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CME Activity

Understanding Long-Term Response Rates and Treatment Dilemmas in Diabetic Macular Edema

Antonio Capone Jr, MD, moderator
David M. Brown, MD
Jorge A. Fortun, MD
Adam T. Gerstenblith, MD

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TARGET AUDIENCE

The target audience for this program is retina specialists.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- Recognize the importance of early diagnosis and treatment of diabetic macular edema
- Assess the response of anti-VEGF intravitreal injections for diabetic macular edema
- Discuss the current and potential future therapies to treat patients with diabetic macular edema who do not respond in a timely fashion to initial treatments
- Formulate strategies to best treat diabetic macular edema using a multimodal approach

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FACULTY CREDENTIALS

Antonio Capone Jr, MD
Associated Retinal Consultants
Royal Oak, Michigan

David M. Brown, MD
Retina Consultants of Houston
Houston, Texas

Jorge A. Fortun, MD
Bascom Palmer Eye Institute
Miami, Florida

Adam T. Gerstenblith, MD
Mid Atlantic Retina Specialists
Hagerstown, Maryland

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Understanding Long-Term Response Rates and Treatment Dilemmas in Diabetic Macular Edema

The prevalence of diabetes is growing exponentially on a global scale; as such the number of people affected by vision-threatening diabetic retinopathy (DR) is likewise expected to increase rapidly. 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] Perhaps more telling—by 2035 it is estimated that 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 forego annual screenings for DR.[3] The American Diabetes Association recommends initial screening within 5 years of diagnosis if type 1 diabetes is confirmed and annually for both types 1 and 2.[4]

In the interest of providing more complete care to patients, Evolve gathered a trio of retina specialists to discuss current insights into management strategies and patient dilemmas in diabetic macular edema (DME).

—Antonio Capone Jr, MD

Antonio Capone Jr, MD: Before we can begin a discussion on diabetic retinal disease, we need to have a good understanding of the systemic disorder and prevalence. According to the Centers for Disease Control, more than 29 million people in the United States (or about 9.3%) are affected by diabetes, and diabetes is the seventh leading cause of death in the United States.[5] The 2012 National Health and Nutrition Examination Survey (NHANES) data revealed a prevalence of 12% to 14%, with 38% of US adults having prediabetes.[6] Once we start discussing people older than 65 years, 83% have diabetes or prediabetes.[6]

The most common microvascular complication associated with diabetes is DR.[7,8] DME is a chronic form of DR characterized by slow, progressive retinal thickening until the center of the macula is involved.[9] We commonly see patients in our clinics with mixed mechanism disease, particularly if they are older when presenting. There are some who will present with pure ischemic disease, but they generally do not have edema. We know DME accounts for about 75% of cases with visual loss.[9]

Figure 1 is from a retrospective study of about 25,000 commercially insured working-age adults. Patients with diabetes and DME experience much higher rates of complications, such as myocardial infarction, stroke, congestive heart failure, peripheral vascular disease, cerebrovascular disease, and renal disease, than do diabetic patients without DME.[10] In a separate pooled analysis of almost 23,000 patients with diabetes, Yau et al found a 35% prevalence for any DR, about 7% for proliferative DR (PDR), about 7% for DME, and about 10.2% for vision-threatening DR (either PDR, DME, or both).[11] As might be expected, these endpoint percentages increase with A1C levels, blood pressure levels, and disease duration.[11] Globally, these figures are staggering—28 million people with vision-threatening DR.[11]

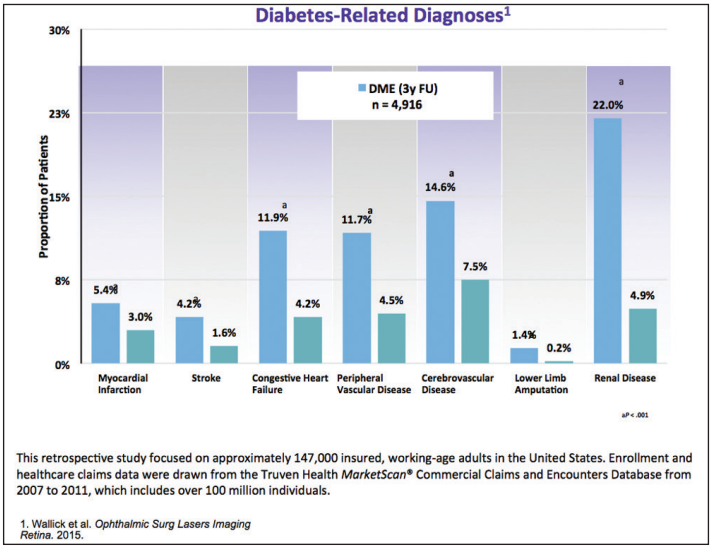
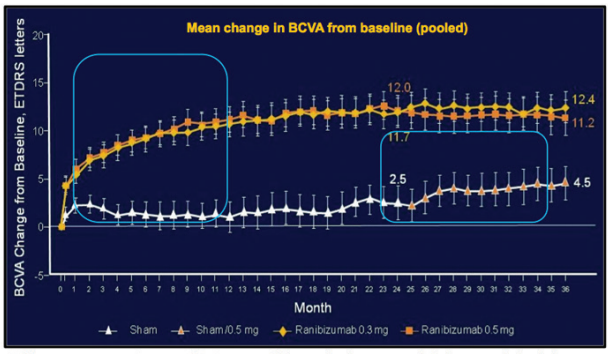


Figure 1. Patients with diabetes and DME experience much higher rates of complications, such as myocardial infarction, stroke, congestive heart failure, peripheral vascular disease, cerebrovascular disease, and renal disease, than do diabetic patients without DME.

In the United States, about 8 million people with diabetes have DR, but only 5.8 million are diagnosed.[5,6,12,13] That leaves a large number of undiagnosed or underdiagnosed people, either as a result of lack of access or lack of care.

THERAPEUTIC APPROACHES

The pathogenesis of DME is fairly well understood.[14-18] Glycemic control is the overriding variable that patients themselves have



With crossover to 1 year of 0.5-mg ranibizumab therapy at third year, original sham treatment group's visual gains were lower than those seen in first year of ranibizumab-treated groups (**2.8** vs **10.6** and **11.1** letters)

Delayed treatment reduced magnitude of VA benefits of anti-VEGF therapy

BCVA=best corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; VEGF=vascular endothelial growth factor.

Brown DM et al; RIDE and RISE Research Group. *Ophthalmology.* 2013;120(10):2013-2022.

Figure 2. One of the things we have learned from the anti-VEGF studies is that delaying treatment results in leaving vision on the table.

potential impact on with regard to inflammatory mediators. Anti-VEGF therapy obviously targets what is likely the predominant player of the inflammatory cytokine mediators. Steroids, however, have impact on both arms of the inflammatory mediator pathway.

