AMD, RVO, & DME Update: Case Studies in Patient & Practice Management

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and decreased vision-related quality of life may be modified by treatment, including new modalities that provide practitioners with the flexibility of customizing management based on each patient’s needs. Focal macular laser photocoagulation (FML) has been the primary treatment for DME for more than 2 decades. The Early Treatment Diabetic Retinopathy Study (ETDRS) outcomes focused on the preservation of vision, finding a 50% reduction in the likelihood of severe vision loss with grid-style FML. In 2010, the Diabetic Retinopathy Clinical Research Network (DRCR.net) reported a 10-letter gain in nearly one-third of patients treated with a laser, but 19% of subjects experienced progressive visual loss. Emerging therapies have recently shown promise, both as adjunctive and possibly first-line alternatives to laser therapy. Several pharmaceutical therapies for DME are currently in clinical development, the majority of which are intravitreally injected anti-inflammatory or anti-angiogenic agents. These include VEGF inhibitors, such as ranibizumab (Lucentis, Genentech), aflibercept (VEGF Trap-Eye, Regeneron) and pegaptanib sodium (Macugen, OSI Eyetech), and intravitreal delivery systems, which release corticosteroids, such as fluocinolone acetonide (Iluvien, Alimera), dexamethasone (Ozurdex, Allergan), and triamcinolone acetonide (I-vation SurModics).

A full knowledge of the dynamics of retinal therapeutic treatment options will be beneficial for arming both specialists and general ophthalmologists who use these drugs with a more complete understanding when counseling patients and initiating treatment. It is expected that providing this education would remove a potential barrier to greater acceptance of this area of disease management. Finally, in the interest of providing more complete care to patients, arming clinicians with current insight into the management strategies for retinal therapeutics may assist in the reduction of treatment complications and prevent further loss of vision.

STATEMENT OF NEED
The impact of vision loss due to macular degeneration and ocular manifestations of diabetes is a major public health burden facing our society, given the large aging population at risk for sight-threatening ocular conditions. Significant challenges lie ahead in addressing the needs of patients at risk for vision loss, as well as the impact on society that comes with an increasing population with impaired vision. Macular degeneration, retinal vein occlusion (RVO), and diabetic macular edema (DME) present related physiologic problems for retinal specialists and ophthalmologists in the management of these conditions. Given the coincident systemic disease associated with diabetic retinopathy, the present and predicted burden and health care impact is substantial.

According to the 2012 Vision Problems in the US Report from the Prevent Blindness America Foundation, diabetic retinopathy affects more than 7.6 million persons aged 40 years and older. This contributes significantly to the more than $50 billion in direct economic costs due to vision disorders in people aged 40 years and older.

As new therapies enter the market, therapeutic options and dosing strategies can be affected by the cost of treatment, which continues to be a major factor in treatment planning. Clinicians need to consider multiple options for therapy in order to properly gauge the right treatment plan for any given patient’s needs. More broadly, the American Diabetes Association confirms that more than 150 million people across the world are affected by diabetes. By 2025, that number will likely increase to 324 million, including 35% who are expected to develop diabetic retinopathy (DR). For nearly 20 years, diabetic retinopathy DR has been documented as the leading cause of blindness and decreased vision-related quality of life in working-age Americans.

DME frequently follows the onset of nonproliferative diabetic retinopathy, resulting from abnormal capillary permeability and associated leakage of fluid leakage into the tissue of the retina. In recent years, new understanding of the pathophysiology of DME has focused researchers on the involvement of intracellular hyperglycemia, which induces free radicals (oxidative stress), protein kinase C (PKC) activation, and formation of advanced glycation end products (AGE). This process results in hypoxia, ischemia, inflammation, and alteration of vitreomacular interface. Inflammation produces an increase in VEGF production, endothelial dysfunction, leukocyte adhesion, and PKC production. In fact, DR is now considered to be a state of low-grade inflammation.

When not treated properly, which is often the case, DME progresses to proliferative DR (PDR) and retinal neovascularization, hemorrhaging, and permanent loss of vision. Approximately 50% of untreated patients with PDR will become blind within 5 years of the initial diagnosis. Such outcomes can frequently be avoided, however. Both decreased vision and decreased vision-related quality of life may be modified by
LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

• Describe the current epidemiology of major retinal diseases, including AMD, RVO, and DME
• Assess clinical studies involving new approaches to treat DME
• Utilize expert case examples to differentiate between clinical study dosing protocols and alternative dosing schedules
• Interpret retinal imaging case examples describing the treatment of DME
• Explore the management of treatment complications and secondary therapies
• Educate patients on ophthalmic implications of systemic diabetes management
• Demonstrate optimized patient flow, inventory flow, and office efficiency

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.

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EPIDEMILOGY, UNMET NEEDS, AND EVALUATION/DIFFERENTIAL DIAGNOSIS

The clinical and research practice of the vitreoretinal surgeon has changed over the past decade, as retinal vascular diseases (diabetic macular edema [DME] and retinal vein occlusion [RVO]) and neovascular processes (age-related macular degeneration [AMD]) have become treatable and occupy much of our time. Based on National Eye Institute data, we can project that the advanced form of AMD affects 2.2 million individuals in the United States. While most AMD patients (85% to 90%) have the dry form of the disease, wet AMD affects 10% to 15% of the overall AMD population (220 000 to 330 000 individuals). The prevalence of AMD in the United States is expected to increase to nearly 3 million by 2020 (295 000 to 440 000 with wet AMD) as the baby boomer population ages.

