Current Insight Into Retinal Disease Management: Focus on DME and Intravitreal Corticosteroids

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alteration of vitreomacular interface. Inflammation produces hypoxia, ischemia, inflammation, and formation of advanced glycation end-products. Lary permeability and associated leakage of fluid leakage into the coincident systemic disease associated with diabetic retinopathy (DR), the present and predicted financial health care impact is substantial.

According to the 2012 Vision Problems in the US Report from the Prevent Blindness America Foundation, diabetic retinopathy impacts more than 7.6 million people 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, treatment 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 therapy options 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 is projected to reach 324 million, including 35% who are expected to develop diabetic retinopathy. Monitoring, diagnosing, and treating the vision care needs of this potential population is essential to prevent vision loss.

In 2010, the Diabetic Retinopathy Clinical Research Network (DRCR.net) reported a 10-letter gain in nearly one-third of patients treated with laser, but 19% of the subjects experienced progressive vision 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), as well as intravitreal delivery systems, which release corticosteroids, such as flucinonide acetone id (Iviion SurModics). A study conducted by the DRCR.net has shown that patients treated with 0.5 mg ranibizumab plus prompt (n = 187) or deferred (≥ 24 weeks) laser (n = 188) had better visual acuity outcomes at 1 year than patients who received sham injections plus prompt laser treatments (n = 293). Outcome measures in the study included change in visual acuity and mean central subfield thickness measurements. Visual acuity improvement (± standard deviation) was significantly better in the ranibizumab plus prompt laser group (+9 ± 12, P < 0.001) and in the ranibizumab plus deferred laser group (+9, ± 12, P < 0.001), compared to those undergoing sham injections plus prompt laser (+3 ± 13) treatments. Visual acuity was not significantly better compared to patients treated with triamcinolone plus prompt laser (+4 ± 13, P = 0.3). Reduction in mean central subfield thickness was similar in all studied groups. Cataract progression and intraocular pressure increases were more frequent in the triamcinolone plus laser group.

More recently, researchers revealed the 2-year primary
The DA VINCI study, a phase 2 randomized clinical trial, administered every 2 months or on an as-needed basis, these regimens were just as effective as monthly treatments.

A new 2013 report from the PLACID study demonstrated higher gains in BCVA up to 9 months posttreatment for diffuse DME in patients receiving dexamethasone intravitreal implant 0.7 mg combined with laser photocoagulation compared with laser alone, but no significant between-group differences at 12 months.22

Most recently, Alimera Sciences announced that the FDA has rejected “the sustained-release Iluvien (fluocinolone acetonide) intravitreal implant for the treatment of diabetic macular edema” due to safety concerns.23 It is presently unknown if additional clinical trials will be undertaken in the US in order to seek future approval for DME treatment.

Also of recent note in 2013, 2 phase 3 comparison studies (VIVID-DME and VISTA-DME) demonstrated positive 1-year results for treatment of DME comparing aflibercept to laser photocoagulation.24 Subjects were randomized into 3 arms: 2 mg of intravitreal aflibercept injected monthly, 2 mg of intravitreal aflibercept injected every other month (after 5 initial monthly injections), or laser photocoagulation. In both studies, the 2-mg aflibercept treatments demonstrated mean increases from baseline in visual acuity of 10.5 to 12.7 letters, while photocoagulation treatment demonstrated mean increases of 0.2 letters in VISTA-DME (P < 0.0001) and 1.2 letters in VIVID-DME (P < 0.0001). Ocular complications were reported as conjunctival hemorrhage, eye pain, and vitreous floaters. Three-year follow-up is planned.

Photocoagulation remains the gold standard for the treatment of DME. However, continuing increases in studies evaluating different therapies may lead to a better understanding of pathophysiology and lead to more efficacious treatments. Because of the continuation of research designed to investigate pathophysiology and the rapid evolution of multiple clinical trials with emerging treatments, updated information on new diagnostic and treatment trends has become increasingly important to retina specialists, as well as other ophthalmologists who treat patients with DME.

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. Addressing optimal practice management strategies can improve the efficiency and delivery of care to this growing pool of patients at risk for vision loss. 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 further vision loss.
LEARNING OBJECTIVES
Upon completion of this activity participants should be able to:
• Understand the present an anticipated public health burden attributed to diabetic eye disease and DME
• Differentiate existing DME therapy options from recent primary and secondary treatments
• Interpret clinical research data comparing laser therapy to new DME treatment protocols
• Review the use of intravitreal steroids as single and combined approaches to DME
• Define complications and strategies to minimize vision loss with intravitreal steroids
• Educate patients about treatment regimens and risks associated with DME
• Improve practice management issues encountered with retinal therapies

TARGET AUDIENCE
This certified CME activity is designed for retina specialists and general ophthalmologists involved in the management of patients with retinal disease

METHOD OF INSTRUCTION
Participants should read the CME activity in its entirety. After reviewing the material, complete the self-assessment test, which consists of a series of multiple choice questions. To answer these questions online and receive real-time results, 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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The rise in obesity has led to a prediabetic US population that has reached more than 86 million,¹ and shows no sign of slowing down. By 2035, it is estimated close to 600 million people worldwide will have diabetes.² Our challenge as eye care professionals is to provide access to treatment to a group of people who may be unaware that their systemic disease may progress to ocular disorders and lead to vision loss if left untreated. Examining optimal management strategies is essential to improving delivery of care to the increasing number of people at risk for vision loss from these conditions.

