Supplement to RETINA TODAY September 2015

CME ACTIVITY

Anti-VEGF Update: When is Switching Patients Acceptable and Preferable?

David Eichenbaum, MD, Moderator
Caroline Baumal, MD
Victor Gonzalez, MD
Rahul N. Khurana, MD
Carl D. Regillo, MD

THE DULANEY FOUNDATION

A CME activity jointly provided by
The Dulaney Foundation and *Retina Today*.

Supported through an unrestricted educational grant by Regeneron Pharmaceuticals.

Jointly provided by The Dulaney Foundation and *Retina Today*
Supported through an unrestricted educational grant by Regeneron Pharmaceuticals
Release Date: September 1, 2015
Expiration Date: September 1, 2016

STATEMENT OF NEED

The introduction of anti-vascular endothelial growth factor (anti-VEGF) therapies for the treatment of retinal vascular disorders has been revolutionary, and the class of drugs is now considered standard of care for the treatment of diabetic macular edema that involves the fovea.[1-4] With two approved intravitreal drugs (aflibercept and ranibizumab)[5,6] and one used off-label (bevacizumab), clinicians have a host of potential treatments. Yet there remains a limited consensus on best practices, from which drug to begin therapy in treatment-naïve patients, to when to treat patients [monthly, PRN, or treat-and-extend (TAE)], to when to switch patients and how to assess or quantify "treatment failure." In the DME patient, a decreased response or failure to respond is typically determined by optical coherence tomography (OCT) central thickness and volume. Laser photocoagulation is still a viable option, especially for those patients in whom a complete response (ie., complete resolution with improvement in vision) is lacking.[7]

A complicating factor in treating these patients is a lack of a universally accepted nomenclature that would describe the different types of non-response.[8] Certain ethnicities have a higher prevalence of developing DME,[9] leaving the question about when and with which therapies to intervene debatable.

Corticosteroid treatments are limited in the US–the most recent product to be approved (dexamethasone) was limited to pseudophakic patients or those scheduled to undergo cataract surgery as a result of the high incidence of cataract in phakic patients.[9] While the cost of these steroids is considerably lower than the anti-VEGF treatments due to the former's infrequent dosing, the latter remains a more effective treatment for maintaining and providing visual gains.

Leading retina specialists are unlikely to switch patients to a steroid before opting for a different anti-VEGF in phakic patients.[10] Pseudophakic nonresponders are much more likely to be switched to a corticosteroid. Still others will discontinue intravitreal injections altogether and treat with vitrectomy if the patient does not respond.[11]

A full knowledge of the dynamics of treatment options for DME will be beneficial for eye care specialists who use these treatments. An understanding of when to treat, coupled with when to switch to an alternative treatment in nonresponders, would provide these specialists with a more complete understanding when counseling patients. It is expected that providing this education would remove a potential barrier to greater acceptance in this area of disease management. Diabetes is a systemic disease, and the primary treatment involves optimal glycemic and blood pressure control. By providing detailed insights into management strategies in this chronic and often bilateral disease, clinicians will be able to reduce treatment complications and further loss of vision.

1. Ford JA, Lois N, Royle P, et al. Current treatments in diabetic macular oedema: Systematic review and meta-analysis. *BMJ Open*. 2013;3(3).
2. Stewart MW. Critical appraisal of ranibizumab in the treatment of diabetic macular edema. *Clin Ophthalmol*. 2013;7:1257-67.
3. Kent C. Treating DME: Laser, anti-VEGF or steroids? *Review of Ophthalmology*: Jobson, 2013.
4. Gupta N, Mansoor S, Sharma A, et al. Diabetic retinopathy and VEGF. *Open Ophthalmol J*. 2013;7:4-10.
5. Eylea [package insert]. Tarrytown, NY: Regeneron, 2014.
6. Lucentis [package insert]. South San Francisco, CA: Genentech Inc., 2014.
7. Jampol LM, Bressler NM, Glassman AR. Revolution to a new standard treatment of diabetic macular edema. *JAMA*. 2014;311(22):2269-70.
8. Weiner G. When anti-VEGF fails in AMD patients: 3 treatment approaches. EyeNet: American Academy of Ophthalmology, 2012.
9. Ozurdex [package insert]. Irvine, CA: Allergan Inc., 2014.
10. Kaiser PK, Duker JS, Ho AC, Martin DF. Clinical trial updates: Putting research into practice for retinal diseases. Retinal Physician. Ambler, PA: PentaVision, 2014.
11. Boyer DS, Humayun MS, Staurenghi G, Yeh S. New modalities for treating diseases of the choroid and retina. *Retina Today*. Bryn Mawr, PA: Bryn Mawr Communications, 2014;Suppl: July-Aug.

TARGET AUDIENCE

This certified continuing medical education (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 treatment therapies for common retinal diseases, including AMD and DME
- Discuss the benefits of anti-VEGF therapies over other potential therapies and how to educate patients on appropriate expectations
- Develop plans to initiate treatment for conditions such as AMD and DME, as well as better understand when to change therapeutic strategies and/or therapeutic classes of treatment

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 STATEMENT

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of The Dulaney Foundation and *Retina Today*. The Dulaney Foundation is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

The Dulaney Foundation designates this enduring material for

a maximum of 1 *AMA PRA Category 1 Credit.*™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

FACULTY CREDENTIALS

David Eichenbaum, MD, Moderator
Retina Vitreous Associates of Florida
Clinical Assistant Professor of Ophthalmology
University of South Florida
Tampa Bay, Florida

Caroline Baumal, MD
Boston Eye Physicians and Surgeons
Brookline, Massachusetts
Assistant Professor of Ophthalmology
Tufts University School of Medicine
Boston, Massachusetts

Victor Gonzalez, MD
Founder, Valley Retina Institute, P.A.
McAllen, Texas

Rahul N. Khurana, MD
Northern California Retina Vitreous Associates
Association Clinical Professor of Ophthalmology
University of California, San Francisco
San Francisco, California

Carl D. Regillo, MD
Director of the Retina Service
Wills Eye Institute
Professor of Ophthalmology
Jefferson Medical College of Thomas Jefferson University Hospital
Partner at Mid Atlantic Retina
Philadelphia, Pennsylvania

DISCLOSURE POLICY

It is the policy of The Dulaney Foundation that faculty and other individuals who are in the position to control the content of this activity disclose any real or apparent conflict of interests relating to the topics of this educational activity. The Dulaney Foundation has full policies in place that will identify and resolve all conflicts of interest prior to this educational activity.

The following faculty/staff members have the following financial relationships with commercial interests:

David Eichenbaum, MD, has had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant/Advisory Board:* Allergan; Genentech. *Grant/Research Support:* Genentech; Ophthotech; and ThromboGenics NV. *Stockholder:* Hemera Biosciences; and USRetina.

Carol Baumal, MD, has no financial agreements or affiliations to disclose.

Victor Gonzalez, MD, has had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant/Advisory Board*: Allergan; Eyetech Pharmaceuticals; Genentech; Iconics; National Eye Institute; Pfizer; and Regeneron Pharmaceuticals.

Rahul N. Khurana, MD, has had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant/Advisory Board:* Allergan; Genentech; and Regeneron Pharmaceuticals.

Carl D. Regillo, MD, had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant/Advisory Board:* Acucela; Genentech; Novartis Pharmaceuticals; and ThromboGenics NV. *Grant/Research Support:* Acucela; Genentech; GlaxoSmithKline; Regeneron Pharmaceuticals; Ophthotech; and ThromboGenics NV.

Cheryl Cavanaugh, MS, director of operations, The Dulaney Foundation; Michelle Dalton, medical writer; and Melanie Lawler, PhD, reviewer, have no financial relationships with commercial interests.