Right now, there are four major therapeutic strategies for treating DR and DME: anti-VEGF drugs, steroids, focal laser, and vitrectomy, or any combination of the above. One of the things we have learned from the anti-VEGF studies (aside from the efficacy of the class of agents) is that delaying treatment results in leaving vision on the table (Figure 2).[19-22] We know from RISE and RIDE that when the sham group was offered treatment during the extension studies, the increased vision gains never overcame that period of nontreatment.[19]

But does the data demonstrating superior visual results when patients are treated promptly and consistently translate to clinical practice? A retrospective review study of fully de-identified electronic medical records from an integrated health system found 40% of patients only get one injection in the first 12 months, and the mean number of injections was 2.6.[23] Vision gains were not robust either—a mean gain of 4 letters on the ETDRS scale at 6 months, dropping to a mean gain of 3.7 letters by month 12.[23] That is in stark contrast to the approximate 11 letter gains seen in RIDE and RISE.[22]

DRCR.NET

The Diabetic Retinopathy Clinical Research Network (DRCR.net) has tried to bring clarity to the anti-VEGF therapy regimens. Protocol I evaluated ranibizumab (plus prompt or deferred laser) or triamcinolone plus prompt laser.[24] Results showed a clear superiority of ranibizumab to both the sham and prompt laser and triamcinolone options. But over the long term, there were still patients who continue to lose vision even with both an anti-VEGF and laser.[21,24,25]

It continued to remain unclear which of the three commonly used anti-VEGFs was superior, and the DRCR.net attempted to answer that in its Protocol T.[26] The Year 1 data showed patients who were treated do well, averaging between 10 and 13 letter gains.

What strikes me as more interesting, however, is the significant number of patients across all the anti-VEGF clinical trials who have an incomplete response. Fewer than 50% of patients gain 2 lines, even after 2 years of treatment.

—Antonio Capone Jr, MD

Statistically, bevacizumab fared the worst, and aflibercept the best.[26] But again we need to ask if that is a clinically meaningful difference?

What strikes me as more interesting, however, is the significant number of patients across all the anti-VEGF clinical trials who have an incomplete response.[27-30] Fewer than 50% of patients gain 2 lines, even after 2 years of treatment.[27-30]

THE EARLY ANALYSIS

It remained unknown if there was any pattern on the response curve that could let clinicians make an educated determination about how a patient would respond and when the patient would respond. The goal of the EARLY analysis (an independent, post-hoc analysis of a subset of eyes from Protocol I) was to evaluate anti-VEGF treatment response at 12 weeks compared to the long-term BCVA outcomes.[31] There is no consensus about how to define a "partial responder" to the anti-VEGF therapies, but such eyes are thought to represent approximately 30% to 40% of all those treated. That supports a multimodal therapeutic approach, but there needed to be reliable predictive

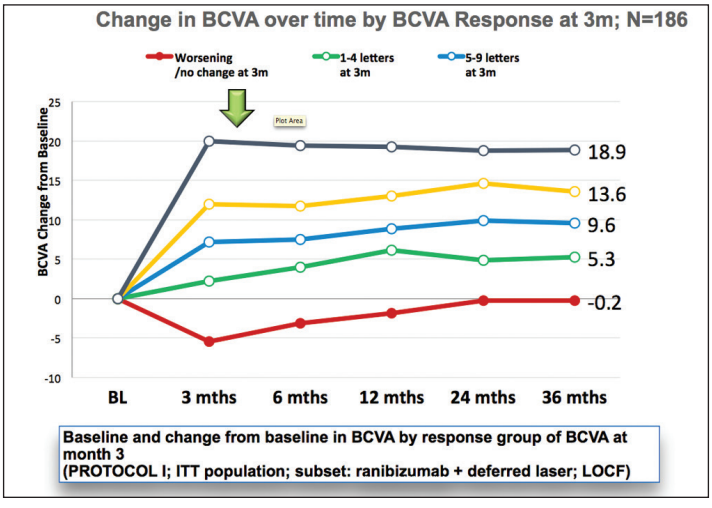


Figure 3. Peak response with anti-VEGF occurs at 3 months, and patients do not improve significantly over the longer term.

factors to guide clinicians about when to consider adjustments to patients' treatment regimens. EARLY stratified data according to the observed response rate at 12 weeks in the patients who had received ranibizumab (n = 375), and compared those BCVA results to BCVA at weeks 52, 104, and 156.[31] Figure 3 shows that peak response with anti-VEGF occurs at 3 months, and patients do not improve significantly over the longer term. Generally, if a patient has done well in those first 3 months, they will maintain those vision gains. EARLY also found that patients with early BCVA responses in Protocol I had lower baseline visual acuity and thicker retinas, while the patients with limited early BCVA response tended to be older.[31,32]

Is there a ceiling effect? Two statistical analyses (a logistic regression analysis and a sensitivity analysis) were performed to address just that issue. The observation that the less-than-5-letters-gained group continued to see the same results at 1 year and 3 years based on their 12-week results is not influenced by the fact that they had better vision at baseline. These analyses confirmed a strong correlation between response at 12 weeks and 52 weeks, and further, confirmed that in eyes with poorer vision, response at 12 weeks correlated to results at 1 and 3 years.[31]

In our real-world clinics, though, many of us tend to switch among the anti-VEGF agents, and we do find on occasion that there is a differential response from patient to patient.

CORTICOSTEROID THERAPY

Corticosteroid therapy continues to be an option for patients with DME, but tends to be used in individuals who are suboptimal or nonresponders to the anti-VEGFs. The likelihood of cataract formation coupled with an IOP rise seems to be the primary reasons behind not incorporating corticosteroid treatments earlier in our regimens. However, clinically significant rises in IOP are case by case.[33] Some of the larger cohort studies found even IOP increases to 30 mm Hg do not always translate into glaucoma.[34,35] It is important to bear in mind that modest pressure elevations may indicate a predisposition.

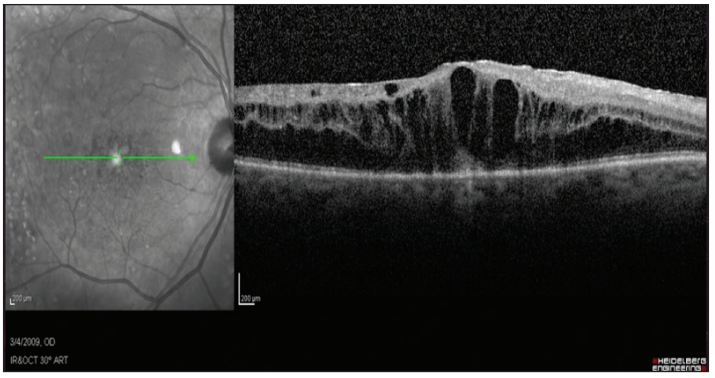
In the dexamethasone pivotal trials for DME, mean IOP returned to baseline between treatment cycles.[36] In MEAD,[37] 28.1% of patients had a pressure rise of 10 mm Hg or more from baseline and peaks somewhere around 6 weeks after initial injection, but pressure levels returned to baseline once the drug is exhausted, at about 180 days.