Concurrent with this supplement is an interactive video case series, where our panelists provide thought-provoking scenarios that do not necessarily have tried-and-true easy treatment decisions. At the time of this round table, the Diabetic Retinopathy Clinical Research Network’s “Protocol T” had not yet been published; we were unable to discuss its findings or its potential impact on treating this patient population.

—Allen C. Ho, MD

THE CHANGING OPHTHALMIC LANDSCAPE

Allen C. Ho, MD: Macular degeneration, retinal vein occlusion (RVO), and diabetic macular edema (DME) have related physiologic problems. The number of patients projected to develop diabetic retinopathy (DR) is continually increasing. One of the greatest public health challenges is to encourage people who are not being treated to seek treatment. Why do you think patients avoid coming into the office for treatment until they notice an acute change in their vision?

SriniVas R. Sadda, MD: Part of the problem might be because some diseases (such as DME) remain silent for a long time. This disease usually occurs in busy working-age people. Sometimes, this patient population will have been given advice, but too often, they put it off because they are not experiencing serious symptoms.

Rishi P. Singh, MD: There is a disparity between ischemia and DME, too. Some people come in with proliferative disease, but the edema is minimal or nonexistent. Consequently, they feel relatively good.

Michael D. Ober, MD: And conversely, people with fovea-involving DME come in precisely because they are symptomatic.

Dr. Singh: The landscape of ophthalmologic care has become complicated. Some people go to optometrists or ophthalmologists seeking care from retina specialists only when complications arise. They perceive that having a diabetic eye examination is unnecessary. But is an optometrist generally able to detect the early signs of DME?

Dr. Ober: Historically, many optometrists did not have access to tools sensitive enough to detect serious retinal problems. The Optos camera has become very popular with optometrists and greatly aids in the detection of diabetic retinopathy.

Dr. Sadda: That is true. Optos screening is more sensitive than other methods in detecting retinopathy and other such problems. And optometrists do have these devices. Another issue affecting the number of people seeking care is a matter of insurance. Without insurance, people typically do not get a checkup unless they are symptomatic.

Dr. Ho: What about treatment? Who should be treating patients with DME? Should retina specialists alone be handling these cases? Should comprehensive ophthalmologists be administering injections? Before we had anti-VEGF therapy, some comprehensive ophthalmologists were providing laser treatments.

Dr. Sadda: Comprehensive ophthalmologists regularly referred patients with neovascular age-related macular degeneration (AMD) to us. Even when we had a DME indication for intravitreal therapies, most ophthalmologists were still referring these patients to the retina specialist.


TREATMENT OPTIONS

Dr. Ho: With regard to treatment options, Dr. Ober, can you summarize the results of the RISE and RIDE study?

Dr. Ober: RIDE and RISE was the first randomized, multicentered, controlled trial that showed anti-VEGF to be effective therapy for DME. In the study, however, ranibizumab (Lucentis, Genentech) was not compared to a competing treatment, but laser rescue was allowed after 3 months. Nonetheless, it changed the landscape in many ways, as it allowed the FDA to approve an anti-VEGF agent for the treatment of DME. We had options with the anti-VEGFs before this by using bevacizumab (Avastin, Genentech) off-label, but patients responded better to ranibizumab than anything else up to that point.

Dr. Ho: Would you consider ranibizumab a first-line treatment?

Dr. Ober: Yes. I do use ranibizumab as a first-line treatment, but I still use a fair amount of bevacizumab. When it was the only anti-VEGF available for DME, I found many of my patients responded well to bevacizumab and, therefore, still use it first-line today.

Dr. Ho: Is bevacizumab still your first choice?

Dr. Ober: That depends on several factors. If the DME is severe, I often begin with ranibizumab to allow for more rapid acceleration to adjuvant therapy in the event of a subresponse. But for average patients with mild to moderate DME, bevacizumab is my first choice.

Dr. Ho: There is another anti-VEGF that was approved quickly on the basis of the VIVID- and VISTA-DME studies. Dr. Singh, can you compare the aflibercept (Eylea, Regeneron) trials with the ranibizumab trials for DME?

