were my eye, I would be afraid of extending treatment, but at the same time I would want the least number of injections to keep my best possible vision.

Dr. Lakhanpal: The PAT Survey found retina physicians would treat themselves differently than they would treat their patients.2
is not justifiable. So I will observe the patient until there is progression of the disease, worsening of vision and the patient is symptomatic.

**Dr. Lakhanpal:** Diabetic swelling can wait a bit longer than AMD swelling. If diabetic patients are are 20/20 and have a little fluid on the first visit, I will tell them about the intravitreal treatments, but I will not inject. I do council my patients about getting their HbA1c levels under control and that we will review our strategy in a month or so.

**Dr. Albini:** The hurdle to treat an asymptomatic patient is very high. So unless there are really convincing data that I am helping that patient by treating and harming him or her by not treating, I opt against initial treatment.

**Dr. Moshfegh:** When I have a little more time with diabetic patients, I just show them a normal OCT and compare it to their OCT.

**Dr. Kaiser:** What if the patient has 20/50 vision with DME. How do you treat this patient?

**Dr. Berrocal:** I will try bevacizumab first, but I will also consider steroids.

**Dr. Lakhanpal:** It depends on the patient’s insurance and the cost. If the insurance company agrees to pay for the drug, I would probably start with Lucentis first—I want to use an FDA-approved drug if I can. We have data to show it can be effective in patients who have a VA of 20/40 or worse. If that does not work after a few injections, then I would switch to Eylea or Lucentis if I started with Eylea.

**Dr. Albini:** I start with Lucentis. But I also get an angiogram to look for a focal aneurysm, and maybe treat with a laser, because I think that helps a lot to control the problem.

**Dr. Wykoff:** In this patient, I would strongly recommend monthly anti-VEGF therapy up front. I do have a long discussion with patients (most of whom are still working age) and tell him or her about the significant burden with monthly treatment but that it is recommended initially. I often do not inject on the first visit, because the patient needs to fully agree with and accept the treatment regimen first. I do not want to give one injection and then have the patient lost to follow-up. If they do not come back, I was going to lose him or her anyway. I recommend that my patients talk to their endocrinologist, family, and friends, and that they will need a lot of injections up front. However, based on the Open-Label Extension (OLE) study following RISE/RIDE, within 3 to 5 years, we have a 25% chance of no longer needing injections at all.9

**Dr. Lakhanpal:** Patients also need to know that regardless of who treats them, it is going to be an injectable treatment. The choice of drug may be different depending on the doctor, but injections are inevitable.

**Dr. Berrocal:** What about intravitreal steroids? Some diabetics respond beautifully to steroids.

**Dr. Wykoff:** Steroids are fantastic, but the risk of cataract and IOP are not trivial.

### SWITCHING DME TREATMENTS

**Dr. Kaiser:** What makes you switch treatment regimens in your DME patients? What do you switch to?

**Dr. Lakhanpal:** I switch to Eylea because it is my next option for DME.

**Dr. Wykoff:** Are you worried about cost?

**Dr. Lakhanpal:** Not necessarily. I think my experience with Eylea in diabetics is really, really good. We have encouraging data now that are becoming available, so I would stay with that unless evidence is overwhelmingly leaning against that choice.

**Dr. Albini:** I have started having conversations with my patients about treatment burden. If the patient is pseudophakic, then we discuss using Ozurdex (dexamethasone, Allergan) to try to reduce injection burden and frequent visits. Since Ozurdex is only recently approved, it has not yet taken hold in my practice, but I do think that steroids may be preferable for those patients who find the anti-VEGF treatment burden intolerable.

**Dr. Berrocal:** But are those not the patients you have been treating with anti-VEGF and still have a cystic component?

**Dr. Albini:** Yes, if they cannot come in for monthly injections.

**Dr. Lakhanpal:** In my experience, there are certain insurance companies that will absolutely not pay for anything other than Avastin. In our practice, Avastin works extremely well.

**Dr. Berrocal:** There are those diabetic patients who have a cystic component and when you add steroids to their treatment regimen they do beautifully.
Dr. Kaiser: When I use steroids, I like to challenge patients with something that does not last as long as Ozurdex, so I will use intravitreal triamcinolone first. If they start getting into trouble, at least it is not for 4 to 6 months.