CASE STUDIES

Steroids and Anti-VEGFs Together

David M. Brown, MD: I have been a firm believer in the anti-VEGF agents almost to the point of exclusivity until one patient convinced me some cases need more than anti-VEGFs can provide.

In this case, a 50-year-old attorney is being actively treated with rosiglitazone for his systemic diabetes. In 2008, he underwent cataract surgery. He presents with DME in Asia and flies to Los Angeles for treatment under the care of Steven Schwartz, MD; his visual acuity is 20/200 for 1 year with a history of previous focal grid and panretinal photo-



[Courtesy of Steven Schwartz, MD]

Figure 4. A 50-year-old patient with visual acuity 20/200 for 1 year with a history of previous focal grid and panretinal photocoagulation.

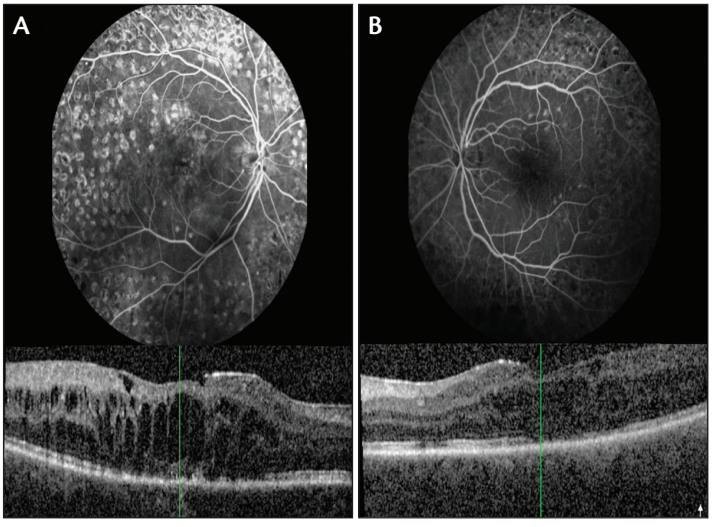


Figure 5. After 12 months on ranibizumab, the patient is 20/200 OD (A), 20/400 OS (B), pseudophakic OD, and has a cataract in the other eye.

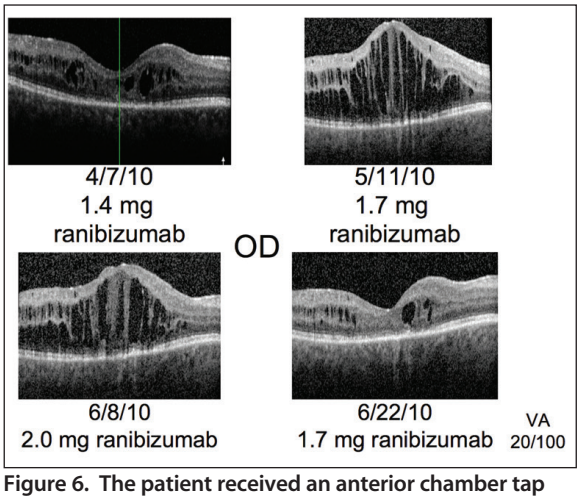


Figure 6. The patient received an anterior chamber tap and 0.15 to 0.20 cc ranibizumab every 2 weeks, and his vision improved to 20/60 or so, but if his injections go longer than 2 weeks, the patient's edema returns.

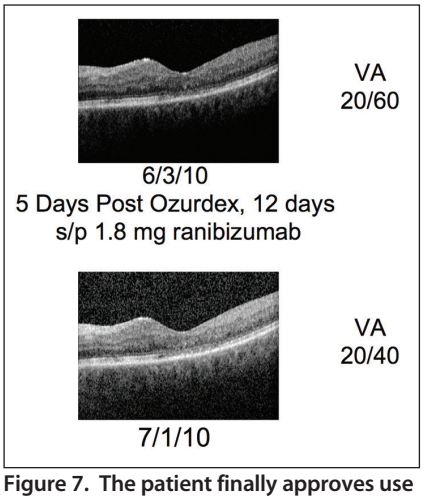


Figure 7. The patient finally approves use of the dexamethasone implant, and he is 20/60 in one eye, 20/40 in the other.

coagulation (Figure 4). In 2009, he has diffuse edema and at the time our only approved treatment was ranibizumab. The patient was relocating to Houston, and Dr. Schwartz referred him to my practice. After 12 months on ranibizumab, he is 20/200 OD, 20/400 OS, pseudophakic OD, and has a cataract in the other eye (Figure 5). His complaint is not with the cost of the drug—which he is paying out of pocket—but with the dismal results. He improves for 4 to 5 days and then regresses immediately. I recommended he discontinue rosiglitazone and change oral agents, but continue bilateral monthly ranibizumab 0.8 mg (off-label dose), but that did not improve his vision. A doubling of bevacizumab to 1.25 mg did not help much either. He was particularly concerned about cataract in his phakic eye, and skeptical about any steroid treatment. I did an anterior chamber tap and began injecting 0.15 to 0.20 cc ranibizumab every 2 weeks, and vision improved to 20/60 or so, but if his injections go longer than 2 weeks, the edema returns (Figure 6). With everything we have been administering to this eye, it is still not enough. He finally approves use of the dexamethasone implant, and he is 20/60 in one eye, 20/40 in the other (Figure 7).

Six years later, he now receives aflibercept (about two to four injections a year), and dexamethasone implant every 3 months. His vision is stable at 20/70 OD and 20/60-20/100 OS. He can drive his beloved sports cars again.

Dr. Capone: I think the case makes a variety of clinical points that may fly in the face of what our insurers would ask us to do. Insurers will say this patient should have been on bevacizumab from the start. In our area, some insurers require that we interact with a pharmacist—not physician medical director—who tells us that they will only approve bevacizumab for initial therapy and that the physician has to demonstrate failure. Prior failures in the same insured patient when on another insurance plan do not count. This was a great example of why individualized clinical trials are necessary. When they are first presenting, we can discuss what the clinical trial population results were, but there is an extraordinary amount of individual variation. Here was a patient who clearly did not improve until there was a mixed treatment approach.

Dr. Brown: Steroids. Absolutely—he still needs some anti-VEGF intermittently, but he is seeing better than he has in 10 years. He is consistent with his dexamethasone dosing, and he is very good at telling us when he notices vision changes. When he travels and misses the steroid injection, we will have to combine that with an anti-VEGF to get him back on track. Since we started the steroid, he has never had a pressure rise.