Dr. Singh: There were several key differences between the RISE and RIDE studies and VIVID and VISTA. One was the randomization of patients on day 0. RISE and RIDE patients were randomized on day 0 to ranibizumab or sham injections. The macular laser was available for protocol-specified criteria and was used for 90 days after enrollment. In VIVID and VISTA, patients were randomized at day 0 to aflibercept or laser photocoagulation. The other difference was that in the VIVID and VISTA trials, patients who were assigned to the aflibercept group could receive continued rescue therapy with aflibercept if necessary. Patients assigned to the focal laser group received rescue treatment with additional focal laser treatments.

For the first time, we had a pure head-to-head comparison of laser versus anti-VEGF. The results were quite impressive. Focal laser is still effective for some patients, particularly for those with noncentral-involved DME. For patients with central-DME, I use anti-VEGF agents almost exclusively.

PATIENT MANAGEMENT

Dr. Ho: Dr. Sadda, how do you manage your patients with noncentral and central DME?

Dr. Sadda: I find that although the laser generally works well over time, patients can experience progression of disease or vision loss while you are waiting for the laser to work. This is one of the reasons why we would treat patients who had nonfoveal edema threatening the center with laser—in order to prevent progression and damage to the center while we were waiting for the laser to work.

Anti-VEGF therapy differs in that its effects are more immediate, and it is now the gold standard for treating center-involved DME. In addition, so far, we do not have any studies suggesting that the addition of laser photocoagulation to anti-VEGF therapy is of any value. However, it is possible that certain subgroups, such as suboptimal responders or those with specific morphologies, may benefit from laser treatment, but this has yet to be demonstrated in conclusive studies. In addition, there are some data from long-term follow-up from DRCR Protocol I that indicate patients who were treated with ranibizumab and prompt laser had worse visual outcomes than those patients in who the laser was deferred.

With the availability of rapidly acting anti-VEGF therapy for DME, the treatment of nonfoveal DME is less certain. One could potentially watch it closely to see if it progresses before intervening. I generally do not treat nonfoveal edema with laser unless the patient has a lipid exudation that has the potential to threaten the fovea.

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CASE STUDY PRESENTATION

DME AND INTRAVITREAL CORTICOSTEROIDS

By SriniVas R. Sadda, MD

A 60-year-old female with decreased vision OD is referred for persistent macular edema. She has had diabetes for 10 years, an A1c level of 7; cholesterol and blood pressure are medically controlled. She is currently on valsartan, rosuvastatin, nifedipine, and metformin. Her ocular history includes nonproliferative diabetic retinopathy bilaterally, clinically significant macular edema OD treated with focal laser twice, and has been given 3 intravitreal bevacizumab injections (the last one 5 weeks prior to referral).

At her first presentation to me, her visual acuity was 20/30 on the left and 20/80 on the right. She had undergone cataract surgery in the right eye, but not the left. She had significant lipid exudation.

The patient elected to switch to ranibizumab 0.3 mg, and underwent 3 monthly treatments, but was still not improving visually or anatomically. We opted to next try the dexamethasone 0.7-mg intravitreal implant. Six weeks after the initial implant, she was 20/30, and 4 months later, she was 20/25.

Figure 1. On initial presentation, vision was 20/80 in the right eye, 20/30 in the left. The right eye had already undergone cataract surgery, with a PC IOL; the left eye presented with a 2+ NS cataract.

Figure 2. Optical coherence tomography confirmed significant edema.

Figure 3. After 3 months of intravitreal ranibizumab injections, the eye was unresponsive to treatment.

Figure 4. Four months after dexamethasone 0.7 mg implantation, vision had improved to 20/25, and edema was almost completely resolved.

It is rare that I have a patient who does not respond to steroids. —SriniVas R. Sadda, MD

Dr. Ho: Would you say you avoid the laser on the basis of findings of long-term follow-up in these studies?

Dr. Sadda: I still watch these patients closely, but I am waiting for the definitive study that shows me that patients in a subgroup assigned to laser treatment truly benefit from it.

Dr. Ober: I agree that there is no definitive evidence showing that laser mono or combined therapy is advantageous at this point; however there is enough anecdotal evidence to prevent me from declaring an end to focal laser treatment. Preliminary results from the CavNav trial showed an advantage to using navigated laser using the Navilas laser system (OD-OS) in combination with an anti-VEGF. The study found that navigated laser combined with anti-VEGF injections reduced the need for repeated anti-VEGF injections when compared to anti-VEGF injections alone. The combination may prove to be superior to using anti-VEGF therapy alone.

In contrast, the RESTORE trial, which compared ranibizumab with sham laser to ranibizumab plus laser treatment...
to sham injection plus laser, showed no advantage to using the laser.\textsuperscript{8} The core component of RESTORE was a 1-year study, and we know effects with laser therapy are delayed,\textsuperscript{8} so I have not written the laser off just yet.

\textbf{Dr. Ho:} What about the ETDRS Protocol I issue of prompt versus deferred laser treatments,\textsuperscript{9-11} where the deferred laser group did consistently better over time?

