Supplement to NRMD New Retina MD 2017/Issue 2

CME Activity

A Review of DME Treatment Guidelines and the Role of Early Appropriate Therapy

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A CME activity jointly provided by Evolve Medical Education LLC, *New Retina MD*, and *Retina Today*.

Supported by an unrestricted educational grant from Regeneron Pharmaceuticals.

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Supported through an unrestricted educational grant by Regeneron Pharmaceuticals.
Release Date: September 2016
Expiration Date: September 2017

CONTENT SOURCE

This continuing medical education (CME) activity captures content from roundtable discussion held in June 2016.

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, the participant should be able to:

- Assess the most recent monotherapy and combination therapy clinical study evidence using available anti-VEGF therapies for common retinal diseases, including DME.
- Discuss the 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 DME, using anti-VEGF agents, as well as better understand when to change therapeutic strategies.

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A Review of Treatment Guidelines and the Role of Early Appropriate Therapy

The prevalence of diabetes is growing globally; as such the number of people affected by vision-threatening diabetic retinopathy (DR) is likewise expected to continue to increase. Prevent Blindness America has estimated more than 7.6 million people in the United States have DR as a result of their systemic disorder.[1] By 2035, it is estimated close to 600 million people worldwide will be living with diabetes, a marked increase from the 382 million in 2013.[2] Yet according to the American Academy of Ophthalmology, upwards of 40% of people with diabetes do not receive the recommended annual screening for DR.[3] The American Diabetes Association recommends initial screening within 5 years of diagnosis of type 1 diabetes and then annually, and annually for type 2 diabetes.[4]

Medical therapies have reduced the severity of diabetic macular edema (DME) and DR, and timely treatment can reduce severe vision loss by 90%.[5] Treatment options for DME include intravitreal anti-VEGF injections, focal/grid macular laser, and corticosteroids that are either injected or implanted into the eye. These treatments can be used alone or in combination to treat DME and appear to have additional benefits impacting DR itself. Despite good efficacy of the anti-VEGF medications, many patients require close ongoing monitoring and frequent re-treatments, and many patients will demonstrate persistent DME.[6,7]

Retina Today *convened a panel of experts to discuss what today's DME and DR treatment landscape looks like, insights from new clinical trials, advances in retinal imaging, and what clinicians can expect down the road.*

—Charles C. Wykoff, MD, PhD, moderator

Charles C. Wykoff, MD, PhD: Diabetes mellitus is a common and growing problem. The World Health Organization in April estimated that about one in 12 adults on our planet has diabetes.[8] In the United States, the Centers for Disease Control and Prevention has stated that as many as 50% of Americans over the age of 65 either have frank diabetes or can be classified at a substantial risk of developing diabetes.[9]

As retina specialists, we know diabetic retinopathy (DR) is one of the most common vascular sequelae of diabetes and can lead to vision loss, primarily through macular edema (DME) and proliferative DR (PDR). But DR seems to have a substantial negative impact on patients' health-related quality of life even within nonproliferative stages without DME.[10] We know from the pivotal studies on anti-VEGF treatments that a substantial proportion of patients treated regularly with VEGF blockade experience both reduced progression of retinopathy severity and also improvements on the retinopathy severity scales.[11,12] Do you see such changes in your clinical practice? And are they important to you in management of these patients?

David Eichenbaum, MD: DR is an excellent biomarker for the overall diabetic eye disease burden. There are vascular components, inflammatory components, and mechanical components if we include proliferation of epiretinal membranes. The level of visible DR severity can serve as a proxy for local disease status and progression. The more venous dilation, the more intraretinal microvascular malformations, the more neovascularization—these can all be signs of disease worsening. When those same markers improve, the situation is improving and hopefully sight is returning.

So it is important to me to take color photographs, not at short intervals, but at fairly long intervals to both re-evaluate severity oneself and show patients how the disease is going. It is a way to synthesize all of the concepts that we split up and parse out in papers and presentations and meetings about how DR works.

Dr. Wykoff: Dr. Baumal, in your clinical practice do you feel like you are able to see changes in retinopathy severity over time when you are treating your patients? How do you follow those changes?

Caroline R. Baumal, MD: I have noted significant improvement in the overall severity of DR after extended intravitreal therapy with VEGF inhibitors. This is especially true for my patients with moderate nonproliferative DR (NPDR) who were receiving anti-VEGF injections for DME. The retinal hemorrhages disappear over time on clinical examination and this can be verified with red-free fundus photography. This observation mirrors findings from the RISE and RIDE studies that demonstrated improvement in the DR severity score after anti-VEGF injections.[6,12]

Dr. Wykoff: Dr. Shah, does DR status impact your management of DME?

Chirag P. Shah, MD, MPH: It does to a certain degree. When you are treating DME, you are not just dealing with the DME—you are treating DME, you are treating the optical coherence tomography (OCT), vision, and the patient. All those variables come into play when we make our decision on whether or not to treat, or how regularly to treat, or how frequently we need to see our patients. Our decision tree is altered if someone has PDR, or severe NPDR, or if there is a fair amount of capillary dropout in nonperfusion. In those cases, I might treat a little more aggressively with anti-VEGF therapy, because I know that I am getting multiple effects from it in terms of improving the degree of DR, perhaps slowing the rate of nonperfusion,[13] and maybe, as one study has suggested, decreasing the amount of nonperfusion.[14]

It is a conversation I have with the patient about overall health, ability to get to the office, age, visual demands—all of those factors play a role in how I manage DME in any one individual patient.