Dr. Albini: What are you concerned about? Pressure?

Dr. Kaiser: Yes, intraocular pressure. We know the risk for glaucoma with steroids is related to the amount of time the steroid is in your eye. The length of time in the MEAD studies was too short to show what happens over a long time.\textsuperscript{10,11}

Dr. Wykoff: The dosing schedule for Ozurdex treatment at 6-month intervals in MEAD\textsuperscript{10,11} was less frequent than that needed to maintain a dry retina in clinical practice, in which I find that retreatment every 3 months is more realistic. There is also the cataract issue—it is easy for us as retina specialists to say cataracts are not a big deal, but from a patient perspective, they can be.

Dr. Albini: I do not use steroids often in phakic patients.

Dr. Berrocal: If a phakic patient has been treated with anti-VEGFs but is not drying out, what is the next step?

Dr. Wykoff: I do not trivialize the effect that steroids will have on cataract formation, and that the patient will need surgery. I use the engine versus the windshield analogy: You have to fix the engine first (treat the DME), but then you may also have to replace the windshield (treat the cataract). I explain that the cataract is like a foggy windshield—you can replace the windshield but that will not fix the car’s engine, and if the car does not run, it is not as important that the windshield be clear.

THE CONTINUING ROLE OF LASERS

Dr. Kaiser: Is there a role for laser treatment in DME, and if so, when?

Dr. Moshfeghi: I think there is. I get angiograms at baseline for my patients with OCT-documented center involved swelling of the macula. If I see a sectoral area of edema, I will treat that with laser or adjust with anti-VEGFs.

Dr. Kaiser: The DRCR.net study on prompt versus deferred laser did not find the laser was beneficial initially, but the 3-year results seemed to differ.\textsuperscript{12} How do those results affect when you plan to use laser?

Dr. Moshfeghi: I used to do a lot more laser for diffuse DME but now I only use laser for focal.

Dr. Albini: Dr. Berrocal, do the results you find on wide-field angiography change your laser treatment at all?

Dr. Berrocal: No. I use laser as a last option complementing my treatment in patients that have been on anti-VEGFs and steroids and there is still some leakage in a specific area and there are some microaneurysms, then I will laser those.

Dr. Kaiser: I have done a lot of wide-field angiography in RVO with targeted PRP to ischemic areas, but doing this in RVO rarely changes the number of injections. But in DME, I think PRP does work to reduce the number of injections needed (Figure 2). Moreover, I can make the argument that I am helping prevent neovascular proliferation, so I am helping the patient. So while there are no studies to back this, if I see peripheral ischemia and perhaps some early neovascularization, I will use laser.

ANTI-VEGF EQUIVALENCY

Dr. Kaiser: The comparison studies to date show that the anti-VEGF medications we use appear relatively similar in efficacy in wet AMD. Do you think that is also true in DME and RVO?

Dr. Wykoff: For noncenter involving focal DME with good visual acuity, I believe focal laser targeted to causative microaneurysms is a great option. The 5-year data from the DRCR Protocol I suggested that early focal laser may decrease the number of needed injections—an idea that deserves further study.\textsuperscript{13} In regard to areas of peripheral retinal ischemia identified on wide-field fluorescein angiography, the value of targeted laser to these regions is still incompletely defined and ongoing trials and are evaluating this.

Dr. Kaiser: I have done a lot of wide-field angiography in RVO with targeted PRP to ischemic areas, but doing this in RVO rarely changes the number of injections. But in DME, I think PRP does work to reduce the number of injections needed (Figure 2). Moreover, I can make the argument that I am helping prevent neovascular proliferation, so I am helping the patient. So while there are no studies to back this, if I see peripheral ischemia and perhaps some early neovascularization, I will use laser.
Dr. Albini: My suspicion is they are not the same.

Dr. Berrocal: Anecdotally, I have a patient who was started on Lucentis, switched to Avastin, and only after he was switched to Eylea did he dry out. I have been able to extend his treatment much longer.

Dr. Kaiser: What about a patient with bilateral DME? Do you treat both eyes on the same day?

Dr. Berrocal: I treat both eyes on the same day.

Dr. Albini: I prefer not to, but I leave it up to the patient. I will do it if that is what the patient wants.

Dr. Kaiser: Does your treatment protocol change at all?