\textbf{Dr. Ober:} The concept behind this finding is that you reduce the macular edema first and then use the laser with less power, resulting in less damage. Essentially, you load anti-VEGF therapy to reduce the edema before you provide laser treatment. This step allows you to provide focal treatments for microaneurysms. Using the laser with a higher power risks collateral damage and can plunge you into the edematous abyss.

\textbf{Dr. Sadda:} That is a really good point, because many of us are probably not even following the ETDRS protocol for laser use anymore. As you pointed out, using the laser is not without consequence. Patients are obviously going to experience scotoma. I, myself, think twice about using the laser on a patient. Now that we have multiple agents, I might want to see how my patients respond to other pharmacotherapies before I consider using the laser.

\textbf{Dr. Ho:} Even for patients with extrafoveal noncentral DME?

\textbf{Dr. Sadda:} I tend to observe those patients. I do not feel the urgency to treat them because I believe I have time. The patients with foveal DME who will require treatment more urgently. If a patient comes in with a new diagnosis of nonfoveal DME and there appears to be a lot of associated lipid, I would want to treat him or her with the laser and track the response. But if it is in the fovea, the best option is anti-VEGF therapy.

\textbf{Dr. Ho:} There is a very different anti-VEGF management paradigm for wet AMD, where there is no time to lose, compared with DME, where watchful waiting may be indicated. This is an important point difference in approach. There is urgency to inject with neovascular AMD early in the course of treatment, with exceptions, of course. Although consistent anti-VEGF therapy in the first year of DME injections may afford the best level of visual acuity, many patients need significantly fewer injections in year 2 and beyond.

\textbf{Dr. Singh:} There are, however, subsets of patients with wet AMD where there is an occult lesion without progressive visual loss, subretinal fluid, and 20/40 visual acuity. The natural history for this patient is often good. Even if there is a decline in visual acuity, with good monitoring these patients will do well. I think that watchful waiting can be a useful approach in some of our AMD patients. We should not necessarily rush to use anti-VEGF injections for all patients.

\textbf{Dr. Ho:} It is true that there are some patients with wet AMD, the minority to be sure, in whom watchful waiting is a reasonable therapeutic strategy, but this is tolerated more in the setting of DME. Fortunately, we have several options in anti-VEGFs, types of lasers, and long-lasting and short-acting steroid drugs. Dr. Singh, what role should dexamethasone (Ozurdex, Allergan) play in the treatment of DME?

\textbf{Dr. Singh:} When there is chronic inflammation and subsequent changes in epithelial cells, steroids offer an advantage. Although we try to avoid the glucocorticoid effect of steroids, some patients do not respond to anti-VEGF treatments. I have given some patients in my own practice up to 8 injections with little diminution of fluid, even despite good monthly follow-up with registered OCT scans. In those patients, the steroid often works quite well. Some conditions might involve both an inflammatory and a VEGF-mediated process, even more so than that found in patients with neovascular AMD.

\textbf{Dr. Sadda:} How many patients have you seen who did not respond to corticosteroids but who did respond to VEGF? I have seen the reverse in many situations, but it is rare that I have a patient who does not respond to steroids. If somebody does not respond, I would suspect cystoid degeneration of the retina.

\textbf{Dr. Ober:} Anti-VEGF can have an adjuvant effect with steroids in DME.\textsuperscript{—Michael D. Ober, MD}

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\textbf{Dr. Ober:} Anti-VEGF can have an adjuvant effect with steroids in DME. For example, patients can have a 50% reduction in edema with improvement in vision following steroid therapy, but have persistent edema that responds to anti-VEGF treatment while the steroids are still present in the eye. I reserve the term “cystoid degeneration” for cases when therapy results in reduction or resolution of edema with thinning of the retina but no improvement in vision.

\textbf{Dr. Sadda:} Do you have patients who do not respond at all to steroids, but who do respond to anti-VEGF therapy?

\textbf{Dr. Ober:} I cannot say definitively because I use anti-VEGF first-line, so the patients receiving steroids have already received anti-VEGF therapy.
Dr. Ho: I have seen the same. At least in my hands, corticosteroids are the second-line treatment. By the time a patient receives a corticosteroid, he or she is not usually treatment naïve.

Dr. Singh: I have had the same experience. Every patient I have had has responded to corticosteroid treatment; albeit, there have been some who have glucocorticoid effects that you have to manage.

Dr. Sadda: Sometimes, anti-VEGF therapy takes a while to reach its maximum drying effect for DME. DRCR.net Protocol I recommends that you continue treating as long as the edema is decreasing, and only hold off on treating when no further reduction is observed. I wonder, sometimes, whether giving a patient a steroid would improve his or her maximum vision outcome when his or her edema levels off with anti-VEGF therapy and without complete drying. Giving steroids may be a way to ascertain whatever their maximum effect would be. I have always felt it to be a nice interrogation tool.

Dr. Ober: Even when the vision is relatively good, if there is persist edema with or without treatment, it can lead to a slow loss of vision over time. If you dry the retina completely, in theory, you could stabilize the vision at its current level.