OFF-LABEL STATEMENT

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by FDA. The opinions expressed in the educational activity are those of the faculty. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

DISCLAIMER

The views and opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of The Dulaney Foundation, *Retina Today,* or Regeneron Pharmaceuticals.

To view the digital version of this print activity, scan the QR code or visit www.eyetube.net/cme-center and choose the appropriate title.

eyetube.net

Anti-VEGF Update: When is Switching Patients Acceptable and Preferable?

The introduction of anti-VEGF therapies for the treatment of retinal vascular disorders is now considered standard of care for the treatment of diabetic macular edema (DME) that involves the fovea.[1-4]

With two approved intravitreal drugs, aflibercept (Eylea, Regeneron Pharmaceuticals) and ranibizumab (Lucentis, Genentech),[5,6] *and one used off-label—bevacizumab (Avastin, Genentech)—clinicians have a host of potential treatments.*

Retina Today *gathered a group of world-renowned retina experts during the Vit-Buckle Meeting in February 2015 to find out how they have interpreted the various trial results and how they implement treatment and switching strategies in their own practices.*

—David Eichenbaum, MD, Moderator

TREATING AGE-RELATED MACULAR DEGENERATION (AMD)

David Eichenbaum, MD: We have several pivotal registration trials—among them MARINA and ANCHOR, and VIEW 1/VIEW 2.[7-10] What do those tell us about treating macular degeneration?

Carl D. Regillo, MD: These studies show that continuous, fixed injections of an anti-VEGF agent, either ranibizumab or aflibercept, work very well as a monotherapy regimen to achieve and maintain good vision outcomes for up to 2 years. The VIEW 1/VIEW 2 studies evaluated a p.r.n. strategy in year 2, but still held good results with both drugs. Furthermore, these vision gains were achieved with an excellent safety profile for both drugs as well.

Rahul N. Khurana, MD: Those studies emphasize that fixed, regular dosing has the best outcomes. We need to continually bear that in mind when deciding which treatment strategy to employ.

Caroline Baumal, MD: These studies have changed the way we manage this disease. Anti-VEGF agents have turned exudative AMD from an untreatable disease with progressive visual loss to a treatable disease where vision can be not only stabilized but possibly recovered. Regular, frequent dosing with an anti-VEGF agent leads to cessation of exudative features in most eyes.

Victor Gonzalez, MD: MARINA, ANCHOR, and the VIEW1/VIEW2 trials showed us that with monthly continuous treatment of wet AMD with anti-VEGF agents, regardless of the drug used, we can expect about a 95% stabilization or decrease of severe vision loss in our patients, with 34% to 40% achieving a 3-line gain in visual acuity.[7-10]

Dr. Eichenbaum: These trials certainly give us an idea of how these drugs perform, and how they perform in a particular published dosing regimen. I believe regular therapy remains important, and, per these pivotal trials, I believe patients should be dosed more regularly, which is in contrast to some physicians in the community.

Dr. Regillo: The findings set a gold standard for outcomes. When we deviate from these regimens, we need to compare the results with those gold standard outcomes. VIEW 1/VIEW 2 did include a bimonthly maintenance arm for the first year with aflibercept, whereas MARINA/ANCHOR did not with ranibizumab.[7-10] So, we do not really know how they stack up in terms of dosing. That said, aflibercept performed well and was essentially equivalent to monthly ranibizumab. This tells me that maybe we do not routinely need to treat monthly.

Dr. Gonzalez: What we saw in MARINA/ANCHOR and VIEW 1/VIEW 2 is that most patients do not require monthly treatment.[7-10] We need to individualize our treatment with every patient.

Dr. Baumal: The trials left us with further considerations about whether it is possible to eventually reduce the treatment regimen, or if the anti-VEGF agents could affect retinal atrophy. Most of the trials followed patients for 2 to 3 years. How do we approach our patients after that time period if the macula remains dry? More practical information about the best way to treat those patients would be useful.

Dr. Eichenbaum: CATT[11] did provide some suggestion, but in general, there are less overall data and less granular data as we get to longer periods of follow-up in neovascular AMD. I think that is still an area of debate, and one we will all need to address for our long-term patients.

Dr. Gonzalez: We know that anti-VEGF agents do not directly address all of the factors contributing to vision loss found in neovascular AMD, including the inflammatory component, the fibrosis, and cell apoptosis seen in this condition. Future therapies will require combination agents that will hopefully address these other important elements of the pathophysiology of neovascular AMD.

TREATING DME

Dr. Eichenbaum: Moving onto other studies, what are the implications of monotherapy in the various DME studies—specifically, RIDE/RISE, VIVID/VISTA, Protocol I, and MEAD?[12-16]

Dr. Gonzalez: DME is a very complicated condition. These studies all showed that we can improve the diabetes-associated edema in many of these patients. RISE and RIDE included strictly regimented monthly treatment regimens that found a 3-line improvement in about 45% of patients, while also demonstrating an improvement in the severity of diabetic retinopathy (DR).[14] VIVID had a very similar improvement with bimonthly injections after the dose-loading period.[13] Protocol I was instrumental in showing us that monthly treatment is not necessary to achieve vision stabilization and letter gain comparable with the more continuous treatment regimens in RISE/RIDE.[16,17]

Dr. Khurana: The great outcomes in RISE/RIDE, VIVID/VISTA and Protocol I require a very heavy burden, especially in that first year. That is one of the real key points, as there is a fair amount of undertreatment in the community in the first year. In AMD, the initiation phase/loading dose has usually involved three injections; and people have been applying this concept to DME. However, in DME, there is a much heavier injection burden in the first year. The visual acuity curves in RISE/RIDE show an improvement after the first three injections, but the curve continues to gradually go up over the first 18 months. It is a very steady, gradual improvement in both visual acuity and OCT outcomes.

In DRCR.net Protocol I, patients were started off with a loading dose of four injections, but if patients did not have 20/20 vision and no edema, they were given an additional two injections.[12] So in reality, it was a six-dose loading phase. Comparatively speaking, in AMD it is traditionally a three-dose loading phase. Most of the AMD studies that utilized a p.r.n. dosing strategy required six to seven injections in the first year in comparison to Protocol I and T, where the average was higher with nine to 10 injections.[12, 18]

Dr. Baumal: In the VIVID/VISTA studies, the DR severity score (DRSS) also improved.[13] So, in addition to anti-VEGF agents treating the DME, these medications also improved DR, which is exciting. Eyes with DME should be treated regularly until the edema is gone, but when the edema has resolved, it may be possible to reduce that treatment burden. DME is not the same disease process as AMD—in the latter, missing an anti-VEGF injection may result in recurrent exudation and secondary vision loss. In DME, there is a little more leeway.

Dr. Regillo: It is important to distinguish wet AMD from DME—these are, indeed, two very different diseases. For patients with wet AMD, we are treating choroidal neovascularization with exudation. For patients with DME, we are only treating edema, the source of which is retinovascular incompetence. While we are trying to get that macula to a satisfactory dry status, the burden over time tends to fall off in DME. In wet AMD, there is more of a continuous burden year after year for an indefinite time frame in most patients. In DME, studies with discontinuous or p.r.n. style therapy such as Protocol I and Protocol T, many patients were eventually able to cease therapy.[12,17-19]

Dr. Gonzalez: DME, unlike AMD, requires less treatment, and we can have a very profound effect on the health of the retinal vasculature. This improvement in DR severity comes from vessel stabilization that results from using anti-VEGF agents. Tolentino and colleagues performed an elegant study in which they demonstrated that injection of VEGF into the vitreous cavity of nondiabetic monkeys resulted in a production of a vasculopathy very similar to diabetic retinopathy.[20] So, it is not surprising that even though you do not alleviate all the retinal edema, improving the general health of the retinal vasculature can be beneficial in both stabilizing vision and improving the amount of edema involving the central macula.