If he had a pressure rise, his story might have been different because we might have put a valve in. The risk of endophthalmitis with a valve is very low, but if it controls his edema I think the risk is worthwhile. He was already legally blind for years so I think the risk would have been mitigated by the benefits.

Dr. Capone: Yes. The pressure response with dexamethasone is more predictable than with other steroids.

Dr. Brown: And it goes away. The big advantage of the dexamethasone implant over intravitreal triamcinolone is that the implant gives 40+ days of super high-dose steroid and then almost no steroid. It is true pulse therapy like what is used in many systemic conditions to lower corticosteroid side effects. While up to 40% of patients do get an IOP rise in the month after their implant injection, in many patients their IOP is back to baseline well before they need another implant.

The big advantage of the dexamethasone implant over intravitreal triamcinolone is that the implant gives 40+ days of super high-dose steroid and then almost no steroid.

—David M. Brown, MD

Jorge A. Fortun, MD: And I think when it comes to IOP, too, our knee-jerk reaction from our experience with other steroids is that if the pressure shoots up it is going to stay up. But now I consistently monitor the pressure. If the pressure rise happens around the first 6 weeks, all that means is the patient is responding similarly to how those in the MEAD study did, and I do not necessarily treat. I will watch and observe, and the pressure is usually back to baseline when I see them on the following visit.

Dr. Capone: It is also notable that the incisional glaucoma procedure rate for dexamethasone was 0.3%.[37] The rate for fluocinolone is much higher.[38]

Dr. Fortun: What about a sub-Tenon approach? The effect can last a long time and when it is well placed (primarily posteriorly), we do not see the same kind of pressure spikes that we might see otherwise, and at a much lower cost than some other treatments. We need to consider a patient's ability to pay.

Dr. Brown: In this case, the patient was very wealthy and did not care about cost as long as the treatment was effective. The DRCR.net looked at sub-Tenon injections and found no consistent improvement in DME with sub-Tenon Kenalog injections.[39]

Dr. Fortun: It is something to consider, but when it has not been shown to work it has been as a monotherapy. Perhaps a low level of inflammatory suppression combined with anti-VEGF may work. We do not have that trial to tell us, but to Dr. Capone's point, these patients are different. To Dr. Brown's point, we need

Case Study: Using Dexamethasone in a Real-World Setting

By Adam T. Gerstenblith, MD

A 79-year-old woman with a 12-year history of type 2 diabetes mellitus presents in March 2015 with decreased central vision in her left eye. Her past medical history includes hypertension and hypercholesterolemia in addition to the type 2 diabetes. At presentation, she is on several medications, including insulin, metformin, amlodipine, lisinopril/hydrochlorothiazide, and atorvastatin. Her past ocular history includes bilateral cataract surgery about 5 years prior to presentation. At the time of presentation, her right eye had only mild nonproliferative DR with no macular edema and did not require treatment over the course of her visits.

Her initial visual acuity in the left eye was 20/60, with a central subfield thickness (CST) of 384 µm (Figure 8). She was treated with ranibizumab 0.3 mg. She was subsequently treated with ranibizumab on three additional visits at essentially monthly intervals.

After 5 months of consistent treatment, there was still macular edema (Figure 9) that led me to alter treatment to aflibercept, which she received in July, September, and December 2015. When she returned in January 2016, her macular edema had resolved with a CST of 289 µm, so no treatment was given.

In May 2016 when her CST had increased to 362 µm, I decided to use dexamethasone implant for the first time. The following month, there was no discernible fluid on imaging (Figure 10), and at her last visit (December 2016), she was still maintaining her vision without additional fluid (Figure 11).

In summary, this is a patient who underwent seven monthly doses of anti-VEGF (using both ranibizumab and aflibercept) over the course of 9 months yet the intravitreal injections were unable to control the edema. After one dexamethasone implant, however, the patient remained edema-free after 7 months.

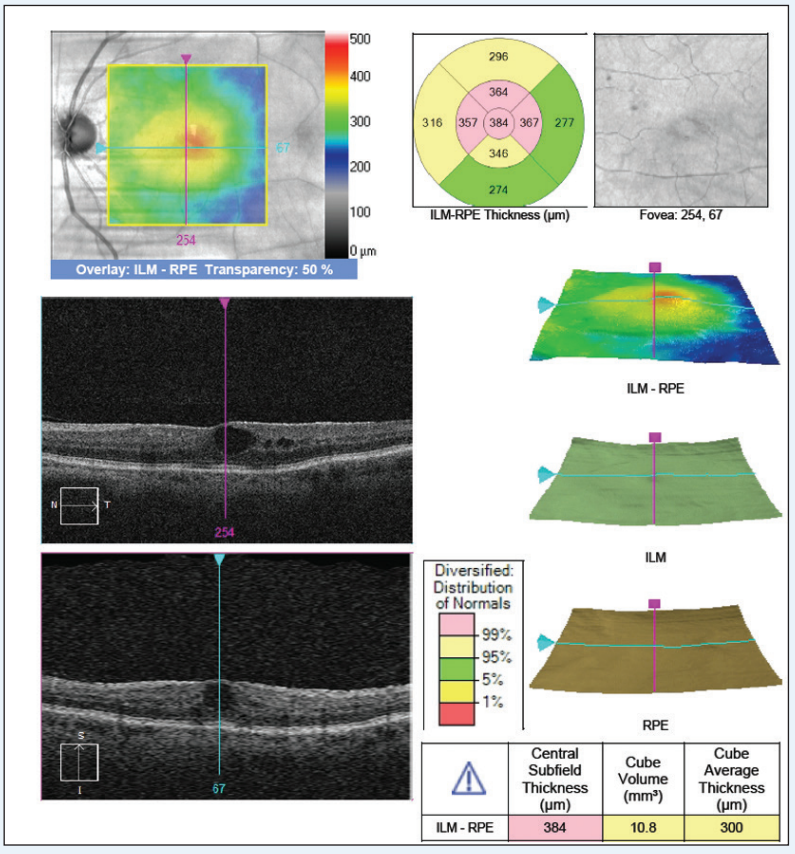


Figure 8. The patient's initial visual acuity in the left eye was 20/60, with a central subfield thickness (CST) of 384 µm.

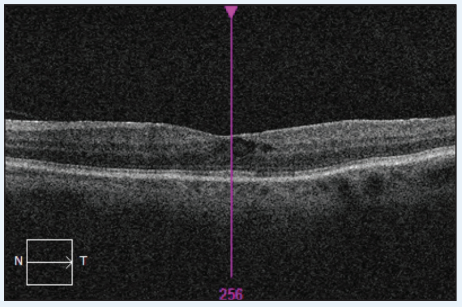


Figure 9. In July 2015, the patient had fluid on imaging.