Dr. Lakhanpal: I try not to use the same lot in both eyes of 1 patient.

Dr. Moshfeghi: We get Avastin from 2 different compounding pharmacies for that reason.

Dr. Wykoff: We have a separate consent form for bilateral injections on the same day, and we have a separate consent form for compounded medications. I will do bilateral same-day injections, but I prefer not to do same-day injections in both eyes, especially when using a compounded medication.

Dr. Kaiser: What does that consent say that is different than the consent for a unilateral injection?

Dr. Wykoff: It says that we discussed the very small but possible risk of bilateral infection and that could be visually devastating.

**ANTI-VEGF SAFETY**

Dr. Kaiser: What do you tell your patients about the safety of anti-VEGF drugs?

Dr. Wykoff: I do talk with my patients about safety. First, I discuss the safety issues related to compounding pharmacies if relevant to the patient. Second and concerning systemic anti-VEGF exposure risks, I recognize and address 2 issues—the first issue is molecular structure, and the second issue is clinical safety. I see a difference in molecular structure between the 3 agents. Whether there is a safety signal, I think that question is still an open box. I do not think there is a smoking gun saying one is safer than another, but I think the molecular design is such that we need to be aware of that possibility and keep looking for it.

Dr. Albini: I do not have this conversation in detail with patients because it is very technical and can be misleading. My take-home message is that we have not seen any consistent, convincing safety issues across multiple trials. I target my treatments on efficacy and not on safety because I do not think there is enough convincing data concerning relative safety one way or the other about any of the anti-VEGFs.

I do think it is imperative we remain aware of the discussion concerning relative safety. There may indeed be differential safety signals that have not been appreciated yet.

Dr. Kaiser: In the oncology literature, there is considerable worry about the side effects of systemic anti-VEGF treatment. Why do you think we are not seeing that in ophthalmology, when numerous articles suggest systemic VEGF levels are actually affected?

Dr. Albini: Well, systemic VEGF levels are affected, but they are not affected to the same degree as with oncology dosing. I suspect the VEGF levels are reduced to a much greater extent with systemic dosing and certainly do not think we should assume the 2 modes of delivery are similar in safety concerns.

Dr. Lakhanpal: Correlating a serious adverse event to the timing of the intravitreal injection is difficult, too. Even if the patient is being dosed monthly, he or she already have an elevated risk for MI or stroke. So by injecting, are we pushing them over the edge? I do not know—no one does, and that is the problem. All the data on the levels of VEGF in serum and plasma levels do not definitively state there is a major difference between any of the drugs. I tell the patients that there is no difference in risk that we know of yet.

Dr. Albini: It has been shown that aflibercept and bevacizumab reduce systemic VEGF levels more than ranibizumab. It is hypothesized that this occurs because ranibizumab is cleared more rapidly as it is a smaller molecule and does not have an FC portion. The FC portion on aflibercept and bevacizumab enables it to bind to the FC portions on various cells, and consequently stay in circulation longer, thereby reducing systemic VEGF levels. But we have yet to see the consequences of this effect in our patient population.

In the CATT study, the GI hospitalizations in the Avastin arm were 4-fold higher than in the Lucentis arm. GI perforations are a labeled complication of systemic Avastin, so that is not completely unexpected. The judgment of the CATT researchers was that the events did not seem to be related to the anti-VEGF injections, but we should bear it in mind. If there is an effect it seems small, and currently available studies have not been sufficiently powered to convincingly demonstrate the effect.

Dr. Wykoff: In CATT, when the Avastin and Lucentis...
groups were pooled respectively, there was a significant difference in the rates of “serious systemic adverse events,” at 24.1% and 19.0% for the Avastin and Lucentis groups, respectively, and this seemed to be driven by hospitalizations.\(^8,19\)

**Dr. Kaiser:** We have the highest decrease in VEGF levels with monthly Avastin injections but that group did not have the highest serious adverse event rate in the IVAN study. If we look at the CATT or VIEW, hypertension is the most precise indicator of a VEGF inhibition, and there was no difference there.\(^8,19\)