DEFINING TREATMENT FAILURES

Dr. Ho: The idea of using steroids as an interrogation tool is interesting. As you said, we see changes in form (OCT), but not necessarily improvements in visual function. What defines a treatment failure for a particular modality, and what drives you to switch to different classes and different agents within a class?

In an anti-VEGF phase 3 trial with mandatory monthly dosing, you can push the limits to achieve the best vision in your study population while examining the safety effects of a particular agent. In a review of the anti-VEGF trials for DR (RISE, RIDE, VIVID and VISTA), the change in visual acuity curve was different than what we experience with AMD. In the DME studies, the curve rose slowly during the first 12 months while subjects received very frequent and up to monthly anti-VEGF injections. In other words, in DME it may take time—even longer than a year of frequent injections to achieve best vision. But in practice, we tend to be less patient. How then do we define a treatment failure for patients with DME?

Dr. Singh: I take a quantitative approach. I usually give patients an injection and have them come back in 7 to 10 days. If I do not see a response to the edema via spectral domain optical coherence tomography (SD-OCT) at that time, I consider them potential nonresponders. We see at least a 10-μm reduction at each visit, I am fine with the slow rate of resolution and the protracted time it sometimes takes to reach a peak effect with anti-VEGF in patients with DME. After all, there are other potential benefits associated with anti-VEGF therapy, in terms of modulating the retinopathy and possibly reversing the disease process. If patients are improving, I will continue therapy. I can accept that there will be a slower rate of gain, particularly if there is a reduction in edema.

When patients’ progress levels off and they are not dry, then I follow Protocol I and observe them using a new baseline. That is when I might use my steroid interrogation, and if the steroid gets them dry, I figure this is going to be the patient’s best vision. I would consider treatment a failure once a patient’s vision has leveled off and he or she is not dry.

Another scenario to consider might be when a patient has a suboptimal response. I have some patients who dry out, but develop rapid recurrence of DME with poor durability in their treatment response. In that case, I might want to challenge them with steroids. I also consider other factors when entertaining the possibility of using steroids, such as whether patients are phakic or whether they have intraocular pressure issues.

Dr. Ho: These are all valid approaches to understanding what is the optimal, patient-tailored approach for achieving optimal vision in DME. Our clinical trials provide guidelines based on DME patient populations, but there is significant variability for individual patient response.

—Allen C. Ho, MD

Dr. Ober: Do you see a difference between your 7- to 10-day outcomes versus your 1-month outcomes? In other words, do your patients improve more over time?

Dr. Singh: No. They might improve slightly more in 1 month, but outcomes are similar, and this is also supported in the studies. In RISE and RIDE and VIVID/VISTA, there is a nice reduction in the curves of patients’ retinal thickness in 7 days, and then there is a slight increase over that until month 1. Patients find it reassuring knowing they have a response, even if it is only an anatomical one. This is also how I determine whether to try a steroid on a patient earlier or later.

Dr. Ho: What defines a treatment failure for you, Dr. Sadda?

Dr. Sadda: So, long as they are still improving and that we see at least a 10-μm reduction at each visit, I am fine with the slow rate of resolution and the protracted time it sometimes takes to reach a peak effect with anti-VEGF in patients with DME. After all, there are other potential benefits associated with anti-VEGF therapy, in terms of modulating the retinopathy and possibly reversing the disease process. If patients are improving, I will continue therapy. I can accept that there will be a slower rate of gain, particularly if there is a reduction in edema.

Another scenario to consider might be when a patient has a suboptimal response. I have some patients who dry out, but develop rapid recurrence of DME with poor durability in their treatment response. In that case, I might want to challenge them with steroids. I also consider other factors when entertaining the possibility of using steroids, such as whether patients are phakic or whether they have intraocular pressure issues.

Our clinical trials provide guidelines based on DME patient populations, but there is significant variability for individual patient response.

—Allen C. Ho, MD
Current Insight Into Retinal Disease Management: Focus on DME and Intravitreal Corticosteroids

TREATMENT OPTIONS FOR DME
By Michael D. Ober, MD

A 54-year-old woman with poorly controlled diabetes presented in November 2010 with initial visual acuity of 20/80-. She had a considerable amount of tissue exudate, tortuous vessels, and frank edema. Angiography showed several areas of capillary drop-out and findings of early proliferative diabetic retinopathy were confirmed. At the time of her presentation, Protocol I had just been released, and we did not have any approved anti-VEGF treatments (the first of which was not approved until 2012).

Given the patient’s advanced disease, observation was an unacceptable option. At the time, grid and focal laser were still the gold standard, and Protocol I was just beginning to change perceptions. After 6 months of monthly bevacizumab injections, 1 course of grid laser, and 2 rounds of panretinal photocoagulation, we were losing the battle as her visual acuity dropped to 20/200, edema had increased, and subretinal fluid had just started.