Data from the peer-reviewed literature and the Centers for Disease Control and Prevention (CDC) demonstrate that the number of patients with diabetes is rising rapidly and consistently, mirroring the increasing rate of obesity in the Western world. There are approximately 29.1 million US adults with type I and type II diabetes, accounting for 9.3% of the population. Approximately 25% of these adults who have diabetes are not currently diagnosed. From 2005 to 2008, 4.2 million (28.5%) diabetics older than aged 40 years had diabetic retinopathy, and 655 000 (4.4%) had advanced diabetic retinopathy, including proliferative diabetic retinopathy (PDR) and clinically significant macular edema (CSME). The total cost of care for the disease (direct and indirect) in 2012 was estimated to be $245 billion. Only 50% to 75% of Americans with diabetes receive annual dilated eye exams, and nearly 1 in 3 cases of DME are undiagnosed.

Branch and central RVO (BRVO and CRVO, respectively) are common causes of retinal vascular disease. The Beaver Dam Study estimated the 15-year cumulative incidence of RVO at 2.3% in the population, with most of these (78%) being BRVO. These diseases affect males and females equally, with peak incidence occurring between the ages of 60 and 70 years.

People aged 65 years and older represented 12.4% of the population in the year 2000, and by 2009, there were 39.6 million people older than aged 65 years, representing 12.9% of the US population, or about 1 in every 8 Americans. That number is expected to grow to 19% of the population by 2030—to about 72.1 million, which is more than twice the number in 2000.

The high incidence and prevalence rate of these conditions has placed a new set of challenges on physicians who care for patients with these diseases, and it appears that we will continue to become more efficient at meeting the coming demand for our services. Prospective trial results demonstrate that frequent, fixed-dosing schedules return excellent outcomes for patients, but we often modify those treatment regimens with what we hope are similar outcomes. One should keep in mind Dr. Mant’s comments published in The Lancet that state the “paradox of the clinical trial is that it is the best way to assess whether an intervention works, but is arguably the worst way to assess who will benefit from it.”

Making the Diagnosis

With the high incidence and prevalence of AMD, RVO, and DME, appropriate screening is critical to identifying patients at risk of developing advanced disease. An annual examination by an experienced ophthalmologist is perhaps the most effective means of screening for retinal diseases. Modifiable risk factors including hypertension, hypercholesterolemia, obesity, and smoking should be attended to, but many risk factors, including age, family history, and race, cannot be changed.

A well-performed screening examination is critical, as the findings on that exam will determine in large part the risk of progressing to advanced disease, dictate the need for nutritional supplementation, and establish the frequency of follow-up. Patients with moderate pathology may benefit from examination by a retinal specialist, as subclinical disease is not uncommon, and can be missed without the high-resolution multimodal imaging utilized by retina physicians. Screening remains a challenge, and patient-initiated home screening devices may prove effective in identifying changes in visual function going forward.

Once a presumptive diagnosis of advanced retinal disease, such as AMD, DME, or RVO is made, the patient should be evaluated by a retinal specialist. Although an examination and optical coherence tomography (OCT) test can make a retinal vascular disease seem like a straightforward diagnosis, the nuances of the diseases make them a continuous challenge.

Working through these differential diagnoses is critical
and requires a multitude of imaging modalities that include spectral-domain OCT, fluorescein and indocyanine green angiography (FA and ICG, respectively), and autofluorescence imaging.

Utilization of these imaging modalities is critical not just to properly diagnose the disease but also to help identify subtypes of these conditions that respond to a particular treatment modality. Recognizing and responding to these nuanced differences in presentation and subtypes is critical for maximizing patient outcomes with these diseases.

— Jonathan L. Prenner, MD

EVIDENCED-BASED CARE

Jonathan L. Prenner, MD: Dr. Regillo, can you review some of the level 1 evidence from the trials of ranibizumab (Lucentis, Genentech) and aflibercept for these conditions? What are the key features of the topline data that you use to drive your clinical decision making?

Carl Regillo, MD: I like to compare and contrast the 3 diseases, because what we do in practice with the anti-VEGF treatments is similar during the induction phase among these conditions, but it may be very different thereafter in the maintenance phase of therapy.

Our first large-scale prospective studies on patients with wet AMD examined the safety and efficacy of intravitreal pan-VEGF-A blockers, on-label ranibizumab and aflibercept, and off-label bevacizumab (Avastin, Genentech). For ranibizumab, we have the pivotal phase III trials, MARINA and ANCHOR, that showed ranibizumab to be far superior to the standard of care at the time being either observation or photodynamic therapy.9-13 The CATT and IVAN studies for bevacizumab indicated comparable efficacy of bevacizumab to ranibizumab with monthly dosing.14-16 Finally, with aflibercept, there are the VIEW studies that showed the equivalency of aflibercept dosed either every 4 or 8 weeks during the maintenance phase of therapy compared with ranibizumab dosed every 4 weeks.17

From the very beginning, when these drugs first became available to treat wet AMD, there have been attempts to reduce the treatment burden in practice by individualizing anti-VEGF therapy. With the CATT and IVAN studies showing as-needed (PRN) regimens did not measure up to monthly injections in terms of the degree of visual gain after 2 years of treatment, there has been a shift both in the United States and elsewhere to adopt the treat-and-extend (TAE) style of therapy.18 There are emerging data, both retrospective and prospective, to suggest that the visual gains with the TAE approach are well maintained for up to 3 years.19 That being said, at this time we do not really know what the best anti-VEGF regimen is for managing wet AMD in the long term. Ongoing studies will help to guide us in the future in this regard. For the time being, we know that early detection of wet AMD and effectively suppressing signs of exudation help to obtain the best visual outcomes, regardless of the treatment algorithm utilized.