Dr. Eichenbaum: I look at the DR level by color fundus photograph (CFP) differently than the perfusion level by fluorescein angiography (FA). I consider the fluorescein angiographic areas of nonperfusion as more impactful than I consider almost any change in the CFP. I agree that it is nice to see the retinopathy get better over time on CFP.

When I see nonperfusion, I do not just take fundus photographs and get an OCT—I repeat the FA periodically to determine if those areas are enlarging or improving. It is important to think about how we are distinguishing DR levels versus nonperfusion and how those differences can impact our decision to use anti-angiogenic treatments, steroid treatments, and/or laser treatments.

IMAGING CHOICES

Dr. Wykoff: That is an excellent distinction about the issue of angiography versus what we see with our clinical examination. Does everyone obtain an FA in your diabetic patients when you are starting treatment?

Dr. Shah: I do. We have wide-angle angiography in our primary office. There are things we will see in the periphery that are not detected on standard angiography. Wide-angle FA is much better at detecting very subtle areas of neovascularization and nonperfusion that I cannot see with my naked eye, so it gives me a good baseline. An important benefit of the angiogram is evaluating the size of foveal avascular zone and assessing macular perfusion. This will impact what the ultimate vision may be, even in the absence of macular edema.

"I have had patients tighten up their blood sugar control just after looking at their angiogram, because they realized how they are contributing to their disease."

—Chirag P. Shah, MD, MPH

It requires a fair amount of buy-in on the part of the diabetic patient to come into the office and get treated—usually they are younger and they are still of working age—and wide-angle angiography is incredibly valuable to show them the effect of hyperglycemia inside their eye. It helps our patients understand this is a potentially long-term commitment to treatment. When patients can see their retinal perfusion, it has a significant impact. I have had patients tighten up their blood sugar control just after looking at their angiogram, because they realized how they are contributing to their disease.

Dr. Baumal: I consider a baseline FA in selected individuals with moderate or worse levels of DR. I like to consider whether the results of FA will affect my clinical management after I have obtained preliminary noninvasive imaging results. FA may be especially useful in scenarios where the visual acuity loss is out of proportion to the clinical findings, when multifactorial causes may contribute to visual loss (ie: eyes with concurrent glaucoma, if prior retinal laser photocoagulation has been performed, and if occult retinal neovascularization is suspected). I have access to OCT angiography (OCT-A), which is a new imaging modality to image the foveal avascular zone. If patients are going to have anti-VEGF injections for DME, any subtle peripheral neovascularization will be concurrently treated by the anti-VEGF therapy and in those eyes, so my management strategy may not be altered by the fluorescein results.

Dr. Eichenbaum: I get initial angiography on all of the patients who come in with DR for whom I am considering treatment. My angiography protocol is a little bit different because I think it is important to look for the foveal perfusion, although we also use

the ultra-widefield lens in two of our five offices. My preference is to shoot a 55-degree widefield lens angiogram through transit to look for macular perfusion and the regularity of the fovea. I would agree the 55-degree wide-angle angiography might provide a slightly better quality image than the ultra-widefield lens in the Heidelberg system. Ideally, I have the technician switch to the ultra-widefield to show me what is going on in the periphery, because even if there is non–high-risk proliferative disease, I will be a more aggressive with the anti-angiogenics than if I am just treating DME with moderate to severe NPDR.

HIGH-RISK AND NON–HIGH-RISK PDR

Dr. Wykoff: You have all brought up the issue of peripheral lesions that you might not be aware of before widefield imaging. So let us say you have an asymptomatic patient with PDR with a limited number of peripheral neovascular fronds without significant DME—how would you manage this patient? Would you use panretinal photocoagulation (PRP) at some point?

Dr. Eichenbaum: High-risk PDR, based on the Diabetic Retinopathy Study (DRS), is a different diagnosis than what we are seeing with our extremely high-resolution widefield angiographic imaging systems and photography systems.

We now have great data to guide our decision-making processes, and I use the Diabetic Retinopathy Clinical Research Network's (DRCR.net) Protocol S[15] and the DAVE study data[16] as primary guidelines for what I think is best for the patient. I tell patients with PDR that in 2016 our best results for quality of vision are to make anti-angiogenic therapy the backbone of treatment.

If I think the patient will commit to a series of injections, I will start there. If, however, I get the feeling they cannot commit, or they are not going to come in regularly, I will start with PRP but with about half the number of spots as I used to give. Now it is more like 1,000 spots, light and small. I try to keep it anterior.

But I do offer the anti-angiogenic therapy first—we know if we load the patient with nine or 10 injections that first year, there is a much reduced burden of keeping proliferative disease at bay over the next 1 to 4 years without universal PRP.