Continuing anti-VEGF agent at this point did not seem like a good option, as her condition was deteriorating. We opted to switch therapy to centrifuge concentrated intravitreal triamcinolone. At 1 month, her visual acuity had improved to 20/80, but still some significant edema remained. We reintroduced intravitreal bevacizumab, and 1 month following that, her vision improved to 20/60, and anatomic improvements were noted as well. Four months after continued bevacizumab injections and fill-in panretinal photocoagulation, her vision is 20/40+. Once triamcinolone was no longer visible in the vitreous, her visual acuity dropped to 20/100. At 46 months, she has undergone 32 anti-VEGF injections, 6 intravitreal steroid injections, and 3 grid laser sessions. Her visual acuity is 20/40+. Based on DME patient populations, but there is significant variability for individual patient response. Considering several anti-VEGF treatment options and several steroid options, along with macular laser photocoagulation, I consider an “activist” approach in DME treatment; for example, if 1 anti-VEGF agent shows on OCT little to no anatomic improvement after 3 injections, I will switch to another anti-VEGF agent. I consider anti-VEGF therapy first-line treatment for center-involving DME, but I am comfortable switching to steroids after a discussion of potential side effects. Steroids will often “reset” the diabetic macula, improving treatment response to subsequent anti-VEGF injections or extending their durability. Dr. Ober, what is your definition of a treatment failure in light of slower visual acuity responses observed with DME therapies?

Dr. Ober: I use several assessment tools. Vision is certainly one of them, but I use OCT as my primary guide.
Even if a patient responds to anti-VEGF in 2 weeks, but does not have a good response at 4 weeks, a change will be required. Furthermore, if he or she was not making meaningful improvements—such as a continued reduction in OCT until the patient is dry—I would again either change the anti-VEGF agent or add steroids. The trigger to adding steroids is determined on an individual basis. For patients with a history of glaucoma or for young phakic patients, the threshold is higher.

For patients who have made steady improvements after 2 visits, but who still have a significant amount of edema, I might switch them to another anti-VEGF or add steroids early.

**TREATMENT OPTIONS**

**Dr. Ho:** If you had an elderly pseudophakic patient, that is, glaucoma, pressure of 10, with DME whom you treated 3 times with an anti-VEGF agent and who has had some response, what would you consider an incomplete response and what would be the next step? Would you switch to another anti-VEGF, chose an interrogation with a steroid, or would you provide long-term steroids?

**Dr. Ober:** I would provide short-term steroids before I would choose another anti-VEGF.

**Dr. Singh:** I typically make my drug choices based on the safety profiles. I usually stick within the class I am using to treat patients or migrate to steroids. In time, we will have further direction from the Protocol T results, when they are available.

**Dr. Sadda:** I have not used bevacizumab to treat this condition very often because in my initial anecdotal experience, I did not think it worked as well. Also, there are compounding pharmacy related concerns. With regard to the use of nonapproved agents such as bevacizumab, as physicians, do we have a mandate to think about societal issues and costs or just the patient in front of us? I usually take care of the patient in front of me and treat them as I would my own mother.

More recently, aflibercept has become available. As Dr. Singh alluded to earlier, the Protocol T press release is now available; however, it will not change my management pattern until I actually see the data.

**Dr. Ho:** You all alluded to potential safety issues with our current DME treatment options. While on label, anti-VEGF medicines are exceedingly safe in the eye, and steroids have the potential for ocular side effects. Will you address and compare the safety profile of the implantable steroid options, dexamethasone 0.7 mg and fluocinolone (Iluvien, Alimera Sciences)?

**Dr. Ober:** The dexamethasone implant 0.7-mg has done a very good job for all 3 indications for which it was studied, and it fills a niche that the anti-VEGF drugs do not, particularly in vitrectomized eyes.

—Michael Ober, MD

The dexamethasone implant 0.7-mg has done a very good job for all 3 indications for which it was studied, and it fills a niche that the anti-VEGF drugs do not, particularly in vitrectomized eyes. With the steroid inserts, there is a well-known side effect profile, whereas with various anti-VEGFs, there remain small but indefinable unknowns at this point because no study has been powered to properly evaluate systemic side effects.

With the dexamethasone 0.7-mg implant, you know you are looking at glaucoma and cataracts. If you compare the studies for the dexamethasone implant with those of triamcinolone, with the SCORE being the best example, there are lower rates of glaucoma and cataracts. My use of dexamethasone 0.7-mg implant, however, is markedly different from its use in the trials, where injections were given every 6 months. In my practice, I use it most commonly as a 3-month drug. The studies showed that IOP peaks at 2 months, so the greater frequency of use may lead to an increased incidence and severity of glaucoma. If the patients have a history of glaucoma, there is a much higher chance they will have a steroid response. Studies with triamcinolone showed that if your baseline IOP is 20 mm Hg or more, you are much more likely to have a significant IOP response. In addition, I expect a 100% rate of cataracts over time with repeated use every 3 months.