For RVO-related macular edema, we have the phase III BRAVO and CRUISE studies for ranibizumab to treat BRVO and CRVO, respectively,20 the COPERNICUS21 and GALILEO22 studies for aflibercept in CRVO, and the VIBRANT study for aflibercept in BRVO.23 There are steroid studies as well: SCORE with triamcinolone24 and the dexamethasone intravitreall implant 0.7 mg (Ozurdex, Allergan) phase III trial25 that led to the approval of the implant for treating both BRVO and CRVO.

The anti-VEGF RVO studies are all fairly similar in their overall design and patient populations; initially, they all show a mean visual acuity improvement of around 2 lines with fixed monthly dosing within the first 6 months. But we also know that time frame is very limited. Natural history studies and anecdotal experience indicate that some RVO and the associated edema improve over time without any medical intervention. That means that some patients with RVO may not need ongoing treatment for the edema.

With DME, there is also level 1 evidence with prospective randomized clinical studies: RIDE and RISE for ranibizumab,26-28 and DaVinci, VIVID, and VISTA for aflibercept.29-32 As with RVO, there are also steroid studies: MEAD for the dexamethasone implant, and FAME for the fluocinolone implant.33 All of these studies led to their respective product FDA approval.

For anti-VEGF therapy, RIDE/RISE26 found a mean visual acuity improvement of about 11 to 12 letters with the 2 doses of ranibizumab (0.3 mg and 0.5 mg) at month 24 (primary endpoint), and showed a continued effect through month 36. That study also showed an improvement in the level of diabetic retinopathy, so there may be some favorable disease-altering retinopathy that occurs with frequent exposure to anti-VEGF therapy in this setting. These studies also confirmed that late introduction of the anti-VEGF treatment did not yield visual results equal to earlier treatment, even though the macula was comparably dry.

The take-home point is that a delay in therapy by 1 or 2 years is not likely to yield visual results as positive as if treatment were initiated early on. The VIVID and VISTA studies showed a very similar magnitude of effect to the RIDE/RISE studies. With aflibercept, there were similar mean visual acuity improvements, and about 30% or so of eyes improved a mean of 2 or more steps in the level of DR.

With all these DME studies, the visual acuity improvement tends to be a little slower if we analyze the slope of the mean visual acuity change over time.26,29 What can be extrapolated from that, of course, is that there will be patients with center-involving DME who respond slowly to anti-VEGF therapy, in contrast to the slope of the mean VA curves in both the RVO and the wet AMD studies.

The DRCR.net Protocol I provided very useful information about the need of anti-VEGF therapy to treat DME over time with an individualized (PRN) approach to therapy. In year 1, the mean number of treatments for the ranibizumab groups was 7 to 8, and the visual results were comparable with the pivotal studies using monthly...
therapy. Furthermore, in years 2 and 3, there was a drop-off in the mean number of treatments, which suggests that the need for anti-VEGF therapy decreases significantly over time, unlike most cases of AMD and RVO. By year 3, the mean number of injections had been reduced to 2 to 3, with many patients coming off treatment. Similarly, in the RIDE and RISE extension trial in which patients received ranibizumab on a PRN basis, about 25% of patients who were treated for 36 months did not receive further injections going forward.

Dr. Prenner: What are 3 take-home messages from the DME registration trials that help drive your evidence-based care?

Dr. Regillo: First, frequent and regular injections benefit most patients over time, but the effect is quite variable. Second, some patients can ultimately come off therapy and maintain the improvement (visual gains, macular status, and diabetic retinopathy level of improvement) they received during treatment. Finally, aflibercept and ranibizumab were evaluated in a large, prospective fashion, achieved comparable results, and have a very good safety profile in a group of patients that may be at increased risk for systemic events.

Chirag P. Shah, MD, MPH: We are currently awaiting published results from the DRCR.net Protocol T, the head-to-head-to-head comparison of aflibercept, ranibizumab, and bevacizumab for DME. Until that time, however, do DME patients need to be treated until they are totally dry, like our AMD patients?

Dr. Regillo: Based on the differences in the diseases, the answer is no. Even in the DME studies, patients were not treated until they were dry. It was possible to have a small amount of thickening that did not meet the criteria for re-injection in the PRN studies. In practice, patients can do well and see very well for very long time frames with slight edema. Most of these studies had minimum vision for entry into the study at 20/40 or worse, and so they excluded patients with very mild levels of center-involving edema, otherwise CSME.

Anecdotally, we know that eyes with small amounts of center-involving edema can do very well without treatment. Wet AMD is a different scenario, because you are dealing with the potential choroidal neovascularization growth and destruction with associated vision loss that you may not be able to recover.

OPTIMIZING PRACTICE PERFORMANCE

Dr. Prenner: Let us shift our focus to hypothetical patient scenarios and how we optimize our own practice performance. If a patient presents with typical CSME and nonproliferative diabetic retinopathy, what is your standard workup?

Dr. Shah: My first patient visit includes a significant amount of chair time, depending on the degree of edema. We discuss his or her glycemic control and disease history. We will review their prescribed medications to ensure that he or she is not on a glitazone, as that class of drugs can contribute to diabetic edema. If the patient is on a glitazone, I will ask him or her about pedal edema or pulmonary edema, which can be associated with these drugs.

After assessing the patient history and performing an examination, I will typically check an OCT, which my team often orders before I evaluate the patient. If there is CSME, I will get an FA to see the status of the patient’s macular perfusion. In our office, we use the Optos wide-angle FA, which allows me to see proliferation or nonperfusion in the periphery that I might not have appreciated clinically. I try to assess the degree of foveal nonperfusion to determine how much visual acuity compromise is related to ischemia versus macular edema.