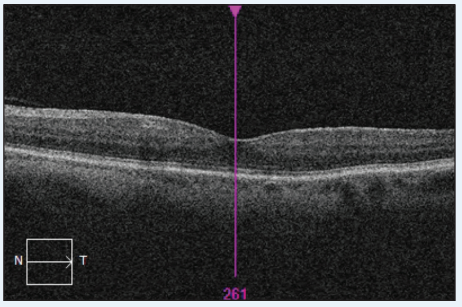


Figure 10. In June 2016, the patient had no discernible fluid on imaging.

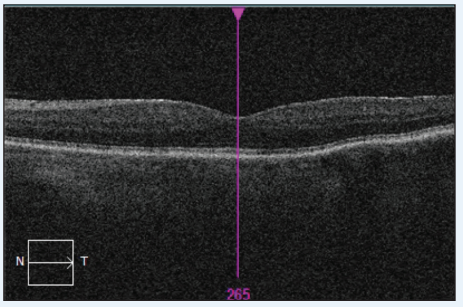


Figure 11. In December 2016, the patient had no discernible fluid on imaging.

to be persistent to try whatever we have at our disposal to help our patients.

Dr. Capone: There are limitations to population data. It is likely there are individual patients who will respond fabulously, but the aggregate response may not support a given conclusion. I have had patients respond nicely to sub-Tenon steroid using the Nozik approach.[40] I am concerned, however, with using steroids long term and the impact on periocular tissue in terms of the tissue laxity—one patient of mine suffered a lacrimal gland prolapse as a result of sub-Tenon. Single shots are not nearly as worrisome, but I am much more cautious about shots every 4 to 6 months for 10 years. There may also be a greater impact on darkly skinned individuals with regard to potential of depigmentation.

Dr. Brown: In my area, I have noticed a good number of physicians are not very familiar with the true posterior sub-Tenon technique, and were performing more of a subconjunctival injection. True sub-Tenon injections are not painful for the patient, and I have not had the same issues Dr. Capone mentioned. I do use them as a type of cost-effective protocol. I will start with a sub-Tenon to see if there is a response in my otherwise recalcitrant patients. If it is not doing what I expect, I might move up to the dexamethasone implant. In some disease states—severe chorioretinitis, for example—I have found the dexamethasone implant lasts for about 3 months and then the duration of effect is negligible.

There are some of us who are investigating a suprachoroidal delivery of Kenalog to see if we can generate a longer duration with less cataracts and glaucoma, but that product has only just begun human testing for DME and would be 3 to 5 years away from FDA approval if it proves efficacious.

Dr. Capone: The FDA-approved anti-VEGFs are by far the most expensive therapy option for DME. Given the dexamethasone implant has a 3-month duration of effect, it is considerably more cost effective.

Dr. Fortun: Before we move on, is there still a role in your practices for laser treatment in a patient with diffuse center-involving DME?

Dr. Brown: There are some cases where it is obvious we need to use laser (circinate rings threatening but not affecting the fovea, etc), but diffuse edema is not one of them. The problem with laser is that it takes a long time before we see an effect. The TREX-DME study used a treat-and-extend approach with or without laser. At 1 year, we found the number of anti-VEGF shots was significantly reduced in the laser arm compared to the monthly anti-VEGF–only cohort arm but it really was not much different from the treat-and-extend–only arm.[41] I would like to believe the best laser in the world is going to work, but to be honest, no one really understands how focal laser works. We are never sure if we are really stopping the microaneurysms from leaking or if we are killing the middle retina where theoretically the ischemic Mueller cells are producing VEGF. Laser is an effective procedure we have had since 1985, but we still do not know the mechanisms. TREX-DME may help resolve those questions.

Dr. Capone: I will use laser when it is a high lob down the middle; if I can attribute the source of edema to a few microaneurysms or a cluster of microaneurysms, I will treat them. We are able to get some patients off injections by performing laser. It does raise the issue of therapeutic burden.

Dr. Capone: We still need to look at the real-world results on how frequently patients are receiving anti-VEGF injections. Campbell et al had extraordinary real-world data showing the mean number of anti-VEGF injections at 12 months was only 2.7.[23] When I saw that, I am sure I am not the only one who thought those cannot possibly be my patients. We know that the anti-VEGF treatments work and if you do not treat, we are leaving vision on the table.

Dr. Fortun: I have a theory. The DME patient is typically younger, and still working age, so there may be some noncompliance as a result. But we are used to treating with laser every 4 months.[42] If we treat aggressively in the first year, the number of injections in the subsequent years drops significantly. We are most concerned about drying out the retina quickly. We are okay treating age-related macular degeneration every 4 weeks, but with DME we feel like that is failing our patients if we have to treat monthly. But we have got a little bit more leeway with DME; patients can tolerate edema a bit better. In age-related macular degeneration, we can get breakthrough subretinal hemorrhage. We are undertreating in DME.

Dr. Brown: I am also brutally honest with my patients, and they get it. It took 20 years of them not managing their diabetes to get all these eye issues, and we are not going to solve it in 3 to 4 months.

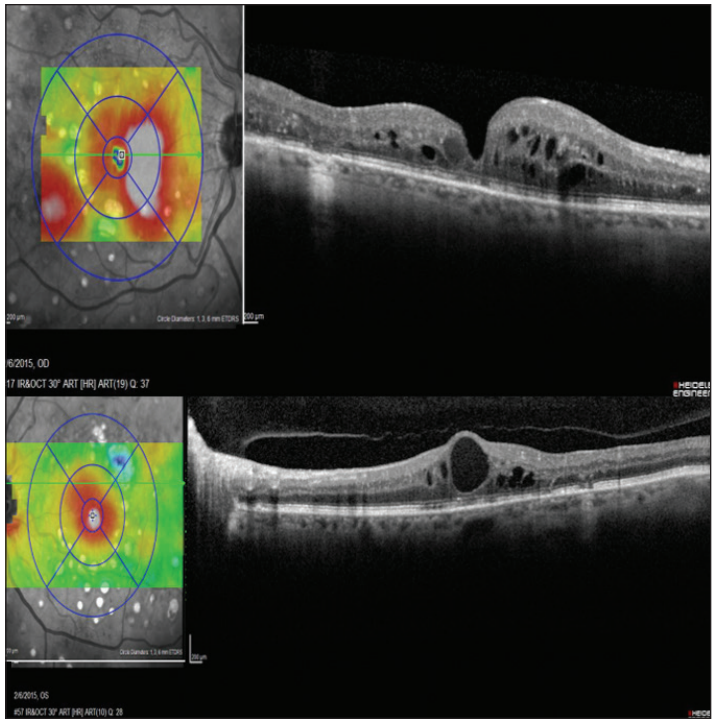


Figure 12. This patient was being managed with sub-Tenon triamcinolone. Yet he had fairly good vision even with a poor-looking photoreceptor layer in that right eye.