Dr. Shah: I have a similar approach. For non–high-risk PDR patients, I do not have a set protocol, but I will use many variables to determine what to do. For example, noncompliance, elevated A1C levels, pregnancy, or rapid progression means I will consider treatment with anterior PRP, but lighter than I used to prior to the anti-VEGF era. The fellow eye status also influences what I do for the eye that I am treating. If the fellow eye has PDR, I have a lower threshold to treat either with anti-VEGF therapy or PRP or possibly both.

Dr. Baumal: I think it is likely that future clinical studies will alter the current treatment paradigm for DR and perhaps sway the benefit-to-risk ratio in favor of treatment before high-risk PDR develops. I treat patients when retinal neovascularization is present, often with anti-VEGF injection. In a similar fashion, Protocol S included eyes with non–high-risk PDR in its design, demonstrating noninferiority of ranibizumab to PRP at 2 years.[15] Anti-VEGF therapy has less peripheral vision loss and has the added benefit of treating associated DME and avoiding exacerbation of DME that can occur after PRP. I may use limited PRP in the far peripheral or nasal retina if I am concerned the patient is not going to be consistent with follow-up.

Dr. Eichenbaum: Does anyone consider treating asymptomatic moderate to severe NPDR without proliferative disease on exam, OCT, or peripheral angiography?

Dr. Shah: Without DME?

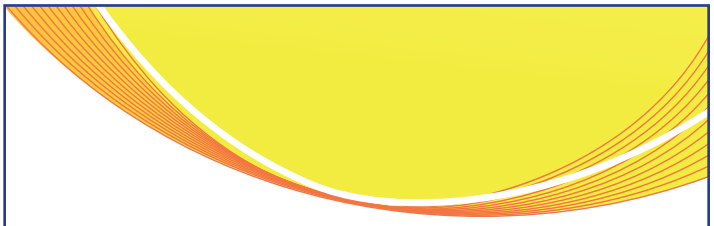
Dr. Eichenbaum: Correct, without DME. Asymptomatic, no DME or maybe just trace OCT DME, visual acuity is 20/16, clear lens or minimal nuclear sclerosis. In other words, there is no reason why the patient would want treatment. Has anyone treated a patient like that with serial anti-VEGF injections?

Dr. Baumal: Down the road there may be a therapy that could reverse or stop DR where the benefit-to-risk ratio would justify treatment at an earlier stage, but currently I do not think there is enough evidence to justify treatment for moderate to severe NPDR without proliferative disease or DME.

Dr. Wykoff: That is a great question, and I agree with Dr. Baumal. Certainly both PANORAMA[17] and the DRCR.net Protocol W[18] address this clinical situation, with both trials actively recruiting patients. We have very good data on the impact of anti-VEGF injections on DR and some data regarding steroid treatments on DR both in eyes with DME, but lack data in eyes without DME. While I assume such treatments will have a similar impact on DR in the absence of DME, we need data to confirm this; it could be that DME is a marker for eyes that demonstrate a stronger benefit from anti-VEGF treatment.

Dr. Eichenbaum: That kind of patient is someone that I cannot bring myself to treat in 2016. I find it hard to enroll patients in a DR study without symptomatic vision loss. It is a tough population—we have to tell them that while they are currently seeing great and asymptomatic, they have a lot of diabetic eye disease, and we want to give a series of shots to get a cumulative benefit towards reducing their disease severity and risk of vision loss in the future. With the current relatively short-acting anti-VEGF agents and the serial injections required to confer DR severity regression, treating DR without DME is a hard sell for patients and will be until we can prove there is some definitive visual benefit.

Dr. Shah: Dr. Eichenbaum is right—and I say this as someone who is recruiting for these trials. It is a tough sell. It is very hard to treat an asymptomatic patient. If one eye is worse than the fellow eye, it is a bit easier because we are trying to proactively protect the better eye. When they see their retinopathy on the screen, it can be a compelling reason to enroll as well. But it is very hard to convince a younger asymptomatic person to commit to monthly injections. This is why we need more data from trials such as PANORAMA and DRCR.net Protocol W.



"I cannot yet expect areas of ischemic retina re-perfusing in a majority of patients unless these anti-VEGF drugs are even more miraculous than we understand them to be."

—David Eichenbaum, MD

MACULAR NONPERFUSION

Dr. Wykoff: Dr. Baumal, can you briefly summarize your subanalysis of the RISE and RIDE dataset in which you specifically considered outcomes among patients with baseline macular nonperfusion?

Dr. Baumal: This was a subanalysis of patients from the RISE and RIDE studies focusing on eyes with macular nonperfusion at baseline.[19] We wanted to assess if eyes with macular nonperfusion at baseline could have improvement in vision and/or anatomy at the end of the RISE and RIDE studies. Our findings showed that the presence of macular nonperfusion at baseline did not adversely affect the improvements in both vision and macular edema at the conclusion of the study. In fact, eyes with DME and macular nonperfusion at baseline gained more vision and had more anatomic improvement with ranibizumab therapy compared to eyes without macular nonperfusion. Thus, eyes with macular nonperfusion should not be excluded from anti-VEGF therapy.