Dr. Eichenbaum: Protocol I, which was essentially a p.r.n. study, still had a very complex algorithm to treat as needed.[12,17,19] That algorithm produced an injection burden similar to the monthly, fixed-dose trials for the first year, triggering around nine injections. The DRSS reduction appears greater in RISE/RIDE than in VIVID/VISTA. However, it is not exactly like comparing apples to apples, either.[13,14] There were more patients with proliferative DR enrolled in RISE/RIDE than in VIVID/VISTA; the three-step reduction is greater in RISE/RIDE when you evaluate topline data, but it's not head-to-head. Does that mean ranibizumab is a more potent drug for reducing DR severity? We cannot state that unequivocally from the data. It does appear to be a more efficacious in reducing severity, but that may be because of the baseline level of DR severity at enrollment. The evolution of Protocol T may help answer whether one drug is superior to another regarding DRSS reduction more clearly.

Based on the results from MEAD,[15] in your practice will you be using intravitreal dexamethasone implant(s) as a monotherapy treatment?

Dr. Gonzalez: Protocol I also found that regardless of whether you provided patients with laser treatment immediately or in a delayed fashion, the presence of the drugs seemed to be the important driving force in visual stability and gain as compared to laser alone therapy.[12,17,19] The MEAD trial demonstrated intravitreal dexamethasone resulted in a statistically significant decrease of vision loss and a statistically significant improvement in letter gain compared to the placebo comparator.[15] Overall, these studies indicate that pharmacotherapy can be beneficial and appears to be superior to laser-only regimens for the treatment of center-involving DME.

Dr. Regillo: We treat DME until the macula is dry, and the full effect may not last for 6 months with the dexamethasone implant. I do not see it becoming a first-line therapy for most of our patients. In my practice, it will be anti-VEGF and then adding a steroid to decrease treatment burden or increase efficacy if the anti-VEGF alone is not producing results I want. The dexamethasone injection is more likely to have a duration of effect in the 3- to 4-month range used in a p.r.n. fashion. In MEAD, retreatment was mandated at 6 months.[15]

Dr. Khurana: MEAD is an interesting study that was started before most of the others, and has a very different design; comparing results of MEAD[15] to RISE/RIDE [14] and VIVID/VISTA [13] will, therefore, be fraught with issues.

However, the results with dexamethasone in regard to visual acuity are not as good as those with anti-angiogenic monotherapy. I do caution, though, that with different studies, there are different designs, enrollment criteria, and methodologies to handle patient drop-out, etc., and those variables make it difficult to compare results directly. There is a role for steroids in DME, although it is not my first-line choice.

Dr. Regillo: With wet AMD, whether it is p.r.n. or treat-and-extend (TAE), the mean number of treatments will typically reach a plateau after the first year. It does not tend to decrease much thereafter. But with DME, p.r.n. treatment studies that we have seen, Protocol I in particular, started with a mean of eight to nine injections in year 1, then three to four in year 2, two to three in year 3 and by years 4 and 5, many had no further treatment.[12,17,19]

Dr. Eichenbaum: Look at the open-label extension for RISE/RIDE.[21,22] A quarter of the patients required no p.r.n. injections in the subsequent 2 years. So, it is a profound reduction in treatment burden over time with anti-angiogenic monotherapy. The key is the gain of vision through and stability in anatomy achieved in that first year or two with anti-angiogenic therapy. That is where the MEAD trial is a really very basic guideline and not how people are going to practice with steroids out in the community. Steroids can be used for reduced burden of treatment as a combination therapy, but probably not as a low-burden monotherapy for most diabetic patients. There may be special cases where steroids are the best choice as a monotherapy, such as in a newly pseudophakic patient who develops macular edema post-operatively, but the results are simply not as robust as with anti-angiogenic therapy.

Dr. Khurana: Protocol I allowed for patients to have DME if it was stable without a decrease in vision.[12,17,19] It was possible to have patients with persistent DME, as long as the vision did not drop and there was not an increase in the OCT thickness. I think that often in the community we believe that if it is not dry—especially in AMD and RVO—that we need to keep treating. But in DME, we now know that persistent DME does not translate into lost vision. With results reported out to 5 years, Protocol I showed those great visual improvements at year 1 could be maintained with an injection burden that dramatically decreased in years 2 through 5.[19]

Dr. Eichenbaum: And with a stable, but not bone-dry, macula. That is a very important point.

Dr. Khurana: And that is a change in philosophy. We were so trained to treat until there is a dry macula in AMD and RVO, but in DME it is a little different. I think a lot of people think they have a failure when in reality, if you look at the progress of the disease, there is actually marked improvement.

Dr. Baumal: There may be individuals who respond more favorably to steroids treatment of DME based on certain OCT features or systemic findings. While anti-VEGF agents are usually first-line treatment, the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) may be considered in individuals who lack a robust response to anti-VEGF agents or cannot return for frequent injections.

Dr. Gonzalez: I incorporate the MEAD findings on dexamethasone monotherapy this way: My patients typically fall into one of three categories. The first is what we all want—a patient who is exquisitely sensitive to anti-VEGF therapy and needs only one injection to have a very dramatic improvement. The second group is what we dread—no measurable response with anti-VEGFs after three or four injections. The third group, however, is what most of us see—people who have some response to the anti-VEGF therapy.

So the spectrum runs from heavily anti-VEGF dependent to heavily inflammatory-dependent and all levels in between. Therefore I have a low threshold for switching—if there is no visual acuity improvement, or less than 10% improvement in edema after a few injections, I will consider switching to a dexamethasone implant. If, however, I have had some response with the anti-VEGFs, I will continue to

inject between three and six times before I consider switching. In those patients who have a good response to steroids and have not demonstrated any steroid-dependent IOP elevation, I will consider the fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera Sciences).

MONOTHERAPY TREATMENT

Dr. Eichenbaum: How do CATT,[11,23] Protocol T,[18] and any other angiogenic studies make us think about monotherapy?

Dr. Baumal: The DRCR Protocol T results are reassuring in that it showed that all three agents are effective to treat DME.[18] Protocol T utilized the ETDRS chart, which differs from the standard office-based Snellen charts. Snellen acuity may measure worse and correspond to a better ETDRS chart score. Protocol T did not address the issue of changing medication if one drug was not effective.

Dr. Regillo: There is time with DME; we have highly effective drugs. No one should be faulted for starting with one anti-VEGF over another for either AMD or DME. With DME, we do have the luxury of time to be able to switch accordingly if we are not getting the responses we want.

Dr. Khurana: Protocol T was very surprising for me. I did not think bevacizumab was very effective for DME, based on my clinical experience. I thought ranibizumab had a better effect, so it was interesting to see the visual acuity outcomes were similar.

If you dig down into the finer details of Protocol T, there are differences among the three agents in both OCT and visual acuity. I did, however, think the changes on OCT would translate into more visual acuity differences, which did not seem to happen at the first year but may appear in the year-2 data.

Dr. Eichenbaum: We may end up seeing a divergence over time, like we did in Protocol I between prompt and deferred laser. Protocol T emphasizes our pre-existing impression that bevacizumab slightly underperforms compared with the FDA-approved agents.

Dr. Khurana: It is also important to emphasize these studies show good results with a noncontinuous treatment regimen. RISE/RIDE and VIVID/VISTA used fixed dosing regimens, while Protocol T did not use a fixed dosing schedule.