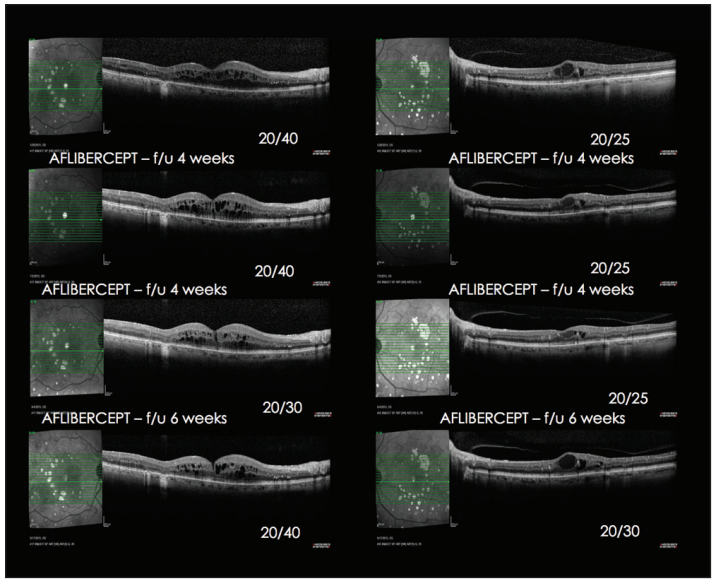


Figure 13. The patient's vision improved, but there was not an overwhelming response.

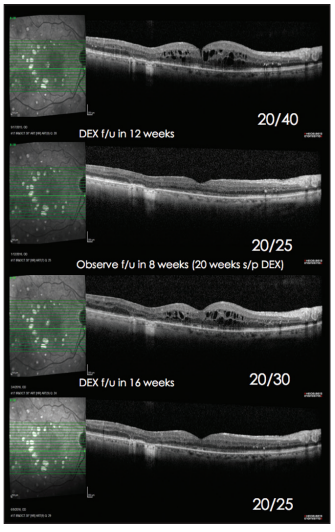


Figure 14. At 12 weeks, the patient's vision improves to 20/25, but his IOP is still high at 28 mm Hg.

They know they are going to have to keep coming back and that we will get some of their vision back but it is a long-term solution to a long-term problem. It is the caregivers who are listening—the husband, the wife, the child; whoever is bringing the patient in. I show the caregiver the wide-field angiograms and the capillary nonperfusion. I try to get the caregiver to understand that if those dead areas exist in the eye, they also exist in the heart, in the kidneys, in the brain. If the patient does not get control of their systemic disease, they will kill their eye. It is harsh, but it works. The fear of going blind scares them.

You can mitigate their vision loss and prevent most from going blind, but the best thing you can do is get them to start taking care of their blood sugar so it saves their life.

Dr. Capone: Anecdotally, I have heard some colleagues question patients just like the primary care doctor does. They ask about A1C as soon as the patient walks in. Others turn off the lights in the room to emphasize what blindness really is if they do not change their habits and get their blood sugar under control.

Dr. Fortun: I always instruct the fellows to listen to what the attending says and to steal those stories. Everyone will have analogies to use to explain just how devastating this disease can be.

This next case is a 69-year-old man, history of proliferative DR, has had panretinal photocoagulation and focal laser. He was previously receiving care at another institution. When he was transferred into our care, he was labeled as "poor response to anti-VEGF" and a fairly bad response to intravitreal triamcinolone. He was being managed with sub-Tenon triamcinolone. Yet he had fairly good vision even with a poor-looking photoreceptor layer in that right eye (Figure 12). He was pseudophakic without any optic nerve cupping so that opened up our treatment options. Like Dr. Brown's patient, this was a wealthy man who flew in on his private plane for treatment. We started treating him before we had the 1-year Protocol T data,[26] but I was already realizing some patients had a poor response to ranibizumab or bevacizumab, so I did what Dr. Capone calls "the anti-VEGF shuffle." We start him on aflibercept. Ideally I would have treated him every 4 weeks, but he came in every 5 weeks. His vision improved, but there was not an overwhelming response (Figure 13). We keep going, but there is persistent edema in the right eye. Treating every 4 weeks seems to help, but every 6 weeks it just gets worse.

He was concerned about steroid injections because he had had a poor response to intravitreal triamcinolone. We discussed the dexamethasone implant and that it really does provide a better IOP response. We try the right eye first, and at 6 weeks I brought him in for an IOP check; IOP had increased to 25 mm Hg. At 12 weeks, vision improves to 20/25, but the IOP is still high at 28 mm Hg (Figure 14). We start him on a carbonic anhydrase inhibitor because he cannot take timolol. Pressure improves to 19 mm Hg. The MEAD[37] and GENEVA[43] studies showed most patients will do well on one to two topical drops. So we continued to watch and observe; he remains stable to about 20 weeks when the swelling begins again. In his right eye, anti-VEGFs were successful out to about 6 weeks before the swelling starts and in that eye we switched him to the dexamethasone implant. His pressure spiked to 26 mm Hg, but at 12 weeks it had returned to baseline. At 18 weeks, there was swelling in the right eye. We are planning on continuing bilateral dexamethasone, every 3 to 4 months.

When do you introduce steroids in your real-world patients? How long do you let anti-VEGF therapy go before introducing steroids?

Dr. Brown: I think we tend to wait too long. If we see a response from the anti-VEGFs, and they are still phakic, we are concerned about cataracts and the patients are even more concerned. But Dr. Fortun's case eloquently demonstrates that for patients with unresolved edema, steroids really help. In Houston, almost every older patient I see is pseudophakic. But our DME patients in their 40s or 50s are concerned about cataract. Even so, we probably need to think about using steroids earlier.

Dr. Capone: I would agree. I am slow to pull the trigger on phakic patients. I will confess.

Dr. Brown: Too slow, right?

Dr. Capone: I will shuffle anti-VEGFs for a long time in phakic patients. In pseudophakes, I have an itchy trigger finger. Largely because of the huge lifestyle advantage of less frequent dosing. I have the conversation with pseudophakic patients in their initial discussion,

especially if they have no history of glaucoma. A study[37] showed a peak in IOP elevation at 6 weeks—is that when you check your patients? And we also know the majority of patients will have an IOP response in the first or second injection, and it is rare to see a first response after the third or later injection.

Dr. Fortun: The latest iteration of injectors is so good that I will still do a subconjunctival lidocaine on these patients; I do not use forceps to stabilize the eye. I use a cotton tip to displace the conjunctiva; I have numerous patients who tolerate the injections well without subconjunctival lidocaine. Low IOP was more of an issue for me with the older version of the injectors because we would get almost instantaneous hypotony.