With the dexamethasone 0.7-mg implant, the vast majority of patients may require treatment with IOP-lowering eye drops, but they usually respond well to them. With the fluocinolone implant, the advantage lies in duration of effect; however, there is a significantly increased risk of severe glaucoma that does not respond to drops.

**Dr. Sadda:** The incidence of incisional surgery for glaucoma was 4.8% in the low-dose fluocinolone implant group, which is quite substantial.

**Dr. Ho:** And in the dexamethasone 0.7-mg implant trials, at the frequency injected, the rate of incisional surgery for glaucoma was approximately 1%. I agree that the profile for the dexamethasone 0.7-mg implant seems much more favorable in terms of lower rates of ocular hypertension that can be managed with topical drops and that the...
MARCH 2015 SUPPLEMENT TO RETINA TODAY

Current Insight Into Retinal Disease Management: Focus on DME and Intravitreal Corticosteroids

TREATMENT OPTIONS AND BEST RESPONSE
By Rishi Singh, MD

This female patient presented with nonproliferative diabetic retinopathy (NPDR) with clinically significant macular edema (CSME). She received bevacizumab in August 2010 (3 injections), then switched to monthly ranibizumab 0.3 mg from December 2010 onward (33 injections). There was 1 focal laser treatment administered in May 2013. Optical coherence tomography (OCT) demonstrated continued CSME, despite multiple injections and focal treatment in the right eye.

Figure 1 shows the OCT imaging after injections number 15 through 17. Visual acuity was 20/60, and traces of subretinal fluid remain. There was almost no change in the OCT morphology over those periods. There was a slight increase in the subfield thickness.

Although vascular endothelial growth factor is 1 of the mediators and causative of the DME from the biochemical state, it does not address the multitude of other factors that occur from the anatomic and physiologic state. In particular, it does not address the inflammatory factors, such as cytokines, seen throughout the diabetic state. We chose to use intravitreal dexamethasone and Figure 2 illustrates the improved anatomy, even if the visual acuity remained about the same. By month 2 after the injection (Figure 3), the patient had a mild steroid response, but the OCT remained stable at month 6.

Dr. Singh: I agree. The frequency of re-treatment is not what we expected. We are re-treating much more frequently with the dexamethasone 0.7-mg implant may be higher in the real world with a different incisional surgery rate.

Dr. Sadda: We probably need to treat our patients more frequently with the dexamethasone 0.7-mg implant than how it was dosed in the trials. You could argue that it is possible to allow a bit of swelling and then treat them at 4 months, but you would certainly not want to wait 6 months for most patients. I do not worry about the cataract issue at all in these patients. These are diabetic patients and will eventually need to undergo cataract surgery, and have it at an earlier age than patients without diabetic eye disease. Developing cataracts was an issue in the drug’s original labeling, which has since been revised. These are very reassuring aspects of this implant.

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The dexamethasone 0.7-mg implant label does not provide requirement for incisional surgery lower. For balance, however, the frequency of injection with the dexamethasone 0.7-mg implant may be higher in the real world with a different incisional surgery rate.

The dexamethasone 0.7-mg implant label does not provide...
Current Insight Into Retinal Disease Management: Focus on DME and Intravitreal Corticosteroids

any information about giving a steroid challenge. I do not even know what the correlation is between patients who have a steroid response to topical therapy and a steroid response to intravitreal therapy. It would be nice to know, and perhaps you could do this as a challenge to patients before treating them intravitreally.

I also like the fact that its effects are reversible, because I do not start out knowing how a particular patient will respond. I am a believer in using the least amount of medicine necessary to do the job for a patient. I may eventually wind up treating a patient with the dexamethasone 0.7-mg implant every 3 or 4 months for 3 years, but I do not necessarily know this when I start treating a patient.

If we can begin to figure out a treatment regimen, that would help us a lot. Lacking that, I think I would prefer to start with an agent that I could try a few times to see how it is working. One of the big challenges with the MEAD trials was that so many patients in the placebo arm exited the trial. The reswelling seemed to decrease, but there was a saw-toothed pattern that might have been a result of the last observation carried forward, that is, an artifact. But if we knew without question that the recurrence would attenuate over time, I would feel better about using intermittent therapy.

Dr. Ober: The saw-toothed pattern told me that data was missing somewhere. Patients did not seem to have extraordinary spikes on subsequent treatments; whereas with triamcinolone, you do not know if they were on their second, third, or fourth injection, which might have caused the spike. The dexamethasone 0.7-mg implant is a very stable drug, pharmacodynamically speaking. So if patients have a steroid response, it should be fairly predictable that their pressure is going to increase on subsequent injections. When I was using off-label triamcinolone, I never really knew how high patients’ pressure was going to go with each subsequent injection. And even though I can get a steroid injection with triamcinolone to last longer with centrifuge concentration, I showed previously that we do not know what the effective dose of drug is at any one time.