If there is reasonable perfusion, I may start the patient on an anti-VEGF medication and have him or her return the next month and continue to treat and look for signs of visual improvement. If the patient just has a pocket of CSME is that is not center-involving, but still within a disc diameter from the fovea and may be amenable to one-time focal laser, I will consider laser as a first-line treatment.

Dr. Prenner: Does that mean you concentrate first on the patient’s overall metabolic control and how his or her current systemic disease is being managed?

Dr. Shah: Yes, and tobacco status.

Dr. Prenner: Attending to the patient’s renal function may be helpful in this scenario as well. Dr. Elliott, how would you proceed with this hypothetical patient? What else do you take into consideration to form your therapeutic plan for this person?

Dr. Eliott, MD: Anti-VEGF therapy is the standard of care for almost all patients with DME. Rarely, I will use laser or vitrectomy as a first-line treatment. If there is circinate lipid surrounding one or more microaneurysms, with thickening that is close to the fovea or involves the fovea, then I will perform focal laser to the microaneurysms (assuming that the microaneurysms are outside of the foveal avascular zone). If the OCT shows a posterior hyloid that is taut and broad (which is uncommon), a concomitant epiretinal membrane (ERM) that is significant, or prominent focal vitreomacular traction, then I will consider vitrectomy surgery.

PATIENTS WITH VITREOMACULAR TRACTION

Dr. Prenner: How do you treat the patient when there is a component of vitreomacular traction (VMT), be it ERM or true VMT? Do you attempt a pharmacologic approach first, either with anti-VEGF or steroid, and withhold surgery until
A 52-year-old man with an 8-year history of type 2 diabetes presents complaining of slowly progressive visual loss in the left eye during the past year. Visual acuity in his right eye was 20/30 and in his left eye was 20/200. Figure 1 is a fundus image of the left eye, which clearly shows vascular changes next to the fovea, and a yellow discoloration of the central macula. The fluorescein angiogram shows some late leakage at the fovea and the area adjacent to the fovea. The optical coherence tomography (OCT) seen in Figure 2 shows posterior hyaloid traction; the patient was diagnosed with tractional DME.

He underwent vitrectomy, but he did not have an internal limiting membrane peel. Fundus imaging confirmed resolution of the macular findings and the pre- and postoperative OCT confirmed resolution of the macular edema (Figures 3 and 4). On OCT, the foveal depression is wider than normal but without thickening. Visual acuity improved to 20/50.

RATIONALE FOR VITRECTOMY
In this patient, vitreous traction drove the decision toward vitrectomy. This patient had mostly anteroposterior traction. Vitrectomy is also indicated for the removal of cytokines and to increase the vitreous cavity is oxygen tension.

The Diabetic Retinopathy Clinical Research Network conducted a large prospective study in eyes with diabetic macular edema and vitreomacular traction (N=87). In that study, preoperative visual acuity ranged from 20/63 to 20/400, and OCT measured greater than 300 μm. There was no control group in this nonrandomized study. It was also nonstandardized, meaning each surgeon could perform additional procedures if necessary.

Epiretinal membrane peeling was performed in 61% of patients, ILM peeling was performed in 54%, panretinal photocoagulation in 40%, and intravitreal steroids were injected in 64% of subjects.

The 6-month results showed that the median OCT thickness decreased by 160 μm, and 68% of patients had greater than a 50% reduction in foveal thickness. Visual acuity improved 10 or more letters in 38% of patients, but decreased 10 or more letters in 22% of patients.

For eyes with DME and vitreomacular traction, vitrectomy is sometimes indicated. This consists of complete vitreous removal, posterior hyaloid elevation and removal, and it may or may not include an ILM peel.
TRACTIONAL DIABETIC MACULAR EDEMA (Continued)

Favorable anatomic outcomes as a result of removing foveal traction are possible in many cases. On average, vitrectomy can result in a 100- to 250-μm reduction in thickening, or an improvement of at least 50%. Visual acuity improvements are more limited, however, with some patients improving a line or 2, whereas others may worsen.

We typically reserve vitrectomy for refractory cases that have long-standing edema and possibly irreversible macular damage, and that may account for the limited visual results.

In this case, however, we had a positive outcome with anatomic resolution and visual acuity improvement from 20/200 to 20/50.


you have determined that there is a suboptimal response? Do you manage those people differently or observe them differently after you inject them?

Dr. Regillo: Typically, I will presume that office-based anti-VEGF therapy will help, and I reserve surgery for eyes that do not respond adequately. It is often not possible to know at presentation whether it is the VMT or the retinal vascular disease that is causing the leakage and swelling.

More often than not, the vitreomacular adhesion is incidental and noncontributory, and anti-VEGF therapy alone will work well. Furthermore, if I jump into surgery too soon and realize later that the vitreoretinal interface disorder detected by OCT was not a major component of the edema, then I may compromise the duration of action of the pharmacotherapy with a vitrectomized eye.

But Dr. Elliott is right—if it is obviously VMT and not really DME at all, you can proceed sooner rather than later. For most of those patients with some vitreoretinal interface disorder, it is often secondary. I have found this particularly true in the more chronic ME scenarios in which ERM eventually forms.

Dr. Prenner: If after 4 to 5 weeks I have yet to see an anti-VEGF effect, I will bring the patient back 2 weeks after the injection to repeat the examination and OCT. At that point, I will determine if there is an interval change that we may have missed because of the initial 4- to 5-week observation interval. If there is no biologic effect, then I will consider surgery.