Dr. Regillo: Protocol T was a surprise with the difference between ranibizumab and aflibercept in those patients with more severe edema on OCT and in vision. And that those differences were statistically significant, unlike in wet AMD where we are not really seeing any one subgroup perform better than any other on a certain drug regimen. Protocol T was fairly definitive with really severe edema, favoring aflibercept both anatomically and visually.

Dr. Eichenbaum: The mean improvement was better with aflibercept in eyes with poorer visual acuity and a lot of edema. A relatively small number of patients–less than 40–did substantially better with aflibercept. That group of patients was at the very tail end of visual acuity in diabetic edema, but before I embrace that single result from a single study with a relatively small subgroup of patients driving the result, I would like to see if that outcome persists and is consistent in 2 years.

Dr. Regillo: Protocol T is a 2-year study, with a 1-year primary endpoint.[18] But it is worth seeing how things evolve over time. It is possible that these drugs could catch up to each other in the next year.

Dr. Gonzalez: I was also surprised by the results from Protocol T in the difference in visual acuity gains between aflibercept and ranibizumab. As has already been mentioned by others, we all had a clinical suspicion that bevacizumab was not as effective as the other two agents in center-involving DME. But I was surprised that the visual acuity gains favored aflibercept in those with 20/50 or worse. Without further testing, including evaluation of the changes in cytokine levels in the vitreous, it is very difficult to understand why one anti-VEGF blockade can produce certain results that another cannot. Regardless of the cause, for those of us who treat DME with monotherapy, the Protocol T results are going to help guide our treatment.[18]

COMBINATION THERAPY

Dr. Eichenbaum: What role is there for combination therapy in neovascular AMD?

Dr. Baumal: Combination therapy may be useful for poor or incomplete responders. If patients respond poorly to one medication, there may be a role for a combination of two drugs with anti-VEGF effect, but slightly different mechanisms. Combining therapies may make the effect of the drug last longer, which would reduce treatment burden.

When I see an individual who is not responding after a series of injections, I repeat the OCT earlier—at 1 to 2 weeks post anti-VEGF injection. This allows me to see if they are completely lacking in response based on OCT appearance. That is almost easier to approach than an incomplete OCT response when trying to decide the next treatment step.

Dr. Regillo: What about photodynamic therapy (PDT)? Does it have a role here?

Dr. Eichenbaum: PDT is a great agent for combination in select patients. What we see is AMD as a phenotype for a lot of different diseases, including polypoidal choroidal vasculopathy (PCV) lesion, retinal angiomatous proliferation (RAP) lesions, or even a hybrid central serous retinopathy/AMD.

About 3% to 5% of my patients get combination therapy with PDT at some point to try and reduce their treatment burden.

Dr. Regillo: For AMD, I use monotherapy, and try to decrease the interval. But if we are treating every 4 weeks, PDT can be useful as rescue therapy. I think PCV is where PDT still has a definite role.

Dr. Khurana: Whenever a patient is not responding, it is good to recheck the diagnosis and consider PDT.

Dr. Eichenbaum: I advocate using angiograms as well—you need a virgin angiogram before you start a treatment that may alter the physiology with anti-angiogenics. Luckily for us, consistent treatment with anti-angiogenic monotherapy works 90% of the time.

Dr. Regillo: Bear in mind that so-called nonresponders may be masquerading as wet AMD—such cases could be pattern dystrophy or central serous retinopathy (CSR). While CSR can certainly evolve into a neovascular process, we should always question our diagnosis if the patient is not responding the way we might expect.

Dr. Khurana: Some cases of uveitis, such as birdshot retinochoroidopathy, can also be misleading. We know AMD should respond to monthly injections. These are chronic, lifelong diseases so if they are not responding, re-evaluate your diagnosis.

Dr. Baumal: Monotherapy is the first-line treatment; however, the burden of treatment is high. Not just on the patients, but on their families and on our offices as well. On occasion, this treatment burden can lead to failure of efficacy because some people cannot return monthly for an injection.

Dr. Gonzalez: PDT plays a really specific and limited role in the management of patients in my practice. All patients with neovascular AMD begin with monthly monotherapy. If, after a 6-month intravitreal course of the anti-VEGF, there is no discernible clinically relevant improvement (stabilization of vision, stabilization and/or improvement of vision, and a dry macula), then I consider diagnostic testing to rule out other conditions that may be causing my anti-VEGF failure.

Obviously, we want to rule out PCV early on. As already mentioned, PCV responds very well to PDT. I believe that the more mature the vessels are in a neovascular complex, the less responsive they are to anti-VEGFs. I tend to use PDT as targeted treatment to try and cause a regression of the mature neovascular complex in these wet AMD patients so that the new vessels are much more sensitive to the anti-VEGF effect. For me, those are the only two examples where PDT is used as a first-line treatment.

COMBINATION THERAPY IN DME

Dr. Eichenbaum: Is there a large role for combination therapy in DME? Or should we stay with monotherapy for these patients?

Dr. Regillo: Monotherapy with anti-VEGF agents or sequential monotherapy, anti-VEGF followed by steroids, gives us a good result. There is a role for laser at some point in the process in selected case such as when there is persistent or refractory edema and you see an obvious source of leakage on fluorescein angiography (FA) with large, leaking microaneurysms. Targeted focal laser can provide adequate drying and stabilization, so I do consider it. I almost never use it for center-involving DME, but there is a role for laser as an adjunctive or second-line treatment.

Dr. Baumal: There are multiple chemical mediators in DME. The dexamethasone intravitreal implant 0.7 mg is a sustained-release intravitreal steroid that is easy to place and effective against DME. Combined with anti-VEGF agents, steroids may have potential to augment the treatment effect and reduce the treatment burden.

Dr. Khurana: After all the studies, I think it is safe to say anti-VEGF is our first-line defense. We have long-term outcomes from the studies, and those results are extremely efficacious. But it is a complex disease. Even when you look at the results from Protocol T, the agent that worked the best (aflibercept) still left one-third of the patients with more than 250 microns of edema at 1 year. And that range was as high as 60% with bevacizumab.[18] Most of us are using bevacizumab, and 60% of our patients are going to have persistent fluid after 10 treatments in the first year. That means there's a role for other treatments. We don't have large studies to dictate whether or not the dexamethasone intravitreal implant should be our preferred second-line agent. There are some new studies being undertaken by the DRCR.net on the combination of anti-VEGF and steroids.

Dr. Baumal: Laser may be appropriate in patients with focal extrafoveal macular edema secondary to focal microaneurysms. If one laser treatment could spare them the burden of a series of multiple injections, it may be worthwhile to consider.

Dr. Eichenbaum: The gold standard based on evidence accumulated over the past few years is that for center-involving, symptomatic DME, pharmacotherapy is the gold standard. Laser has a role for the center-involving patient as a deferred therapy, and is still a primary therapy for non-center-involving.

Dr. Gonzalez: Combination therapy can be beneficial in DME; these patients necessitate an individualized

ANTI-ANGIOGENICS COMPARED WITH OTHER TREATMENTS

Dr. Eichenbaum: What are your preferred treatment/dosing for the patient who does well with anti-angiogenic therapy? How do you initially set up patient expectations during those first few appointments?

Dr. Baumal: I discuss that anti-VEGF treatment is an ongoing process and in some ways analagous to chemotherapy. I emphasize that regular injections often keep the disease process under control, may be able to improve the vision. While the initial injections occur monthly, it may be possible to reduce the number of visits or injections over time.

Dr. Regillo: There is a different conversation for the AMD patient and the DME patient. I tell the wet AMD patient that these injections serve as disease control and there is a good chance for good outcomes, but it is going to be an indefinite, ongoing treatment process. I do let them know that, while rare, some patients do improve to the point where we can stop treatment altogether.