There had been—and continues to be—some concern about whether repeat anti-VEGF injections can adversely affect vascular perfusion. That is not always easy to assess, especially now that we know more about retinal perfusion as a result of OCT-A. The retinal circulation is more complex than what is seen with FA, which only images the superficial inner retinal capillary plexus. In addition, there is an intermediate and deep inner retinal capillary plexus that can now be imaged in vivo with OCT-A.

With these results in hand, I feel safer treating patients with anti-VEGF therapy knowing that even if they do not have good perfusion at baseline, I am not making it worse by giving them repeated anti-VEGF injections. This also correlates well with what I find in clinical practice, where anti-VEGF does not appear to negatively impact retinal ischemia.

Dr. Wykoff: Did you see any patients of note that had re-perfusion while you were treating them?

Dr. Baumal: That was not evaluated as an outcome of RISE and RIDE,[12] and thus this subanalysis was not able to review that. Future studies with fluorescein and OCT-A after anti-VEGF therapy may be able to assess for this.

Dr. Wykoff: Dr. Shah, you have also recently studied a population with retinal nonperfusion in the ANDROID series.[14] Can you bring us up-to-date on your findings?

Dr. Shah: The ANDROID study was not a large multicentered randomized control trial. It was a small single-center prospective uncontrolled study in Boston that included 24 patients with proliferative disease.[14]

Of those 24 patients, 15 had PDR and nine had retinal vein occlusion (RVO). We did not have a control arm, so our results need to be tempered with that in mind. Our patients were treated either monthly with aflibercept for 1 year, or monthly with aflibercept for 6 months and then switched to bimonthly treatments. Over the course of the year, that means they received either nine or 12 injections.

We looked at widefield angiography to assess the degree of peripheral nonperfusion to see how that was changing over time. That was the primary endpoint. Images were evaluated by the Duke Reading Center.

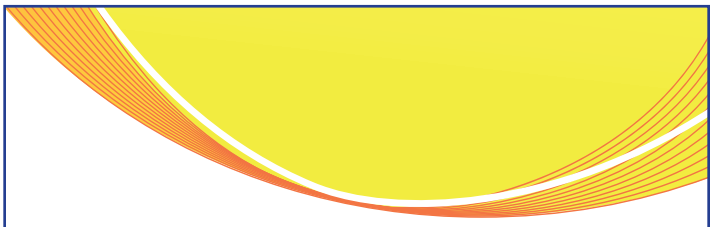
What we found was that there is an improvement in peripheral nonperfusion—this marked the first time results like these were found. In ANDROID, 83% had improvement in peripheral nonperfusion at 1 year, where 17% actually worsened after 1 year.[14] There was no difference between those who had 12 injections and those who had nine injections, and there was no difference between PDR and central RVO.

Dr. Wykoff: So we have one large data-set, RISE and RIDE, with published data showing that by posterior-pole angiography there is a slowing of loss of retinal perfusion with monthly ranibizumab.[12,19] Then we have this data from a much smaller group of patients using widefield angiography indicating that 80% of eyes with more advanced disease may have areas of significant re-perfusion.[14] What do you think?

Dr. Eichenbaum: The dataset from RISE and RIDE[12] is a more substantial dataset. I think a fairly high burden of anti-angiogenic therapy (such as monthly or near monthly treatment) is likely going to significantly reduce or stop progression of retinal nonperfusion, regardless of agent.

I cannot yet expect areas of ischemic retina re-perfusing in a majority of patients unless these anti-VEGF drugs are even more miraculous than we already understand them to be. The drugs do have enough of a biologic effect, based on the data that we have from the RISE and RIDE dataset and the imaging from smaller datasets like ANDROID, that we can expect a significant and impactful reduction in the advancement of nonperfusion, and that is a substantial benefit for visual acuity in patients.

Again, to get that benefit, we probably need a higher burden of treatment in the first year with monthly or near-monthly injections. I believe that high number of "induction" injections in the first year is being more accepted by the retinal community—



"OCT-A is currently limited by its inability to view the peripheral retina; however, it is fast, noninvasive, and can be useful to image both superficial and deep inner retinal vascular plexuses."

—Caroline R. Baumal, MD

Protocol T was close to 10 or 11 injections, more than Protocol I at nine injections.[20,21]

Dr. Wykoff: We will certainly have more data with results from the randomized PANORAMA[17] and Protocol W trials,[18] both utilizing aflibercept treatments. It is fascinating to me to consider how anti-VEGF therapy could lead to retinal vascular re-perfusion. Maybe leukostasis plays a substantial role in some eyes, and perhaps some of the vessels we see as "nonperfused" by angiography are not actually dead, just closed with an inflammatory cell, leukostatic response. Blunting this inflammatory response by blocking VEGF may be able to re-open such channels to the flow of fluorescein allowing it to appear re-perfused. ANDROID provides some of the most recent data I have seen on this topic. Are you planning any follow-up analyses?

Dr. Shah: No, we do not currently have any follow-up studies planned. I agree that Protocol W and PANORAMA will be very helpful when those datasets are closed and published. It will be interesting to see the outcomes.

OCT-A

Dr. Wykoff: We have talked a lot about FA. Dr. Baumal, what changes in perfusion status do you see over time in diabetic eyes imaged with OCT-A?