Dr. Regillo: Dr. Shah brought up the wide-field FA, which we do not routinely perform because we do not yet have the capability. We obtain peripheral sweeps, but I am sure that is not as good as the wide-field technique to image the far peripheral retina. The question is whether any additional findings change the management in any way.

Dr. Shah: We use wide-field FA mostly for further assessment of the patient’s degree of nonperfusion, and that can sometimes improve with anti-VEGF therapy.

Dr. Regillo: I think angiography serves a great purpose. It is not uncommon for an eye to appear to have a relatively mild level of retinopathy by ophthalmoscopy and then find more advanced disease on angiography that prompts closer follow-up.

PATIENTS WITH EDEMA ON CLINICAL EXAMINATION

Dr. Prenner: Dr. Elliott, when someone presents with edema on clinical examination, do you look for the presence of CSME as defined in the ETDRS study as the trigger point for intervention, or do you use another metric? Do the level or location of edema seen on OCT and examination determine the need for treatment? Do you treat if patients do not have CSME on examination but have edema on OCT?

Dr. Elliott: I usually treat patients who have the standard definition of CSME, and I rely on OCT to confirm my examination findings. In some cases, OCT detects subtle thickening that was missed on exam, and I may treat or observe these patients. If I have a patient who does not meet the definition of CSME (such as a small area of thickening that is more than 500 μm from the fovea), then I do not typically treat.

Dr. Prenner: Many diabetic patients have some abnormality on OCT that could be used as evidence for initiating therapy. Is all OCT-based thickening clinically meaningful? How much central subfield thickening is problematic? Does the presence of intraretinal cystic change demand intervention?

Dr. Shah: I tend to individualize treatment. If during routine screening there are no symptoms, visual acuity is 20/20 or 20/25, and the patient is happy, I will use the OCT as a counseling guide. I show patients where they are beginning to have edema and start a discussion on what we can modify: medications, glycemic control, hypertension control, smoking status, etc. I hope to motivate patients to take better care of their own glycemic control, and I ensure we set a schedule of regular visits for comparative OCTs and examinations. Once there is worsening, it is easier for patients to accept that they might need long-term retinal treatment for their ME and DR.

If a patient is asymptomatic, has mild edema, and has good vision, I tend not to treat. As soon as the situation starts worsening, or if feel vision is being threatened, I will treat. We know it is harder to turn things around after the edema has become
A 66-year-old man presented with a 22-year history of reasonably well-controlled diabetes (A1c that ranges in the low 7s). He has some background diabetic retinopathy, he is pseudophakic in both eyes, and he has had fairly recalcitrant DME. The eye has very good profusion, no traction, and what I think is straightforward DME, yet I cannot get the fluid to dissipate. The patient has been treated with everything from focal laser, to antivascular endothelial growth factor therapy with ranibizumab (Lucentis, Genentech), bevacizumab (Avastin, Genentech), and triamcinolone (Triescence, Alcon), yet he remained recalcitrant.

Figure 1 shows the OCT of his right eye. This image was taken after 6 ranibizumab injections, 3 triamcinolone injections, and treatment with 2 focal lasers over the course of approximately 2 years. His visual acuity was 20/60. Figure 2 shows the OCT of the patient’s left eye. His visual acuity was 20/50, and he had received 7 ranibizumab injections, 5 bevacizumab injections, and treatment with 2 focal laser treatments, and I still could not get the cysts to resolve.

About this time, aflibercept (Eylea, Regeneron) received US approval for DME, so we were keen to try it. Following 2 injections of aflibercept, the patient had significant resolution of fluid, as shown in Figure 3A-B. His visual acuity remained 20/60 in his right eye, but considering the duration of edema and the likelihood of photoreceptor compromise, I was not surprised. The anatomic improvement more than made up for the lack of visual acuity improvement.

In his left eye, after 2 intravitreal aflibercept injections, his visual acuity improved to 20/40, and the patient noticed the improvement immediately.

In our clinical practice, we have switched several nonresponders to other therapies, including aflibercept. I have seen a very nice reduction of approximately 75% of the excess fluid with early intervention with aflibercept.

This patient remains a “to-be-continued” case, but had a very nice initial clinical response.

Figure 1. OCT of recalcitrant macular edema in the patient’s right eye.

Figure 2. OCT of recalcitrant macular edema in the patient’s left eye.

Figure 3A-B. The left eye (A) and right eye (B) show vast anatomic improvement of the edema after injection with aflibercept, although visual acuity did not improve.
more florid, but there is a balance between a patient’s visual functioning and the potential risks of treatment.

**Dr. Regillo:** There is no urgency to treat very small amounts of edema. We have the ability to recover a good anatomic and visual status if the edema worsens, as long as the patient is reliable with follow-up. SD-OCT is better than an examination in picking up small amounts of retinal thickening, but that does not mean that all DME needs treatment—even mild DME that involves the foveal center.

**PATIENTS WITH CLINICALLY SUBTLE EDEMA**

**Dr. Prenner:** I wonder if we should treat patients who have thickening identified by SD-OCT that we cannot visualize clinically? Maybe. This disease is nuanced, it is subtle, and although OCT gives us multimodal images of people at various stages of their disease, individualizing therapy is the key for optimizing patient outcomes.

**Dr. Eliott:** These are good points. It is not a flow chart in which, if this is present, then do that; if this is present, then do that. It is much more complicated than that.

**Dr. Prenner:** Dr. Eliott, if a patient also has concomitant, high-risk, proliferative DR, how do you time the sequence of using your anti-VEGF with using panretinal photocoagulation (PRP)?