Dr. Brown: I do not tend to use subconjunctival injections anymore except for patients who are really pain adverse. The newer injectors have really made these so much less worrisome. The subconjunctival lidocaine injection often leads to more subconjunctival hemorrhage than the dexamethasone implant injection alone.

Dr. Capone: I use subconjunctival injections, but I have a higher percentage of patients that end up being pain-free. So for those who are coming in 12 times a year for bilateral injections, I feel it is particularly important.

Dr. Fortun: My advice is also to try to follow the tract of where the pellets are going to come out and try to inject inferiorly; if patients have a well-formed vitreous they may end up with the injection right behind the lens. They will be bothered by that because they will get a floater and will complain. By aiming down, it is a bit easier. I have done a vitrectomy on some of those patients, and it is like there is a little dexamethasone graveyard down there.

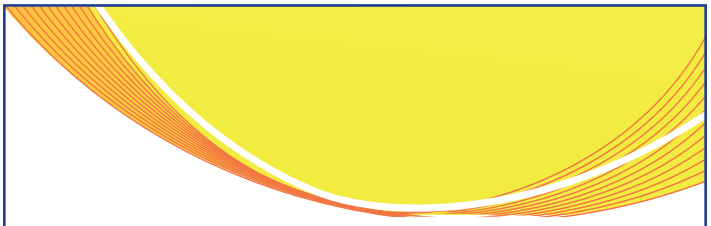
Dr. Fortun: Pravin Dugel, MD, has presented on a subanalysis of Protocol I and found that the response at 3 months with anti-VEGF will determine the long-term outcomes as well.[31] Should we be considering steroids at that time?

Dr. Brown: I think we all go too late to steroids because of the potential side effects.

Dr. Capone: Agreed—absent the elevated IOP risks and cataract risks and considering the longer duration of effect, steroids would be the go-to drug.

Dr. Fortun: An even earlier subanalysis of Protocol I also looked at different rates of response.[32] That analysis found about 50% of people are optimal responders, but there are also variable responders—somewhere between three to four injections was the cutoff. So we have now seen a case where long-term, ongoing edema can be reduced with a steroid. But that patient may be an example and not the mean—in the studies the vision never catches up.[32,44] Central subfoveal thickness may resolve on its own.

Dr. Brown: All the bleeding eventually stops, right?



I am surprised that there is a controversy at all about tolerating edema in the macula. I am very macular edema intolerant, because for any patient, the road to the best vision that patient can have involves having a dry macula.

—Antonio Capone Jr, MD

Dr. Fortun: The problem is that during the time the swelling has been there, you are losing vision. To your point, that may be one of the reasons to go to steroids even earlier than we do—to dry them even faster and improve their vision quicker. Weighing in on the risk-benefits of the side effects will likely mean going to steroids quicker.

Dr. Capone: I am surprised that there is a controversy at all about tolerating edema in the macula. I am very macular edema intolerant, because for any patient, the road to the best vision that patient can have involves having a dry macula. I have never seen any evidence to the contrary. We have intermediate long-term data on our patients that will either bear this out or not. What have you found in your clinics?

Dr. Fortun: These treatments may not only be helping just the macular edema, but they may be disease modifying. The corticosteroid and anti-VEGF studies have shown these treatments to be disease modifying, at least in improvement in the DR severity scale. In some of my patients you can find angiograms where perfusion improves following these treatments. So, certainly aggressive treatment may pay even bigger dividends in the long term.

Dr. Brown: For me, there are two points. One is, it is possible we introduce steroids too late. In vein occlusion, the lymphocytes and the leukocytes response is in the first month. None of us give steroids initially. The perfusion effects are probably an anti-VEGF effect. I think steroids would help earlier. I am one of the worst offenders—when I review my patient data, it is obvious I am not using steroids enough. But if patients get an anti-VEGF effect, they see better and come back every 6 to 8 weeks. As a group, retinal specialists have to get beyond the cataract and IOP elevations.

In terms of edema, I do not have a numeric cutoff. There needs to be a normal fovea with a foveal depression. I will continue to treat until the fovea looks like a normal fovea. Our imaging devices are really good, so we really can concentrate on the morphology. For some patients, that magic number might be 175 µ, because there

is intraretinal atrophy. Others might be great at 300 µ. I have had patients with a central retina thickness of 175 or 185 µ but with 20/20 visual acuity. That patient may not have as good a contrast sensitivity, or as good a dark adaptation, but retinal specialists need to ensure there are no cysts or subretinal fluid.

Dr. Fortun: What are the panel's thoughts on patients with marked peripheral ischemia? How do you approach them?

Dr. Brown: We ran a trial on that topic with targeted laser guided by wide-field angiography; the hypothesis was that if you could obliterate 50 disc areas or more of capillary nonperfusion with a combination of panretinal photocoagulation and indirect laser, that would decrease the VEGF drive and the patient would need fewer injections.[45] It is a 3-year trial. We are at 2.8 years, and there is no difference. Killing the nonperfusion does not seem to matter.

Dr. Fortun: And it may also be that when you get to that degree of nonperfusion, the damage that VEGF was going to make has been done, and now you are maybe dealing with a more proinflammatory issue.

Dr. Brown: We need to make things healthier. We need to intracellularly make things healthier. Or, figure out the rogue cells and an effective method to eliminate them. In this study, we not only killed the blank areas, we killed the penumbra, which is the bright area next to it. We caused visual field defects.

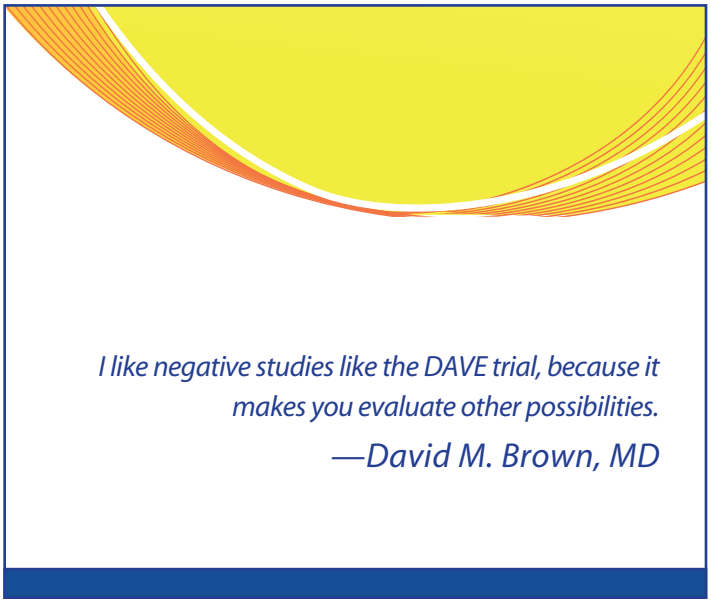
Dr. Capone: By lasering a retina you thought was dead anyway.