Dr. Baumal: It can be difficult to ascertain the macular flow anatomy in eyes with DME because the intraretinal cysts of DME can distort imaging of flow in the perifoveal vessels. Both intraretinal cysts and capillary nonperfusion appear as dark spaces, but cysts have an oval shape with a darker appearance, while a border of capillary nonperfusion has straighter edges. In addition, OCT-A imaging works by detecting red blood cell motion or flow in the vessels. Thus, imaging is sensitive to patient or eye motion and fixation. There can be artifacts in eyes with poor fixation secondary to poor vision. It may be easier to assess the OCT-A flow features in eyes after treatment of DME while on maintenance anti-VEGF therapy. What I have noted in my patients is that the foveal avascular (nonflow) zone and adjacent areas of capillary nonperfusion appear to remain relatively stable as preliminary findings.

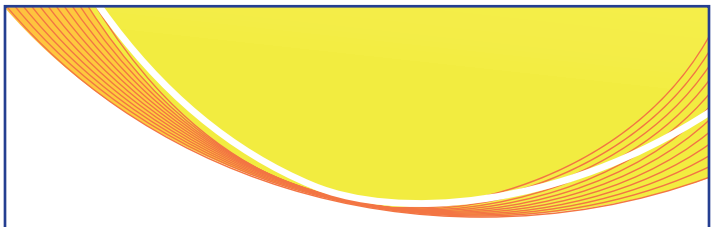
OCT-A is also useful to evaluate neovascularization of the retina. As soon as 1 week after anti-VEGF injection, the flow in preretinal neovascularization is markedly reduced or absent, and then may recur over time as anti-VEGF effect subsides. There are a couple of caveats to consider when interpreting OCT-A. A 3x3-mm square centered on the fovea may be ideal to evaluate the foveal avascular zone as this provides the highest resolution. OCT-A is currently limited by its inability to view the peripheral retina; however, it is fast, noninvasive, and can be useful to image both superficial and deep inner retinal vascular plexuses. Some findings of NPDR on FA may have a different appearance with OCT-A imaging. For example, microaneurysms might be imaged less often with OCT-A, especially if the microaneurysm lacks active flow. OCT-A, however, can localize microaneurysms in the deep or less often superficial inner retinal capillary plexus.

Dr. Shah: It is intriguing to potentially quantify the areas of nonperfusion, and that could be helpful in a different way when we use OCT-A compared to looking at FA. Looking at the various plexuses rather than just the retinal perfusion offers a significant advantage over FA. With OCT-A being noninvasive and only taking a couple of minutes, it has significant advantages over fluorescein. I do not check an FA every month—maybe every 1 or 2 years—so it is nice to have something that is accurate, quick, and noninvasive to use monthly.

Dr. Eichenbaum: I do not have an OCT-A in my practice, but we know from the Protocol T data that between about 40% to 60% of patients, depending on the drug used, required laser treatment, per protocol, during the first 2 years of Protocol T.[21] Do you use the OCT-A to guide your deferred laser treatment? Do you find the OCT-A imaging findings supplant the traditional "hot" leaking microaneurysms that are extra-foveal laser targets on FA? For those of us who do not use OCT-A, what kind of guidance can you give us?

Dr. Baumal: OCT-A imaging also produces a high-resolution OCT B-scan to complement the OCT-A flow image. OCT-A provides static imaging of vascular flow while FA gives dynamic vascular information. OCT-A delineates many changes such as capillary loops, venous beading, and neovascularization; however, it may image fewer microaneurysms than FA. Either there is no active flow in the microaneurysm or its flow is below the threshold of OCT-A detection. The modalities of OCT-A and FA are complementary, and I usually turn to OCT-A first with FA as a backup if I need more anatomic information.

Dr. Shah: I think there is some synergy between the two modalities. With fluorescein, we can see the microaneurysms that are leaking. There is some value to that. On the rare occasions that I dust off my focal laser, there is some benefit in knowing I am treating the aneurysms that are leaking the most. You do not get that dynamic information from an OCT-A.



"I use steroids in combination with the anti-angiogenics to try to get the best of both worlds for the patient while reducing the overall injection burden."

—David Eichenbaum, MD

Dr. Baumal: If they are leaking, you are going to see that on your B-scan anyway.

Dr. Shah: Sometimes. There can be angiographic leakage but the RPE pump can eliminate that leakage before it manifests on the B-scan OCT. There is a gray zone where you might not see collection of fluid.

Dr. Eichenbaum: I agree that the retina and RPE pump likely have some efficiency in reabsorbing vascular leakage, specifically intraretinal leakage. Before I use deferred focal laser, though, I would want to see a hot microaneurysm on FA.

Dr. Wykoff: I use OCT-A infrequently and only on select cases in my clinic. Dr. Baumal and Dr. Shah, you both noted there is interest in looking at the different plexi within the retina. How is that clinically valuable today? We certainly need to collect more data to understand the role of these different vascular layers within the retina and how they are damaged by diabetes. But, how does this impact our treatment decisions today or in the near future?