**Dr. Eliott:** I will start with an anti-VEGF injection, because not only does that improve the ME, but it also often has some effect on the proliferative diabetic retinopathy. The number of injections I give before performing PRP depends on the severity of the condition. It may be a single injection or it may be several.

**Dr. Prenner:** How do you place PRP—do you treat in 1 session or over the course of several sessions?

**Dr. Eliott:** I tailor it. In cases of very mild, high-risk proliferative diabetic retinopathy, I will do 1 session and observe closely. If there is more significant disease, I will do a more thorough PRP and bring the patient back for close observation and possible additional PRP. In the most severe cases, I will perform a very thorough PRP and then an additional 1 or 2 sessions of PRP within a few weeks. I believe that nobody has ever gone blind from too much PRP, but many, many people with very severe PDR have gone blind from not enough PRP.

**Dr. Regillo:** The people who have mild disease often respond to 1 session with 800 to 1200 spots. I do not want to give these patients wall-to-wall PRP when they do not need it. Other patients with very significant disease do not respond to 1 session, while they may respond after 2 or 3 sessions with much more extensive PRP.

**PATIENTS AT HIGH RISK OF PDR AND TRACTIONAL RETINAL DETACHMENT**

**Dr. Prenner:** Dr. Regillo, how do you treat that same patient if he or she now has both high-risk PDR and a component of tractional retinal detachment (TRD)? Does that influence your use of anti-VEGF? Would you think about laser or steroids in the face of detachment?

**Dr. Regillo:** It is a consideration. There is no absolute contraindication to the use of an anti-VEGF agent, even with TRD. Most TRDs will not progress significantly after an anti-VEGF injection, but there is that potential. With a relatively large, broad-based TRD that is threatening the macula, I am more reluctant; if I do feel compelled to use the drug in this setting, then I prepare the patient for the possibility of undergoing surgery sooner rather than later, if the TRD progresses after injection.

Fortunately, significant TRD progression after anti-VEGF therapy is pretty rare, more often talked about than experienced. This phenomenon can also occur after PRP, but again very rarely. Anytime there is significant and relatively rapid regression of neovascularization, we can inadvertently increase rather than stabilize that traction.

**Dr. Eliott:** I would like to assess the fibrovascular membranes that are exerting the traction. If it is a chronic detachment with mostly fibrous membranes, then I do not think it is likely that the membranes are going to contract and result in progressive traction. But if the membranes are more neovascular, then I watch the patient very closely because the tissue is more likely to contract and exert more traction.

**Dr. Regillo:** Agreed—the more cicatricial the fibrovascular proliferation, the less likely it is to contract.

**Dr. Prenner:** I tend to treat with the laser first and delay consideration of my patients’ CSME until I am confident that I have dealt with some component of the ischemia. We are all aware of anecdotal reports of TRD progression to combined rhegmatogenous retinal detachment/TRD after anti-VEGF therapy, but these are generally in eyes not treated with lasers.

**Dr. Regillo:** Panretinal laser is less likely to exacerbate CSME if you are just targeting the areas of nonperfusion, or you can place the scatter laser spots more peripherally. As Dr. Eliott put it, tailor the amount of PRP for the level of PDR, and you are less likely to run into trouble.
A 77-year-old man presented with blurred vision to 20/40 in his left eye from clinically significant macular edema (CSME). Figure 1 highlights his bilateral parafocal microaneurysms, which were more pronounced in the left eye. Fluorescein angiography of the left eye (Figure 2) confirmed the presence of leaking microaneurysms centered supranasal to the fovea. OCT showed minimal thickening in the right macula, but identifies foveal-involving macular edema and subfoveal fluid in the left eye (Figure 3).

The patient was extremely averse to needles, and he also had difficulty returning to the office for regular visits. Thus, we decided to proceed with the focal laser.

On month after the focal laser treatment, the patient’s visual acuity improved to 20/30 with near resolution of his macular edema (Figure 4). His macular edema resolved completely at 3 months. At his last follow-up, 1.5 years after his single focal laser treatment, the patient proved to have a sustained response with 20/25 vision and no macular edema.
use a PRN style of therapy in DME to more easily determine if and when a patient may be able to stop treatment. That being said, it may take 2 or 3 years of anti-VEGF injections on a frequent and regular basis before that is possible.

Dr. Prenner: What do you tell the patient? If it is so highly personalized, what kind of generalizations can we make?

Dr. Eliott: I will tell the patient that he or she is going to have 3 injections, and we will reassess when those are complete. Although some patients may not need additional injections, it is extremely likely that they will need more, and they may even need monthly injections for a long time.

Dr. Prenner: Does anyone add laser treatment routinely after anti-VEGF treatment?

Dr. Eliott: I inform patients that there are other options besides anti-VEGF injections, including laser, steroids, or surgery. For the vast majority of patients, it is just anti-VEGF therapy. However, if the edema is not responding after approximately 6 injections, or if there are microaneurysms on FA, then I will consider the other options.

Dr. Prenner: Achieving the best possible patient outcome requires angiography and expert interpretation of those FAs. We do try to make retinal vascular and neovascular diseases simple by focusing exclusively on OCT to determine treatment, but they are not. Abstaining from angiography may leave physicians with too little information to make the best possible decisions.

Dr. Regillo: It is worth repeating that wet AMD management is essentially anti-VEGF monotherapy. RVO is anti-VEGF therapy for the most part at first, possibly steroids, and very rarely grid laser in the setting of BRVO. Similarly, DME has multiple proven treatment modalities that may also include vitrectomy. I tell patients there is the possibility that we might need additional types of treatment beyond anti-VEGF, and that could include steroid injections and laser. All 3 treatments are potentially in the mix for any given patient.