With DME, I tell patients there will be a lot of treatment up front, a lot of visits initially, as the disease is usually slow to respond. But I also tell them that compared with AMD, there is a better chance of coming off therapy.

Dr. Khurana: I tell my diabetic patients to give me a year, and that the first year is really important with a lot of treatments, and a lot of visits. Managing their expectations up front is essential.

Our AMD patient population is retired and therefore it is usually easier for them to make and keep office visits compared with our DME patients—who are typically working and have other challenges that make keeping office visits more difficult. For the DME patient, I tell them the optimal therapy is this very intensive regimen for the first year. But, if the treatment is working, we may be able to reduce the number of treatments and visits over time.

Dr. Regillo: I have been a strong proponent over the years for using a TAE approach for wet AMD. I do not use a pure TAE for DME, because those patients are much more likely to come off treatment over time. I test the waters in DME patients. I usually treat them more-or-less on a regular and frequent basis up front until the macula is dry. I may try to taper a bit by extending rather than just stopping cold-turkey, but I do "watch and wait" to see if DME recurs. If we are in year 2, it is more likely the patient will not recur. There could be disease modification or lessening of the retinopathy as a bonus to the anti-VEGF therapy, which might explain why the edema does not keep coming back.

Dr. Baumal: Most AMD patients will know someone else with the disease, so they are more aware of the importance of the injections. But the diabetic patients will need more counseling and more explanation about the length of the treatment process to ensure they are prepared for a potentially prolonged treatment process.

Dr. Eichenbaum: Most diabetics affected with vision loss have been sick for a while, and I discuss the momentum of diabetes—that it is a disease analogous to a freight train you just cannot stop quickly. And while we are applying the brakes in that first year with injections and throwing the train into reverse, it is going to take a while for the train to stop moving forward down the track; the hope is that we stop disease advancement before the train runs out of track. One of the great points from the RISE/RIDE data is that there is a reduction of DR severity after as little as 3 months of treatment, so we know that the anti-VEGF drugs begin to have some biologic activity fairly quickly.

I am also comfortable in reducing dosing after year 1 for two reasons. First, a good proportion of them will do well with fairly infrequent dosing, but if we guess incorrectly, we have not lost a whole lot. Second, vision is still salvageable with re-initiation of more frequent therapy.

approach. We begin with an anti-VEGF and are guided by Protocol T. If the patient cannot demonstrate improvement after three intravitreal injections, we consider adding a steroid. We are constantly walking the line between pushing the VEGF or inflammatory component. So we continue with the anti-VEGF in those that do respond until we hit the maximum effect. Once the patient has stable vision, if there is continued macular thickening, we consider introducing either a steroid or laser therapy. I am rather selective in my use of laser—we are very interested in subthreshold laser, but until larger studies demonstrate clear efficacy, it is difficult for me to recommend this with 100% certainty. Anecdotally, I have had very good response in a small number of patients.

Dr. Regillo: We also have the fluocinolone acetonide intravitreal implant 0.19 mg, now with data from the FAME studies.[24] There is evidence this is another effective steroid with a very long-lasting delivery system. Because of the ongoing concerns about IOP increases, I think shorter acting steroids will be used first, but the fluocinolone acetonide intravitreal implant should remain an option.

Dr. Khurana: FAME did show one subgroup with chronic DME for more than 3 years did a lot better on steroids,[24] so that may be a key differentiating point. It is a nice option to have for people who don't respond to our previous treatments.

Dr. Eichenbaum: Especially in a heterogenous disease such as DME.

Dr. Baumal: If combination therapy improves the disease more quickly from an anatomic perspective, will that also improve the visual results? If we hit DME hard and fast and rapidly improve vision, will that have a longer lasting effect?

Dr. Eichenbaum: There is evidence to that in RISE/RIDE, in people who switched over after 2 years.[14] They never performed quite as well as those who were on ranibizumab from the beginning.

Dr. Gonzalez: As Dr. Eichenbaum pointed out, not switching patients soon enough to anti-VEGF therapy resulted in a loss of the visual potential of some of the RISE/RIDE patients.[14] It is the main reason combination therapy is important and requires individualized treatment for DME patients. I am not yet sure exactly of cut-off. Is it 2 years? Is it 6 months? Is it 1 year? But the sooner we stabilize the vision and stabilize the anatomy in the patient, the better the long-term outlook will be for these patients.

MEASURING SUCCESS

Dr. Eichenbaum: How do you measure success?

Dr. Baumal: Vision is obviously important. But vision may fluctuate a line or two between visits, and I do not refract every visit. I usually do a baseline FA before starting treatment and rely on OCT for most decision making: It is easy, it is noninvasive and fast, and it gives us a quantitative and qualitative measure of the extent of edema as well as the response to treatment.

Dr. Khurana: For every patient, I have both their baseline vision and their baseline OCT easily available in their chart each time they return for a follow-up visit. When you are following a patient monthly and examining the OCT, you may not notice a lot of change in their retinal thickening from the previous visit. However, the studies have shown there is a long-term, gradual trend toward improvement but it is not instantaneous. If he or she has a visual acuity of 20/60 at baseline and on visit X the patient's visual acuity is 20/30 but the edema remains—or the retina is not as dry as we would like—we have a reference point to feel comfortable that our treatment regimen is working.

Dr. Gonzalez: I do a baseline FA and OCT to classify the severity of retinopathy and the potential visual acuity that this patient could have with monthly anti-VEGF treatment. I treat patients until the visual acuity and the macular edema no longer improves, and I then start combination therapy if the macula is not normal in thickness. With this treatment paradigm, I have been able to improve the macular thickness to a normal level and stabilize the vision in almost all my patients.

Dr. Regillo: FA helps to set the stage, but I rarely get them after the baseline test. I like knowing the precise level of retinopathy I am treating, and whether the ischemia could explain the decreased vision if that is not recovering. But while they are on therapy, it is OCT and vision that guide me.

Dr. Eichenbaum: As pre-treatment, I use FA to look for retinal nonperfusion and for sites of potential focal leakage. Toward the end of that first year, I usually take another FA because I like to share with the patient the progress of treatment, as well as see if nonperfusion has progressed, or if there are persistent focal leaks. Seeing improvement encourages patients to keep up with their treatments beyond that first year.

Dr. Baumal: Vision and OCT features may correlate. However, when they do not, one should consider the reason why. If the OCT anatomy appears normal but the vision is poor, it may be due to foveal ischemia or cataract.

Dr. Eichenbaum: How do you engage the whole clinical team? Do you try to do more than just treat the eye—do you counsel patients about their systemic disease as well?

Dr. Gonzalez: For DME, I explain to patients that we will require monthly injections for a prolonged period of time, and that as the disease stabilizes, there may be an opportunity for us to increase the interval between injections. I do alert them that there will be multiple injections during that first year but that too will vary from one patient to the next. Once I have a patient's visual acuity and edema within a normal range, I begin a TAE regimen. I inform him or her that we may need to cut back the interval between injections if there is a recurrence. If they have stable vision but thick edema, I will discuss the need to introduce combination therapy.

Dr. Khurana: I always send a letter to the endocrinologist saying anti-VEGF therapy is our best way to prevent vision loss and improve vision, but it requires regular, monthly visits with potentially monthly treatments. I reinforce what we are doing to everyone who works with the patient—family, primary care physicians, specialists, etc. I emphasize that while it is a big commitment, it is also a big payoff. The more people we have to continue encouraging the patient to keep on track with their visits, the better.