**Dr. Wykoff:** None of these studies is powered to see a small difference in event rates. It is important to keep in mind that the annual rate of cardiovascular end-organ events is substantial in the Medicare population in general. For example, 1 Medicare database analysis reported an annual rate of myocardial infarctions and cerebral vascular accidents of 2.2% and 3.5%, respectively.\(^20\) If one believes there is a difference, one can find data to point toward, such as the meta-analysis combining the CATT and IVAN data indicating an increased risk of serious systemic events with bevacizumab over ranibizumab.\(^8,19,21\) On the other hand, one can point to different data if one believes there is no difference in safety between the agents. For example, the CATT and IVAN meta-analysis indicated no differences between the drugs in rates of arterial thrombotic events.\(^21\)

**Dr. Kaiser:** There have been statements made based on a subgroup analysis of the EPAR report that Eylea is unsafe in patients older than age 85 years because there is a higher risk of cerebrovascular events, while Lucentis is unsafe in this age group due to a higher cardiovascular event rate.\(^22\) Do you agree?

**Dr. Berrocal:** I have a lot of elderly patients in my practice—some older than 100 years. I do not think the age of the patient would keep me from not treating with Eylea.

**Dr. Wykoff:** My understanding of the EPAR data was that over the second year, the MI rates began to normalize following intravitreal injection of the non-Fc-containing medications Avastin and Eylea, but not following intravitreal injection of the Fc-containing medications Avastin and Eylea, for example.\(^23-26\)

**Dr. Albiní:** In regard to serum VEGF levels, there is sufficient controversy concerning the validity of the VEGF assay that it is premature to make any decisions that translate back to patient care.

That being said, these drugs are very different and the fact that some of them remain in the bloodstream longer than others could be important. We need to continue this line of inquiry to better understand how much of this science does correlate with what we see clinically.

**Dr. Kaiser:** What about the patient who had an MI or a stroke a month earlier. Do you change your treatment based on that incident?

**Dr. Wykoff:** My discussion with a patient like this focuses on baseline risk. I tell the patient that from the Medicare analyses, we know that about 1 in 20 Medicare patients, up to 5%, will have either a heart attack or stroke in any given year. I do think that our medications can have a systemic effect and I would lean toward one that might have less systemic exposure. I therefore would go with a lower dose of Lucentis in that situation.

**Dr. Kaiser:** What if the data suggests that patients on Eylea can go longer between treatments? Why would you not use a treatment that lasts longer?

**Dr. Wykoff:** The systemic exposure over time with an FC-containing compound is potentially substantially more than a non-FC containing compound, even taking into account 1 extra injection over the course of a year.

**Dr. Kaiser:** But are these marginal differences?

**Dr. Wykoff:** I go back to data that show a difference in the effect of Eylea and Avastin versus Lucentis on systemic VEGF levels, which is dramatic up to a month after the injection. Multiple authors from different countries including the USA, Japan, Austria, and Portugal have reported that significant reductions in plasma and serum VEGF levels are observed following intravitreal injection of the Fc-containing medications Avastin and Eylea, but not following intravitreal injection of the non-Fc-containing medication Lucentis.\(^23-26\)

**Dr. Kaiser:** The issue with any report on VEGF levels is that the ELISA assay used in these studies has a lower binding affinity than EYLEA and a higher binding capacity than Lucentis and Avastin. What this means is that studies using this assay can accurately report the level of VEGF with Lucentis and Avastin, but cannot in the presence of aflibercept, because aflibercept is actually pulling VEGF off the assay. Therefore, the assay is actually suspect.

**Dr. Albiní:** We need more time to vet these things and actually see a correlation in some clinical dataset.

**Dr. Wykoff:** The practice of medicine is based on best available data. The results of VIEW 1 and VIEW 2 showed
the agents to be equivalent clinically. From these data, 1 provocative interpretation could be, why not use one that may be safer and may have less impact on systemic VEGF levels?

Dr. Berrocal: But in reality, we have been treating off-label with bevacizumab for years. In all that time, I have had 2 patients with documented systemic hypertension after an intravitreal injection and I changed agents.

Dr. Kaiser: I think the better evidence to address that issue is in the clinical studies where blood pressure was measured at every visit, and in every one of those studies there has been no BP rise, which is what you would expect if the agent were really sticking around systemically. In fact, most of the studies showed the levels to be diminished.3,27-29

Dr. Berrocal: I do not think the hypertension stays elevated; I think it rises temporarily but enough that some patients may be concerned.