Dr. Prenner: For younger patients, it is often hard to emotionally manage the news that they may need treatment via a process that sounds terribly invasive and may require repeated doses over long periods of time. Dr. Regillo comfort patients by telling them it is a lot of work, but eventually they are likely to reduce the number of injections and probably will not have to be doing this type of “invasive” work forever.

We now have data from the ranibizumab extension studies that show there is real disease modification after 24 and 36 months of anti-VEGF therapy.26-28 So, the progression of the DR is clearly benefitting from and being inhibited by continued therapy. My suspicion is we will see the same benefit once the aflibercept long-term data are analyzed.

Dr. Regillo: It is a lot to throw at a patient. I tell him or her that it is a learning process and that as we continue treatment, we will have a better handle on how he or she is responding. If you put too much on the patient’s plate from the beginning, it can be a bit overwhelming. Sometimes we serve as a wakeup call to prompt the patient to pursue better metabolic control. Other times, we can scare him or her away. So I try to keep it simple at first and with every visit, add to the knowledge base for the patient.

ANTI-VEGF SAFETY ISSUES

Dr. Prenner: Are you worried about the safety of anti-VEGF therapy? None of the registration studies are really powered to teach us about safety events in this vasculopathic population.

Dr. Shah: Yes, I am worried about safety, especially in patients who are known to be vasculopathic. We know from the AMD literature that there is a suggestion that anti-VEGF therapy does increase Anti-Platelet Trialists’ Collaboration (APTC) events compared with placebo.9-12 An AMD population tends to be an older population than diabetics. The RIDE and RISE studies did not find an elevated risk of APTC events for ranibizumab. However, I think we need more data to determine if there are increased risks in a potentially vasculopathic DME population. It is definitely a concern, and a main reason I try to get the best vision possible as quickly as I am able.

Dr. Prenner: Does that influence your choice of drug?

Dr. Shah: No. When Protocol T is published, there might be differences in adverse events among the 3 drugs, but at present, there does not seem to be.

Dr. Prenner: My sense is that Protocol T will not be powered to demonstrate safety in a statistically significant way. However, there have been some intellectually interesting discussions about safety of the 3 drugs, and data from Protocol T may lead to additional debate.

Dr. Regillo: For now, safety concerns do not influence my drug choice. What we know from the studies is that if there is any difference in the drugs, it is really small, it occurs very infrequently, and certainly occurs at an acceptably low level. In certain high-risk patients (prior stroke, substantial concomitant diseases), it may influence the use of one anti-VEGF over another.

With DME, you are not often compelled to be giving these injections very frequently over a very long time frame. We can back off or watch and wait with treatment to minimize exposure. We can use lower doses, although we are already using the lower dose of ranibizumab at 0.3 mg for DME.38

Dr. Prenner: One caveat about anti-VEGF agents in general: the biggest risk that I am worried about is how I source my drug. Having a well-run and vetted compounding
pharmacy from which to get bevacizumab can be an issue. As a result, I tend to use branded drugs rather than using bevacizumab, but this is not because of systemic safety concerns. It is mostly because of the additional risk of having another step in the process, the compounding pharmacy.

**PRACTICAL CONSIDERATIONS**

**Dr. Prenner:** Once you have decided on using an anti-VEGF for a DME patient, what is the next step? How do you consider the financial component in terms of the patient responsibility? Do you use a benefits investigation vehicle?

**Dr. Regillo:** With all these diseases, I am going to use the least amount of drug possible to get the objective accomplished. That alone is 1 way to minimize the total cost of treatment. For a given patient, when the decision is made to use an anti-VEGF drug, we will launch a benefits investigation. We may or may not know the result on the spot. I usually like to treat at first encounter, especially for more severe disease, rather than wait and bring the patient back into the office. We will determine if the patient is fully covered by insurance, and if there is a large copay, we will take it a step further and submit applications for copay assistance programs. Within a month or so, we are usually able to get most patients adequately covered for whatever drug we want to use. Patients understand that their choice of drug may incur some out-of-pocket expense and they know that bevacizumab is an off-label option. Ironically, sometimes there is more patient out-of-pocket expense for bevacizumab than the on-label drugs.

**Dr. Prenner:** There are facilities capable of determining what a patient’s particular exposure would be financially for receiving 1 of these drugs, and there is often times available foundation support for many patients who are either uninsured or underinsured. Both Regeneron and Genentech offer copay card systems to help offset the out-of-pocket cost of the medications. For some patients, even $50 a month can become a real issue.

**Dr. Shah:** We have a fair amount of overhead when it comes to these very expensive drugs, and especially now that patients need a prescription for bevacizumab. We have hired extra personnel to keep everything organized and ensure we are billing the insurance companies for the drugs we are using. If we miss even 1 injection, it is a big financial burden for our practice.

**Dr. Regillo:** This is a large, expensive infrastructure with significant direct and indirect costs. When people look at the cost, they often do not consider everything involved, including time of their clinic personnel and the rent for the space to administer the injections, among other costs. There is a large number of people in our practice now who were not there 10 years ago, solely because we need to keep track of patient benefits and drug reimbursement. The bottom line is that it costs a lot to inject these drugs, more than most people realize.

**Dr. Prenner:** The profits associated with intravitreal injection are unfortunately somewhat modest because of the high infrastructure costs required to effectively use branded medications. These include maintaining a staff and having an electronic inventory management system, both solely dedicated to managing the use of branded drugs. We also have a loss rate in terms of collecting on each vial of drug given, and those losses add up and quickly erode any associated profits.

**Dr. Regillo:** Moving forward, we are going to have more and more branded products. As a practice, we want to be able to offer everything available to patients, which means we need to have this infrastructure in place and be efficient.