Dr. Baumal: OCT-A in DR allows high-resolution, limited field imaging of vascular changes localized in both the deep and superficial vascular plexuses, while FA shows only the superficial vascular plexus with wider field and dynamic flow information. These two technologies provide different information, but OCT-A may be able to determine what is happening to the retinal vasculature over time and fill in the gaps from what has been determined from FA.

OCT-A lends itself to computational image analysis. Large datasets are generated in OCT-A to use in computerized algorithms to numerically measure the foveal avascular area and flow density analysis.

Dr. Shah: I do not know how or if OCT-A will affect how I manage DR, and right now I do not use it on every patient. But when I do use it, it has not impacted my decision-making on DR. OCT-A may impact my choices down the road as we get more information on how to intelligently use the data we are gathering.

Where it has made a significant impact on my management is when I have a patient with central serous retinopathy, and there is the potential for choroidal neovascularization (CNV). If the fluorescein is equivocal, that is where OCT-A can be the tiebreaker for me to figure out whether or not there is CNV. This is a niche where I have found OCT-A to be most valuable.

Dr. Eichenbaum: That is where I see the potential high value of OCT-A. We never really know if we are extending the wet age-related macular degeneration (wAMD) patients appropriately and whether or not there is interval change in the subretinal CNV. With OCT-A, theoretically, you can see the subretinal complex and whether or not there is flow in the complex. That technology may be more reliable and easier to read than what we currently use to evaluate the CNV complex, which is occasional interval fluorescein or indocyanine green angiography.

If we have disease-modifying agents in wAMD that cause CNV to regress more significantly than the monotherapies we have today, we might be able to use OCT-A to more accurately guide our extension regimens or stop serial injection therapy.

USING STEROID TREATMENTS

Dr. Wykoff: Let us consider steroids in the management of DR. We talk a lot about the concept of switching to steroids or using combination therapies with steroids for the management of DME. What about steroids specifically for DR? What do you do for the patient with severe DME who is not responding completely to anti-VEGF treatments and you have now switched the patient to an on-label steroid product? Do you find steroids have the same impact on DR over time as the anti-VEGFs?

Dr. Eichenbaum: There is some evidence going all the way back to the fluocinolone acetonide intravitreal implant 0.59 mg that show steroids affect DR, and that there is some DR regression.[22] I do not think we have enough modern imaging data to show they are as potent affecters of DR or regression as antiangiogenic monotherapy.

We have looked at the FAME data with regard to the progression to PDR, and there was a reduction in patients who were receiving essentially steroid monotherapy.[23] The MEAD data is not as compelling, but shows a similar rate of lower progression to PDR with steroid monotherapy in eyes with DR.[24]

I use steroids in combination with the anti-angiogenics to try to get the best of both worlds for the patient while reducing the overall injection burden.

Dr. Wykoff: I agree. There is good data to show that steroids may be able to significantly slow the progression to PDR. In the combined FAME dataset, through the 2- and 3-year endpoints, 26% and 31% of sham controlled eyes progressed to PDR while fluocinolone treatment significantly reduced this rate to 12% to 13% and 17% to 18% at 2 and 3 years.[23] While certainly more data is needed and there are no head-to-head comparisons, this magnitude of affect with fluocinolone appears similar to that observed with monthly

anti-VEGF treatments.[25,26] Does anyone else use combination therapy when switching to include a steroid in DME management to maintain the effect of DR improvements over time?

Dr. Shah: An excellent question, and I often will not if I am switching because of DME. I tell patients steroids are like atomic bombs—they work fairly well in most cases to reduce edema. I will not continue with anti-VEGF therapy if I am using steroids unless I feel that there is a lot of breakthrough edema so the patient needs everything we have to treat it.

Dr. Baumal: I typically use steroids alone for DME, even though I think there is some effect in reducing DR severity. There is more clinical information on anti-VEGF agents reducing DR severity than steroids.

Dr. Eichenbaum: Yes, the reason to add a steroid is primarily driven by DME and the presence or absence of macular edema. I do not abandon the anti-VEGFs for exactly the reason that Dr. Shah mentioned. But I do think steroids are probably synergistically potent in controlling the DR and helping effect the regression of DR.

LASER TREATMENT IN DME PATIENTS

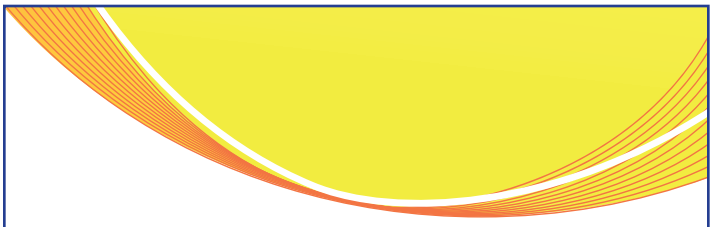
Dr. Wykoff: What are your thoughts about using peripheral laser specifically for the management of DME?

Dr. Shah: In theory, it should make sense, right? So if we are obliterating the ischemic retina, we are decreasing VEGF and the other proangiogenic factors and other cytokines that are being secreted from this sick or dead retina. But this was not evident in the DAVE study.

Dr. Baumal: Dr. Wykoff, can you fill us in on the DAVE study? What were its findings about peripheral laser and the impact on an ischemic retina?