Dr. Lakhanpal: If you are not sure between the 2 on-label drugs, if you can dose less frequently with equal efficacy, you are helping the safety issue.

Dr. Berrocal: But we do not know that, right?

Dr. Lakhanpal: Right, but if you are worried about safety, you can say you are going to treat less frequently, an average of 5 fewer injections over the course of a year.

Dr. Kaiser: I have had patients who have had strokes very soon after injections, but I can’t say with certainty if it was related to the injection or not. I have had that occur with nearly every drug, so now I do combination treatment. There is good evidence that I can reduce the number of injections with photodynamic therapy combined with an anti-VEGF agent, and that is what I do to reduce the number of injections.

Dr. Moshefghi: To me, visual acuity is more important. I feel there is perhaps only a slight advantage for Eylea over Lucentis.

Dr. Lakhanpal: If you tell a patient that because of a stroke or heart attack, you are going to switch medications, they may perceive that the drug caused the adverse event.

Dr. Moshefghi: And if you change a medication and the patient drops 3 lines, they are going to think the same thing.

Dr. Kaiser: I try to avoid switching. I tell my patients that after they had a stroke, there is approximately a 10% risk of having another stroke with treatment, but without treatment, the risk of losing vision is likely 100%. I then leave it up to the patient. I have never had a patient decline treatment just because of the increased stroke risk.

Dr. Berrocal: There are a lot of people who believe that vision is more important than life. I have patients who say with all true conviction that if they lose vision they would rather not live.

Dr. Albini: And there is a strong association between vision loss in AMD and depression.

Dr. Kaiser: The DRCR.net Protocol T may answer our questions once and for all. Only time will tell.1,2

CME QUESTIONS

1. Which diagnostic test is helpful in confirming the initial diagnosis of neovascular age-related macular degeneration?
   a. Color fundus/red-free fundus photography
   b. Optical coherence tomography
   c. Fluorescein angiography
   d. Indocyanine green angiography
   e. All of the above

2. Fluorescein angiography is necessary to determine response to treatment at each subsequent neovascular age-related macular degeneration assessment visit.
   a. True
   b. False

3. You have a 50-year-old phakic patient with chronic and diffuse diabetic macular edema who has responded well with anti-VEGF monotherapy. Visual acuity has improved from 20/150 to 20/30 after 8 injections in 12 months. The patient now tells you that he forgot to mention that he had a cerebrovascular accident in the last 3 months prior to starting treatment with the anti-VEGF regimen. Which of the following is the best recommendation gleaned from evidenced-based medicine?
   a. Suspend all subsequent anti-VEGF treatment and switch to intraocular corticosteroids.
   b. Continue anti-VEGF monotherapy as before.
   c. Decrease anti-VEGF injection frequency by adding into intraocular corticosteroids.
   d. Avoid intraocular pharmacotherapy altogether, and switch to focal/grid laser photocoagulation.
   e. None of the above

4. When considering first-line treatments for a newly diagnosed AMD patient, which of the following is correct?
   a. Efficacy has not been evaluated in head-to-head trials
   b. All agents used in the treatment of AMD patients are FDA approved
   c. Each agent has a different injection frequency
   d. Insurance typically covers all of the agents
   e. None of the above

5. Smoking can affect the treatment of a patient with 20/200 vision who develops a predominantly fibrotic disciform scar in the fellow eye.
   a. True
   b. False

6. If a patient fails treatment with all 3 anti-VEGF agents, they should be considered a nonresponder.
   a. True
   b. False

7. Which of the following is an appropriate initial treatment for a first-visit patient with center-involving DME on OCT with 20/20 vision?
   a. Initiate treatment with intravitreal steroids immediately
   b. Initiate treatment with anti-VEGF on a monthly interval
   c. Initiate treatment with anti-VEGF on a 6-week interval
   d. Council about lifestyle and HbA1c control, and postpone treatment
   e. None of the above

8. It is critical to consider the phakic status of a patient when planning treatment.
   a. True
   b. False
**ACTIVITY EVALUATION**

Did the program meet the following educational objectives?  

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Explain the pathogenesis of VMA and its role in various retinal pathologies

Identify the benefits of induced PVD versus anomalous PVD

Discuss the available data on both surgical and pharmacologic PVD induction

Differentiate between the various vitreolysis agents for PVD induction and their safety and efficacy profiles

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.

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

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