Dr. Regillo: It is all about communication—with the patient, the family, the doctor who is involved with the diabetes management. It is an overwhelming amount of

STEROID USE

Dr. Eichenbaum: What are your preferred treatment/dosing for the patient who does well with anti-angiogenic therapy? How do you initially set up patient expectations during those first few appointments?

Dr. Eichenbaum: When would you use a steroid? When do you think that the role of anti-VEGF agents and steroids can be combined? Can steroids can be used to supplant some anti-VEGFs?

Dr. Baumal: I switch between anti-VEGF agents first because ranibizumab and aflibercept have different mechanisms of effect. If that does not work, I might switch to a steroid, combine medications, or consider a laser, either extrafoveal focal or micropulse.

Dr. Regillo: To get a greater duration of effect and lessen the burden of injections and visits, I will think of a steroid switch if there is a suboptimal response to the anti-VEGF.

Dr. Eichenbaum: In patients with treated, controlled DME undergoing cataract surgery, I am much more likely to add a steroid. I will inject the dexamethasone implant 0.7 mg 1 to 2 weeks before the surgery or 1 to 2 weeks after to reduce the chance of an inflammatory Irvine-Gass component.

Dr. Khurana: There is a really nice niche for steroids in that population. We ran a small IST looking at patients with DME who developed a component of DME and Irvine-Gass after cataract surgery. One dexamethasone implant 0.7 mg injection lasted for 6 months and the patients had excellent visual and anatomical outcomes.[33] Steroids also can be considered for patients who have an increased risk of thromboembolic events and want to avoid the theoretical risk with Anti-VEGF agents, for treating pregnant women with DME rather than potentially exposing the fetus to an anti-VEGF agent, and finally for people who are not willing to tolerate the high injection burden (nine to 10 treatments in the first year) with anti-angiogenic therapy.

Dr. Gonzalez: My steroid of choice would be the dexamethasone implant 0.7 mg. I typically will use this in patients who have had a suboptimal response to anti-VEGFs. If I can maintain the patient with one intravitreal injection of the dexametnasone implant every 4 to 6 months, then I stay the course. For patients who do not respond well to anti-VEGFs but respond splendidly to the dexamethasone implant, yet require a reimplantation every 2 or 3 months because of recurrent edema, I use the fluocinolone acetonide intravitreal implant 0.19 mg. I have converted a limited number of patients, and they continue to do very well with the fluocinolone acetonide intravitreal implant.

information for the patient on that first visit. The education process is ongoing—I try to ensure the patient understands the reasons why we are treating, why systemic blood sugar control is essential, why they play a major role in their disease management. These are younger patients, they are working, and compliance is often an issue. I reiterate that our best results are only achieved if we are on top of everything and if we start to fall behind in any one area, we may not be able to get optimal results.

Dr. Baumal: I try to make it easy for the patient. After I start treatment, if he or she needs bilateral injections, I will perform bilateral injections. And I make appointments available at the end of the day, when a clinical fellow can administer treatment if I am not available. That has helped improve compliance to some extent.

Dr. Eichenbaum: I do not think clinicians outside of our tiny subspecialty really internalize what we do. I focus on the HbA1C with patients, and that they have to get it under control and in the range recommended by their primary care physician. If patients know their HbA1C, it means they are going to the internist, they are working towards a nonophthalmic goal. In my practice, only about 25% to 33% know their HbA1C when they first come to see us.

Dr. Regillo: It is a very important point. The literature clearly points to the correlation between a lower HbA1C and a better course of the retinopathy.[25,26] But that is up to a certain degree. Endocrinologists are starting to consider age and comorbidities to develop an HbA1C target, much like our glaucoma counterparts do for target IOPs. We cannot just uniformly say the HbA1C should be less than 7. For a 95-year-old patient with cardiovascular disease, that A1C level may not be in their best interest from a general health standpoint.

Dr. Khurana: An extreme reduction from 10 to down to 7 can actually be deleterious for their health.

Dr. Eichenbaum: Because of that literature, I have gone away from giving them a target number. I just want them to know it and know it should probably be lower.

INITIATING TREATMENT

Dr. Eichenbaum: After you have started treatment in wet AMD, what do you do if there is presence or

persistence of intra-retinal versus sub-retinal versus sub-retinal pigment epithelium (RPE) fluid?

Dr. Baumal: If there is persistent fluid and the patient's response is not what I expect, I will have the patient return to the office at one week after the injection to repeat OCT. I do not consider this until after three or four injections, because by then I expect a response. If there is no improvement on OCT or examination noted at this one week postinjection assessment, I will switch to another medication. If I have switched and he or she is still suboptimal, then I may consider increased treatment to every 2 weeks. If large pigment epithelial detachment (PED) is present, I am cautious with the treatment regimen, as some patients develop an RPE tear after anti-VEGF injection.

Dr. Khurana: The presence of intra-retinal fluid is more concerning. In the CATT study, eyes with intra-retinal fluid had worse visual acuity compared with eyes without intra-retinal fluid following treatment.[27]

I have always thought patients with PEDs were in need of more aggressive therapy. A subanalysis of the HARBOR study showed that the presence of a PED was not a negative prognostic factor, and in fact, they did rather well even with a p.r.n. treatment regimen with ranibizumab.[28] If there is a PED present, I will treat it and follow a p.r.n.-based treatment regimen as done in the HARBOR trial.[29]

Dr. Regillo: It is still safe to say ideally we want a dry macula. And that should be our goal for most patients. It does not mean that small amounts of fluid cannot be well tolerated. I personally think of it as intra-retinal being the worst, sub-retinal being next, and sub-RPE being the least negative of the fluid pockets or layers. Plenty of patients do well with persistent PEDs and/or shallow amounts of sub-retinal fluid.

Dr. Eichenbaum: My treatment goal is the absence of sub-retinal and intra-retinal fluid. I do not treat the fluid in the PED. If I am extending a patient and the PED is still there, I will continue to extend them as long as the OCT is dry and the FA does not show an expanding membrane. If I am extending a patient and the PED grows or it pushes out some sub-retinal fluid, I will contract that patient. The PED in my experience does flatten in some patients with all of the agents, probably a little bit better with ranibizumab and aflibercept.

IMAGING

Dr. Eichenbaum: How does imaging affect your thoughts about switching agents?

Dr. Khurana: I think we underutilize FA tremendously. It is important, especially in some of these key junctures in our management of AMD. We did a study on the sensitivity and specificity of SD-OCT and time domain OCT with FA and, despite how good OCT is, it does miss a lot which may lead to undertreatment. For instance, when there is no activity detected on OCT, 10% of the time, there is leakage on fluorescein angiography consistent with VEGF activity.[30]

I typically do TAE, so after my loading dose is complete I will get an FA. Even though the OCT maybe flat without any fluid, if there is leakage on FA I am a bit more cautious and conservative in my extension protocol. Furthermore, if I ever elect to proceed without treatment, I will obtain an FA to confirm that there is no activity present as we well.

Dr. Baumal: Although it is not yet available commercially, I use OCT-angiography to look at choroidal neovascularization in AMD. With anti-VEGF therapy, the neovascular network may decrease in size on OCT angiography, and the number of vessels is reduced, but they may not totally disappear. I think that this technology will allow fast, noninvasive imaging of patients with neovascular AMD and DME.

Dr. Eichenbaum: I also use indocyanine green (ICG) if it is not a lumpy, bumpy, sub-RPE lesion and there is some fluid surrounding it. If it has a substantial sub-RPE component on the virgin OCT or the sub-RPE component does not disappear (or worsens) with monthly therapy, I will shoot an ICG. Is there a hot spot? How hot is it? How big is the plaque? How does one know a lesion is really a pure fibrovascular PED that could bleed if under-treated? ICG is a useful imaging modality when you are thinking about changing your therapeutic strategy in any way, or if a lesion is not responding as expected.