**Dr. Prenner:** As our reimbursements per injection decrease, our efficiencies in our back offices must increase.

**Dr. Regillo:** You are alluding to the studies suggesting there may be no net profit—and possibly even a loss—even when the margin is 4.3%. So there is not as much there at the end of the day as people may think.

**Dr. Prenner:** There is a tremendous nuance to delivering this care at the highest level that requires a retina specialist. I also think delivering it in a cost-effective way in which you are not losing money requires a group of people who have a dedicated infrastructure and are doing many things to make it work. Otherwise, I think it is going to be hard to offer these expensive drugs without taking on a loss.

**PLANNING FOR THE FUTURE**

**Dr. Prenner:** Dr. Eliott, you have been caring for diabetic patients for 2 decades. You have had extensive experience managing many of the worst cases of DME. How do you see the world unfolding for diabetic patient care in the next couple of years?

**Dr. Eliott:** We have witnessed nothing short of a revolution in the treatment of patients with angiogenic diseases such as AMD, RVO, and DME. With respect to diabetes, we have medical management, we have laser, we have anti-VEGF drugs, we have steroids, and we have learned more about surgery for this condition. Today we have discussed many of the nuances of managing patients with this challenging condition.

In the future, we will probably have even more anti-VEGF agents, and we will likely have new classes of drugs, such as iCO-007 (iCo Therapeutics), which offers a different mechanism of action than bevacizumab, ranibizumab, and aflibercept. The dexamethasone intravitreal implant 0.7-mg sustained-release device delivers steroids for several months and is currently available for use, while the fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera...
AMD, RVO, & DME Update: Case Studies in Patient & Practice Management

Dr. Regillo: Our nonophthalmic colleagues who manage patients with diabetes mellitus also have better treatments for systemic management. During the past 2 decades, I have noticed trends for better blood glucose control with A1c levels decreasing in patients. Years ago, it was not uncommon for patients to mention an A1c value of 10% or more, if they knew it at all. But now, it is much more common to hear levels of 7 or better.

Dr. Prenner: Medical education and treatment for general diabetes care is indeed much better, but that comes in the face of a huge onslaught of disease that is heading our way.

Dr. Shah: And increasing rates of obesity.

Dr. Eliott: More patients will have diabetes due to poor lifestyle decisions, but there are now options for the more severe cases that did not exist in the past. Even within ophthalmology, it was common for us to tell patients 15 years ago that there was nothing we could do to save their vision. In the past, it was difficult to deliver that news to patients, and as a doctor, you felt helpless. We are fortunate that we do not have to say that very often these days.

Dr. Prenner: With the aging AMD population and the dramatic growth of the diabetic population, we need all of the options in our therapeutic armamentarium to give our patients the best possible experience and outcomes. Research and development in our space has been and will continue to be robust, and will help to combat the treatment burden and unmet need still ripe for further advances in the treatment of retinal disease.

Dr. Regillo: I am not sure we will see the same degree or rate of progress we have witnessed over the past 10 years or so, but the future is still bright for further advances in the management of these diseases.


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CME QUESTIONS

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1. In 2020, the prevalence of AMD in the United States is expected to reach:
   a. 0.3 million
   b. 1.4 million
   c. 3.0 million
   d. 5.2 million

2. Clinical studies have clearly defined the best anti-VEGF regimen for managing wet AMD in the long term.
   a. True
   b. False

3. Which of the following is true regarding the evaluation of aflibercept and ranibizumab in DME registration trials?
   a. Both achieved comparable results
   b. Both were evaluated in a large, retrospective fashion
   c. Only aflibercept had a good safety profile in patients at increased risk for systemic events
   d. None of the above

4. Surgery should be considered a priority in patients with a component of vitreomacular traction.
   a. True
   b. False

5. Data from the ranibizumab extension studies have found which of the following regarding diabetic retinopathy?
   a. Disease modification after 6 and 18 months of anti-VEGF therapy
   b. Disease modification after 24 and 36 months of anti-VEGF therapy
   c. Disease modification after 48 and 72 months of anti-VEGF therapy
   d. Disease progression after 36 months of anti-VEGF therapy

6. To minimize exposure in DME patients who are high-risk, which of the following should be considered?
   a. Decrease frequency of injection
   b. Lower the dosage used
   c. Reduce the total length of treatment time
   d. All of the above

7. The first step in managing the ophthalmic implications of diabetes should be to:
   a. Discuss glycemic control with the patient and review medications
   b. Start on an anti-VEGF therapy immediately
   c. Wait 2 months and re-evaluate; if disease progresses, consider treatment
   d. Discuss a 1-time focal laser treatment with the patient

8. With respect to DME treatment, which of the following is true?
   a. DME should only be treated if it affects vision
   b. DME should be treated urgently, even if minor, to prevent progression
   c. DME should only be treated if progressing over a 6-month time period
   d. Therapy should be individualized to optimize patient outcomes
### ACTIVITY EVALUATION

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<th>Did the program meet the following educational objectives?</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
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<td>Describe the current epidemiology of major retinal diseases, including AMD, RVO, and DME</td>
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<td>Assess clinical studies involving new approaches to treat DME</td>
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<td>Use expert case examples to differentiate between clinical study dosing protocols and alternative dosing schedules</td>
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<td>Interpret retinal imaging case examples describing the treatment of DME</td>
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<td>Explore the management of treatment complications and secondary therapies</td>
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<td>Educate patients on ophthalmic implications of systemic diabetes management</td>
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<td>Demonstrate optimized patient flow, inventory flow, and office efficiency</td>
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