Dr. Wykoff: This is a small, single-center study that compared prn ranibizumab to prn ranibizumab plus targeted widefield laser for DME in 40 patients.[16] All of these eyes had extensive peripheral nonperfusion and significant DME. Most also had small areas of neovascularization in the far periphery. We applied heavy peripheral laser to the ischemic zones and the penumbra, the adjacent area of remaining perfused retina as long as it was well outside of the macula. Through 2-years of follow-up, there has been no substantial decrease in the number of prn injections with addition of peripheral targeted laser. Bear in mind that we treated central DME aggressively and therefore the re-treatment burden was high in both arms, potentially obscuring any impact of peripheral targeted laser. We have also recently completed a similar study in ischemic RVOs with similar results.[27]

Dr. Eichenbaum: There are several small studies that have evaluated this type of treatment to look at peripheral nonperfusion with ultra-widefield guidance, such as RaScaL (Ranibizumab + Scatter Laser) in DME[28] and Spaide's work in central RVO,[29] and none were as large as the DAVE study.[16]



"The holy grail from a patient's perspective is a noninjectable, such as an eye drop, or a pill, or anything that is considered 'less invasive.'"

—Charles C. Wykoff, MD, PhD

Data point to laser not working consistently when used to treat peripheral nonperfusion in an effort to control central edema. In my opinion, there are enough series and small- and medium-sized series to relegate peripheral scatter laser to later stage or salvage therapy in patients with central edema.

Dr. Baumal: It does demonstrate that there are other mediators involved in the development of DME that anti-VEGFs are not treating. Or maybe by the time these eyes have that amount of nonperfusion they are past a certain tipping point where treatment is going to be beneficial—where just one treatment type is not going to reverse the process.

Dr. Wykoff: The other challenge in our series was the unwillingness to laser oblate parts of the visual field that might be valuable. We kept the laser well outside of the macula, but there are obviously ischemic zones inside and just outside of macula. It may be that we are simply not treating enough of the ischemic zones to see the benefit.

LONGER ACTING AGENTS

Dr. Eichenbaum: It seems to me we have moved from "anti-VEGF 101" and are now heading into "anti-VEGF 102" with DARPin (Designed Ankyrin Repeat Protein) molecules and brolucizumab (formerly known as RTH258 and ESBA1008). Based on information we currently have from the phase 2 and phase 3 studies, do you think longer lasting agents and/or more potent anti-VEGF treatments will become a key component in our armamentarium?

Dr. Shah: Longer-acting agents are going to be a big part of our armamentarium. But should we be concerned about too much anti-VEGF treatment? In the CATT study, there was the suggestion in the ranibizumab arm of more geographic atrophy with monthly dosing.[30] Given that we may be able to treat patients for regression of their retinopathy with other agents, it makes sense that if we can deliver fewer injections and achieve the same goals, we are benefitting the patient.

Dr. Baumal: There have been more effective treatment options available, but there is still a large treatment burden on patients to come into the office every 1 to 2 months for injection. This is leading to the enthusiasm to find longer acting medications or combination therapies to prolong effect. These medications or delivery systems still need to be assessed clinically for risk-to-benefit ratio.

Dr. Eichenbaum: Any thoughts about non–anti-VEGF products or noninjectable products? Topical squalamine is a product that could augment (potentially) the effect of existing or potential next generation intravitreal anti-angiogenics as well as the Tie-2 activator, which could restore the Tie-2 signaling pathway to help intraretinal vasculature in a way completely different than intravitreal anti-VEGFs do.[31] What are your thoughts about the potential for different mechanisms of action and/or different delivery locations?

Dr. Wykoff: The holy grail from a patient's perspective is a noninjectable, such as an eye drop, or a pill, or anything that is considered "less invasive." But I think those are still a ways down the road. The potential for combination therapies is intriguing. The RUBY[32] and BOULEVARD[33] trials are combining VEGF and angiopoietin 2 (Ang-2) blockade, both holding great promise. They are both in phase 2 studies. Hopefully as more relevant cytokines are identified and successfully targeted clinically, we will continue to move towards combination-targeted therapy on an individualized basis.

Dr. Eichenbaum: We do have a long way to go. Diabetic patients with severe DR do not get there through years of compliance with best medical practices, so I am cautious about therapies that rely upon self-administration. Concentrating on long-acting local treatments and multiple intraocular targets in the short term and midterm is what I think is going to help our patients the most. I agree with you that the combination or biphasic molecular therapies are exciting, and they are coming down the pipeline with reasonable speed.

Dr. Wykoff: What do you think about a refillable depot? For example, the LADDER trial[34] looking at neovascular AMD in a phase 2 trial with a refillable ranibizumab reservoir? Do you think that is something many patients are willing to undergo?

Dr. Eichenbaum: That is another take on the "anti-VEGF 102" we discussed earlier. It is taking familiar entities and making them more efficient. I think that it will be a really good bridge between what we have now and what we have coming.

Dr. Baumal: While systemic therapy may be easier for a patient and more acceptable, intravitreal delivery provides a high concentration of medication with very low systemic side effects. Diabetic patients may already have systemic vascular compromise, nephropathy, and neuropathy and potentially have multiple side effects from systemic drugs. Local therapy is currently an effective method to prevent side effects.