Does anyone use anti-angiogenic agents to treat PEDs with no sub-retinal fluid? Let us say it is a presenting symptomatic patient with a growing PED, no sub-retinal fluid, and an equivocal angiogram for fibrovascular?

Dr. Khurana: The angiogram is going to tip the balance.

Dr. Baumal: ICG might help in that case.

Dr. Eichenbaum: Those are some of the patients where I will get a primary ICG. I will treat it if the patient's symptomatic, if it is more definitively a fibrovascular PED on ICG angiography.

Dr. Regillo: That is actually one of the scenarios where I stop treatment. If I am not sure if it is a wet AMD-related PED, and nothing happens after five injections or so, vision is still good (20/30 or 20/40), and the patient is asymptomatic or minimally symptomatic, I may see stop treatment, watch closely and see what happens. If nothing changes, then that tells me the PED

was probably never neovascularized and I have not committed them to lifelong anti-VEGF therapy.

Dr. Khurana: The other option is just to watch them and treat only if there is a change in vision. Getting back to the original question about imaging and switching, if the patient's losing vision that makes me very nervous, but that is usually very small subset of the AMD population. Persistent fluid with monthly injections is a consideration for a switch in AMD treatment.

In DME, I am more comfortable with some fluid retention; in AMD I want to dry the macula quickly. I do believe in tachyphylaxis, and a report in *The British Journal of Ophthalmology* suggested some response to the anti-VEGF agents if you alternate them when one agent loses it efficacy.[31]

Dr. Baumal: There was a retrospective review at the 2014 American Academy of Ophthamology Annual Meeting that showed even patients who incompletely respond to anti-VEGF therapy will eventually respond.[32] There are only so many injections that you can give to someone while you are waiting for the response. If the patient's response to the injections is suboptimal, or he or she is not responding after three or four injections, that is my threshold for considering a switch.

Also, if they have improved but have a hard time coming in monthly, I may consider switching to aflibercept because of the 8 week dosing schedule.[6]

Dr. Regillo: We are running a prospective investigator-sponsored study (IST) with aflibercept TAE to tease out how long it lasts.

Dr. Eichenbaum: Even if it is incremental, I will give patients another agent if I cannot extend. If I can get them out to between 8 to 10 weeks, or even to 12 weeks, I am happy. If there is a little bit of fluid at week 9, I do not panic, but instead I will drop them to every 8 weeks for a while. HARBOR showed an average of 9.9 weeks, and VIEW 1/VIEW 2, a protocol-mandated 8 weeks between shots.[7,29] Fewer than 10% of my patients require a switch when I use this criteria.

What clinical or imaging factors affect your initial agent selection in your DME population?

Dr. Regillo: I consider systemic comorbidities. I am concerned about systemic exposure and VEGF suppression systemically because most diabetic patients have bilateral DME and need bilateral, simultaneous treatment that will increase systemic anti-VEGF affects. I am going to try to minimize the systemic exposure. In theory, ranibizumab has the least systemic exposure and may be preferred if the patient has very severe cardiovascular disease. A history of any cardiovascular disease is not enough for me to alter which drug I use.

TREATMENT-NAÏVE PATIENTS

Dr. Eichenbaum: Do you treat previously treated patients any different from treatment-naïve patients?

Dr. Khurana: In Protocol T, patients had a washout of 12 months before enrollment, but RISE/RIDE and VIVID/VISTA were 3 months.[13,14,18] Patients with DME that have been previously treated with ranibizumab, let us say, I am not going to switch and try something else trying to replicate the results from Protocol T. The huge gains seen in those were after patients had not been treated for 1 year with anti-VEGF therapy. I keep the same paradigm, but temper my expectations a bit.

Dr. Baumal: I usually continue treatment with an agent if it was previously effective. I follow the intraocular pressure carefully, as it may creep up after repeat anti-VEGF agents, and I avoid steroids in known steroid responders. I obtain an FA at the beginning of treatment, if I am considering switching therapy, when there is recurrent disease or lack of response to treatment.

Dr. Eichenbaum: If a new patient comes to me who has previously been treated, I would also want to know if the patient is a steroid responder.

Dr. Khurana: I now use Protocol T to determine my agents. If the visual acuity is worse than 20/50 on ETDRS, Protocol T shows that aflibercept performs better. An improvement in at least 3 Snellen lines (>15 letters) was observed in 63% more aflibercept-treated eyes than bevacizumab-treated eyes and 34% more aflibercept-treated eyes than ranibizumab treated eyes.[18] But if they are 20/40 or better on ETDRS, all the drugs are about the same. There is already 10% risk of stroke in diabetic patients older than 35 years. If a diabetic patient has DME, there is a twofold increased risk of stroke compared with a diabetic patient without DME. So with this high-risk population, I am concerned. Ranibizumab is theoretically a safer option in this population. Protocol T did not show any systemic safety concerns among the three agents but it was not powered to detect these potential adverse events.

Dr. Baumal: I discuss treatment with the patient's endocrinologist and nephrologist. I consider using widefield angiography to assess for peripheral retinal ischemia, and to see if there is any differential effect of the anti-VEGF agents in eyes with widefield ischemia.

Dr. Regillo: The balancing act between the efficacy in the eye and systemic exposure probably does put bevacizumab

on the bottom of the list as a first choice, especially in more severe edema as per Protocol T.[18]

Dr. Eichenbaum: A lower systemic burden when there is a suspicion of or a clearly documented recent thromboembolic event, especially a central event like a stroke, is important. Bilaterally treated diabetic patients will have a higher systemic exposure to the intraocular agent than any well-studied population. I lean toward ranibizumab in those cases. But medically stable diabetics with severe vision loss and very thick OCTs? I may try aflibercept in a few patients, based on Protocol T data.[18]

Does anyone switch agents in a DME patient?

Dr. Baumal: After a series of three or four injections with no response, I consider switching. Or if symptoms are recurring before 4 weeks, before the next interval when I can give the patient an injection, I might switch to a potentially longer acting drug.

Dr. Khurana: I treat patients pretty intensively the first year, starting with a six-injection dose-loading regimen. I do not think about switching until the second half of that first year. I am not sure of the value in switching between anti-VEGF agents in someone who does not have the ideal response. If the results are not what I want after a year, I would be more inclined to use a steroid.

Dr. Regillo: For me it depends a lot on what is happening on the OCT and with their vision. If I am not seeing any progress after four, five or six injections, I will make a change. And that change could be to a different anti-VEGF or to a steroid.

Dr. Eichenbaum: I like adding steroids in pseudophakic patients. I am more apt to try another anti-angiogenic agent in a phakic patient before going straight to a steroid. I like steroids for DME, but it is not without a cost. I will probably do at least one antiangiogenic switch between agents after Protocol T before going to steroid in phakic patients. But it will not be a rapid switch.