Dr. Brown: Including the penumbra, we caused visual field defects more than the average. I really thought doing the laser would make a difference. I thought it would at least decrease VEGF production enough to make a difference. It did not decrease the average injection rate. Those patients needed more injections. It was a total negative study.

Dr. Capone: An issue we all need to bear in mind is that by equating one word to a disease (like DME equals anti-VEGF), it gives us a false sense that we understand the pathophysiology of the disease. To Dr. Brown's point, if we obliterate the peripheral retina that does not necessarily mean we are going to impact what is happening in the macula.

Dr. Brown: Right. Why do some patients have so much VEGF in their eye that they get proliferative disease but not DME? They have such a high VEGF level—if I inject that same VEGF level into a rat, it is going to get vascular leakage. So we do not understand yet how or why some patients have DME but not proliferative disease. There may be some other cytokine. We are looking into that. I like negative studies like the DAVE trial,[45] because it makes you evaluate other possibilities. What do you think is causing the inflammation? Is it ischemia or just damage to the blood vessels from the blood sugar?

Dr. Fortun: My theory is that it is all interrelated. It is all one cycle.



There is damage to the ciliary walls, sludging of the leukocytes that then leads to ischemia, which then leads to more VEGF, which then leads to more of that. In different patients, it is different amounts of that mechanism.

Dr. Capone: Agreed—I think it is naïve to imagine that ischemia is only going to induce a single cytokine. The fact that we have all seen nonresponders tells us that more than a single cytokine is involved. Even though there is a great deal of individual variability, in a great number of our patients, there does seem to be one predominant cytokine.

We all appreciate the data that show patients who are injected monthly fare better. But we all want to move our patients off that monthly routine. Some patients will fare well with fewer injections, but others begin to backslide. I have had some of my patients become very depressed when we cannot extend them—they feel they have somehow failed a test and they are not getting any better.

My counsel to them is simply that 10 years from now, they will not care about the extra two injections a year. They will care a lot if they are not 20/20. So, I am not their friend if I lengthen the injection interval, I am their friend if I preserve vision. That is my due diligence responsibility and what we have to do.

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UNDERSTANDING LONG-TERM RESPONSE RATES AND TREATMENT DILEMMAS IN DIABETIC MACULAR EDEMA CME QUESTIONS

1 *AMA PRA Category 1 Credit*™ Expires January 2018

1. **Diabetic macular edema accounts for _____ of cases with visual loss in a diabetic population.**
   a. 25%
   b. 50%
   c. 75%
   d. 100%

2. **In the United States, approximately _____ people with diabetes have diabetic retinopathy, but only _____ are diagnosed.**
   a. 6 million/3.2 million
   b. 8 million/5.8 million
   c. 10 million/8.5 million
   d. 12 million/5.8 million

3. **In contrast to the number of injections reported in some of the pivotal trials (monthly), analyses of electronic medical records found _____**
   a. Almost 80% of patients get only one injection in the first 12 months
   b. The mean number of injections in the first year was 2.6
   c. Almost 60% of patients get only one injection in the first 12 months
   d. The mean number of injections in the first year was 6.2

4. **The EARLY study:**
   a. found that peak response with anti-VEGF occurs at 3 months, and patients do not improve significantly over the longer term
   b. found that peak response with anti-VEGF occurs at 5 months, and patients improve significantly over the longer term
   c. found that peak response with anti-VEGF occurs at 3 months, and patients improve significantly over the longer term
   d. found that peak response with anti-VEGF occurs at 5 months, at patients do not improve significantly over the longer term

5. **Large cohort studies have found IOP increases:**
   a. to 20 mm Hg does not always translate into a patient developing glaucoma
   b. to 30 mm Hg does not always translate into a patient developing glaucoma
   c. to 40 mm Hg does not always translate into a patient developing glaucoma
   d. to 50 mm Hg does not always translate into a patient developing glaucoma

6. **In the MEAD study, fewer than 30% of patients had a pressure rise of 10 mm Hg or more from baseline, and pressure levels:**
   a. could be managed with a combination of drops and surgery
   b. never returned to baseline in 10% of those patients
   c. could only be managed with three topical drops
   d. returned to baseline after the drug is exhausted, at about 180 days

7. **The TREX-DME study used a treat-and-extend approach with or without laser. At 1 year:**
   a. the number of anti-VEGF shots was significantly reduced in the laser arm compared to the monthly anti-VEGF only cohort arm
   b. the number of anti-VEGF shots was significantly increased in the laser arm compared to the monthly anti-VEGF only cohort arm
   c. the number of anti-VEGF shots in the laser arm was no different compared to the monthly anti-VEGF only cohort arm
   d. the number of anti-VEGF shots was statistically noninferior in the laser arm compared to the monthly anti-VEGF only cohort arm

8. **A 69-year-old man presents with a history of proliferative diabetic retinopathy, panretinal photocoagulation, and focal laser. After a year of anti-VEGF treatment every 5 weeks, his vision improves but there is persistent edema. According to the panelists, what should you do?**
   a. Counsel about the potential for increased pressure, but recommend intravitreal steroids
   b. Continue to treat with anti-VEGF and monitor the edema closely
   c. Refer to a glaucoma specialist to determine health of the optic nerve before discussing intravitreal steroids
   d. Start intravitreal steroid injections at his next visit and monitor patient's pressure

ACTIVITY EVALUATION

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Recognize the importance of early diagnosis and treatment of diabetic macular edema	_____	_____	_____
Assess the response of anti-VEGF intravitreal injections for diabetic macular edema	_____	_____	_____
Discuss the current and potential future therapies to treat patients with diabetic macular edema who do not respond in a timely fashion to initial treatments	_____	_____	_____
Formulate strategies to best treat diabetic macular edema using a multimodal approach	_____	_____	_____

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).

Name and email: _____

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

Comments regarding commercial bias:

_____

_____

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

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

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

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

Please identify how you will improve/change: _____

Change the management and/or treatment of patients. Please specify:

_____

_____

Create/revise protocols, policies, and/or procedures. Please specify:

_____

_____

Please identify the barriers to change.

_____ Cost ___ Lack of consensus or professional guidelines _____ Lack of administrative support _____ Lack of experience

_____ Lack of time to assess/counsel patients _____ Lack of opportunity (patients) _____ Reimbursement/insurance issues

_____ Lack of resources (equipment) _____ Patient compliance issues _____ No barriers _____ Other

Please specify: _____

To help evaluate this CME activity, may we contact you by email in 1 to 2 months to see if you have made this change? If so, please provide your email address below.

_____

_____

Please list any additional topics you would like to have covered in future Evolve Medical Education LLC CME activities or other suggestions or comments.

_____

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