Dr. Wykoff: If you had a device that you could implant into the eye and refill it once every 6 months, but it had to be placed surgically in the operating room, how many injections would you give before that would become a reasonable next step?

Dr. Shah: That model would be most beneficial for patients who are already being regularly treated. There are many patients with DR, and particularly DME, who cannot go longer than 5 weeks without their anti-VEGF agent, others cannot go beyond 8 weeks. Those patients are very similar to wet macular degeneration patients. I think that they would be tremendously benefitted by a reservoir that was refilled twice a year. It could save nine to 10 shots per year.

Dr. Eichenbaum: This is truly an exciting time. We have lightning in a bottle with all this development and the pipeline promises, and we are already helping our patients more than we were even a decade ago. So I am excited to be here, I feel fortunate, and I look forward to advancing the field with all of you and helping our patients as best we can.

Dr. Baumal: Imaging is going to give us new insight into the pathophysiology of DR, and it will improve how we monitor therapeutics for DR. There are a lot of new, potential treatments with different mechanisms on the horizon and also potential to extend and improve current therapies.

Dr. Shah: I think the future will hold both different drug delivery platforms and combination therapy looking at multiple pathways, not just for DR but for AMD and RVO, to increase our efficacy and potentially even reduce our treatment burden for patients.

Dr. Wykoff: The manifestations of DR are many and it remains important to regularly reconsider the nuances of our management strategies, taking into consideration new data and deeper understandings. The future of DR management is bright, with improved imaging opportunities and expanded treatment options on the near-term horizon. Thank you, Dr. Baumal, Dr. Eichenbaum, and Dr. Shah, for your astute clinical observations and insights. For our patients' benefit, please keep up your excellent work. ■

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A REVIEW OF DME TREATMENT GUIDELINES AND THE ROLE OF EARLY APPROPRIATE THERAPY CME QUESTIONS

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1. **The Centers for Disease Control and Prevention has stated that approximately _____ of American adults either have diabetes mellitus or can be classified at a risk of developing diabetes.**
   a. 10%
   b. 25%
   c. 50%
   d. 75%
2. **Potential signs of high-risk PDR include all of the following except?**
   a. Neovascularization of the disc
   b. Vitreous hemorrhage
   c. Worsening DME
   d. Neovascularization greater than one-half disc area in the retina and greater than one-third on the disc
3. **The ANDROID study has suggested:**
   a. Intravitreal anti-VEGF therapy may reduce the amount of nonperfusion in PDR and CRVO
   b. Intravitreal anti-VEGF therapy works only in cases of severe NPDR
   c. Intravitreal anti-VEGF therapy always improves the degree of DR
   d. Intravitreal anti-VEGF therapy rarely slows the rate of progression of nonperfusion
4. **Which imaging technology(ies) is/are recommended as options by the panelists to follow the severity of DR?**
   a. Color fundus photographs
   b. Fluorescein angiography
   c. Optical coherence tomography angiography
   d. All of the above
   e. None of the above
5. **What is the recommended treatment for a patient with asymptomatic moderate to severe NPDR without proliferative disease on exam or imaging, visual acuity of 20/16, with minimal nuclear sclerosis?**
   a. Anti-VEGF intravitreal injections
   b. Panretinal photocoagulation
   c. Intravitreal steroids
   d. There is not enough clinical evidence to support treatment
6. **A subanalysis of visual outcomes during RIDE and RISE focused on patients with macular nonperfusion at baseline revealed what findings?**
   a. Macular nonperfusion at baseline adversely affected visual acuity outcomes after anti-VEGF treatment at the end of the study.
   b. Macular nonperfusion at baseline improved visual acuity outcomes after anti-VEGF treatment at the end of the study.
   c. Macular nonperfusion at baseline had no effect on visual acuity outcomes after anti-VEGF treatment at the end of the study.
   d. Macular nonperfusion at baseline improved visual acuity outcomes after anti-VEGF treatment at the end of the study, but was not a factor in disease progression.
7. **Which of the following statements is true concerning OCT-A?**
   a. Images are presented in B-scans rather than in en face projection
   b. With the aid of contrast medium, the data are three-dimensional and depth resolved
   c. The ability to montage OCT-A is readily available
   d. It acquires functional, rather than structural, information with en face projections
8. **In the DAVE study comparing prn ranibizumab to prn ranibizumab plus targeted widefield laser for DME in 40 patients, adding _____**
   a. peripheral targeted laser substantially reduced the number of necessary ranibizumab injections
   b. peripheral targeted laser substantially increased the number of necessary ranibizumab injections
   c. peripheral targeted laser had no substantial effect on the number of necessary ranibizumab injections
   d. peripheral targeted laser decreased peripheral nonperfusion

ACTIVITY EVALUATION

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Assess the most recent monotherapy and combination therapy clinical study evidence using available anti-VEGF therapies for common retinal diseases, including DME	_____	_____	_____
Discuss the 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 DME, using anti-VEGF agents, as well as better understand when to change therapeutic strategies	_____	_____	_____

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).

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Comments regarding commercial bias:

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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.

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