What I think we can state here is that, there is no true standard treatment regimen, no clear preference for when to switch suboptimal responders, and no clear preference for the best way to determine who will be a suboptimal responder. We still have a long road ahead of us before these answers are clear cut. ■

1. Stewart MW. Critical appraisal of ranibizumab in the treatment of diabetic macular edema. *Clin Ophthalmol*. 2013;7:1257-1267.
2. Kent C. Treating DME: Laser, Anti-VEGF or Steroids? *Review of Ophthalmology*: Jobson, 2013.
3. Gupta N, Mansoor S, Sharma A, et al. Diabetic retinopathy and VEGF. *Open Ophthalmol J*. 2013;7:4-10.
4. Ford JA, Lois N, Royle P, et al. Current treatments in diabetic macular oedema: systematic review and meta-analysis. *BMJ Open*. 2013;3(3).
5. Lucentis [package insert]. South San Francisco, CA: Genentech Inc., 2014.
6. Eylea [package insert]. Tarrytown, NY: Regeneron, 2014.
7. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537-2548.
8. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology. 2014;121(1):193-201.
9. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1419-1431.
10. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1432-1444.
11. CATT Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364(20):1897-1908.
12. Diabetic Retinopathy Clinical Research N, Elman MJ, Qin H, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmology*. 2012;119(11):2312-2318.
13. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal Aflibercept for Diabetic Macular Edema. *Ophthalmology*. 2014;21(11):2247-2254.
14. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012;119(4):789-801.
15. Boyer DS, Yoon YH, Belfort R, Jr., et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121(10):1904-1914.
16. Elman MJ, Bressler NM, Qin H, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2011;118(4):609-614.
17. Diabetic Retinopathy Clinical Research N, Elman MJ, Aiello LP, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2010;117(6):1064-1077:e35.
18. Diabetic Retinopathy Clinical Research Network. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. *N Engl J Med*. 2015; 372:1193-1203.
19. Elman MJ, Ayala A, Bressler NM, et al. Intravitreal Ranibizumab for Diabetic Macular Edema with Prompt versus Deferred Laser Treatment: 5-Year Randomized Trial Results. *Ophthalmology*. 2015;122(2):375-381.
20. Tolentino MJ, Miller JW, Gragoudas ES, et al. Intravitreous Injections of Vascular Endothelial Growth Factor Produce Retinal Ischemia and Microangiopathy in an Adult Primate. *Ophthalmology*. 1996;103(11):1820-1828.
21. Elman M. Open-Label Extension of the Phase III RIDE and RISE Trials: Characteristics of DME Patients Associated with Treatment Frequency. Paper presented at: American Society of Retina Specialists 32nd Annual Meeting. San Diego, CA: August 8-13, 2014.
22. Brown D. Ranibizumab for Diabetic Macular Edema: Long-Term Open-Label Extension of the Phase III RIDE and RISE Trials. Paper presented at: American Society of Retina Specialists 32nd Annual Meeting. San Deigo, CA: August 8-13, 2014.
23. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration: Two-Year Results. *Ophthalmology*. 2012;119(7):1388-1398.
24. Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology*. 2012;119(10):2125-32.
25. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977-986.
26. King P, Peacock I, Donnelly R. The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for type 2 diabetes. *Br J Clin Pharmacol*. 2001;48(5):643-8.
27. Comparison of Age-related Macular Degeneration Treatments Trials Research G, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012;119(7):1388-1398.
28. Khurana RN, Chmiel H, Tuomi L. Ranibizumab Treatment in Neovascular Age-Related Macular Degeneration with Pigment Epithelial Detachment: Subgroup Analysis of the HARBOR Study. Paper presented at: American Society of Retina Specialists 32nd Annual Meeting. San Diego, CA: August 8-13, 2014.
29. Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2013;120(5):1046-1056.
30. Khurana RN, Dupas B, Bressler NM. Agreement of time-domain and spectral-domain optical coherence tomography with fluorescein leakage from choroidal neovascularization. *Ophthalmology*. 2010;117(7):1376-1380.
31. Gasperini JL, Fawzi AA, Khondkaryan A, et al. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularisation. *Br J Ophthalmol*. 2012;96(1):14-20.
32. Pieramici D. Update on Anti-VEGF trials for diabetic macular edema. Paper presented at: American Academy of Ophthamology Retina Subspecialty Day. Chicago, IL: Oct. 18, 2014.
33. Khurana RN, Palmer JD, Porco TC, Wieland MR. Dexamethasone intravitreal implant for pseudophakic cystoid macular edema in patients with diabetes. *Ophthalmic Surg Lasers Imaging Retina*. 2015;46(1):56-61.

INSTRUCTIONS FOR CME CREDIT

CME credit is available electronically via www.dulaneyfoundation.org.

To receive *AMA PRA Category 1 Credit™*, you must complete the Post Test and Activity Evaluation and mail or fax to The Dulaney Foundation; PO Box 358; Pine Brook, NJ 07058 – Fax: (610) 771-4443. To answer these questions online and receive real-time results, please visit www.dulaneyfoundation.org and click "Online Courses." If you are experiencing problems with the online test, please email us at support@dulaneyfoundation.org. Certificates are issued electronically, please provide your email address below.

Please type or print clearly, or we will be unable to issue your certificate.

Name _____ ❑ MD participant ❑ non-MD participant

Phone (required) _____ ❑ Email (required) _____

Address _____

City _____ State _____

ANTI-VEGF UPDATE: WHEN IS SWITCHING PATIENTS ACCEPTABLE AND PREFERABLE?

1 *AMA PRA Category 1 Credit™*

Expires September 1, 2016

1. **Pivotal registration studies on age-related macular degeneration found:**
   a. Ranibizumab and bevacizumab are best used as combination therapy
   b. PRN is more effective than treat-and-extend over 2 years
   c. Ranibizumab and aflibercept maintain good visual outcomes through year 2
   d. Bevacizumab and aflibercept are best used as combination therapy

2. **In AMD…**
   a. Fixed, regular (monthly) dosing has the best outcomes
   b. Treat-and-extend has the best outcomes
   c. Monthly evaluation with PRN dosing has the best outcomes
   d. None of the above

3. **The injection burden in diabetic macular edema is _____ than later in the course of therapy.**
   a. Much heavier during the early treatment phase
   b. About the same during the early treatment phase
   c. Much heavier during the later treatment phase
   d. About the same during the later treatment phase

4. **Based on the results from MEAD, the panelists …**
   a. Believe dexamethasone will become first-line therapy
   b. Believe dexamethasone should be used as adjunctive therapy
   c. Believe dexamethasone has a duration of effect beyond 6 months
   d. Believe there is no role for dexamethasone in treating AMD

5. **According to the panelists, Protocol I …**
   a. Showed persistent DME would result in lost vision
   b. Showed visual improvements gained in the first year diminished by year 5
   c. Allowed persistent DME to remain as long as vision continued to improve
   d. Allowed persistent DME to remain as long as there was no increase in OCT thickness

6. **In which of the following retina disorders should the macula be "bone dry"?**
   a. AMD
   b. RVO
   c. DME
   d. All of the above

7. **In Protocol T, OCT changes mimicked visual changes.**
   a. True
   b. False

8. **Photodynamic therapy is still advocated for use in treating which disease?**
   a. Retinal angiomatous proliferation lesions
   b. Central serous retinopathy
   c. Polypoidal choroidal vasculopathy
   d. Birdshot retinochoroidopathy

ACTIVITY EVALUATION

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Understand the most recent monotherapy and combination therapy clinical study evidence using available treatment therapies for common retinal diseases, including AMD and DME	____	____	____
Discuss the benefits of anti-VEGF therapies over other potential therapies and how to educate patients on appropriate expectations	____	____	____
Develop plans to initiate treatment for conditions such as AMD and DME, as well as better understand when to change therapeutic strategies and/or therapeutic classes of treatment	____	____	____

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 (610) 771-4443.

Name and email _____

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

Comments regarding commercial bias:

_____

_____

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

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

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

Do you feel the information presented will change your patient care? ❒ Yes ❒ No

If yes, please specify. We will contact you by email in 1 to 2 months to see if you have made this change.

_____

_____

If no, please identify the barriers to change.

_____

_____

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

_____

_____

Jointly provided by The Dulaney Foundation and *Retina Today*.

Supported through an unrestricted educational grant by Regeneron Pharmaceuticals.