SAFETY AND EFFICACY—THE CORTICOSTEROID CHALLENGE

Dr. Ho: Safety is an obvious concern and it is the driving force in selecting first- or second-line agents. We recognize differences between available steroids, such as the dexamethasone 0.7-mg implant and off-label triamcinolone, and we do not have a lot of experience with Iluvien, but you have got to watch the pressure carefully to avoid complications.

I find the idea of initiating a corticosteroid challenge earlier to determine potential safety and efficacy in response an interesting concept. Although our group is less concerned about developing cataracts and requisite cataract surgery, the issue of pressure rise remains a specter that limits many retina specialists from making corticosteroids first-line DME therapy, even though some of you had said they work almost every time, at least anatomically.

Dr. Ober: I try and hold off on using steroids until I am willing to accept that risk. I do not initiate a trial to classify IOP elevation risk. If everyone underwent a trial, some of those who were exposed to high pressures may never need that class of drug.

Dr. Ho: Ocular comorbidities or the potential for them may drive a choice in treating DME. What about systemic comorbidities that would drive you away from a certain class of drug?

For example, what if you had a diabetic patient who had a TIA within the last 3 months, who has centrally involved DME, and who is symptomatic at 20/50? Is there anything about that patient’s systemic status that might drive you to choose one agent over another, either within the anti-VEGF class or between classes, steroids, and anti-VEGFs, or laser treatments?

Dr. Ober: I find that patients like this require numerous visits to other providers. The biggest driver has more to do with patients’ ability to come in for frequent visits rather
than systemic side effects from anti-VEGF drugs. Steroids have a much longer duration of effect, which can be very enticing. I often discuss the dexamethasone 0.7-mg implant for convenience as well as efficacy. That is where systemic disease will drive me to use a steroid as a first-line agent, where I would otherwise use an anti-VEGF.

**Dr. Ho:** Being able to comply with follow-up is essential.

**Dr. Singh:** Our safety profiles of steroid drugs are very well documented. The problem is that a patient who recently had a TIA would never be admitted to one of our ongoing trials, either anti-VEGF or steroids. So we do lack clinical insight. We all know that every patient has potential risks. With a prior TIA, I might want to migrate that patient to a steroid rather than going directly to an anti-VEGF. I do not think we have enough data right now to determine if anti-VEGFs are completely safe in this patient population.

**Dr. Sadda:** These patients are certainly at a theoretical risk. In the trials, we were not looking specifically at subjects who presented with those issues. Obviously, some of the subjects who developed TIs went on to receive therapy. Still, this does not determine who is at increased risk.

Thus far, I would still treat these patients with anti-VEGF therapy. I think the totality of the data thus far is that there is probably not a big difference in risk between the anti-VEGF agents. In the rare situation in which the patient wanted me to speak to the internist who did not recommend use of the anti-VEGF agent—even though the internist likely did not have a good grasp of the data—I did not administer the drug. But those are isolated instances. I would typically still use anti-VEGF therapy as first-line therapy.

**Dr. Ober:** Having an internist not recommend an anti-VEGF would not prevent me from using it for someone with recent disease. A recent APTC event would prompt a detailed discussion with the patient rather than immediate avoidance.

That said, I do not think that Protocol T is going to be powered to drive changes in treatment based on potential systemic side effects. The efficacy of one drug over another may drive treatment changes, but at this point, I do not think the side effects alone would be enough to make me choose one agent over another.

**Dr. Ho:** It is clear that there is no consensus in this group on whether a recent vascular event such as a TIA would compel our specialists to avoid anti-VEGF therapy. Because these patients are at a theoretical, if not real, increased risk for another vascular event I would prefer to not inject an anti-VEGF agent for several months following an event and considering a general lack of urgency for DME treatment, I am comfortable deferring injection. If there is a need to treat, then I would consider a steroid injection or even macular laser treatment.

**THE DIAGNOSTIC WORKUP**

**Dr. Ho:** We have discussed different DME treatment options, their safety and efficacy. But how do you evaluate the patient in terms of diagnostics? Let me present the case of a 50-year-old diabetic with reasonable control (HbA1c, 7.5). This new patient presents with blurred vision and central involved DME in both eyes. What is your initial workup of this patient, what do you do diagnostically? Is angiography necessary?

**Dr. Sadda:** On clinical examination, I would rate his level of retinopathy and I would conduct a thorough exam. If, for example, you do FA, you will often get a higher stage classification of disease than you might have estimated even by biomicroscopy and ophthalmoscopy.

**Dr. Ho:** Why is that?

**Dr. Sadda:** Maybe we are not as good at being examiners as we should be. There can be very small areas of periphera; neovascularization that may be difficult to detect unless you are doing a 3-mirror examination. But few of us do those. If I see a patient whom I think has severe nonproliferative diabetic retinopathy (NPDR) or very severe NPDR and edema with foveal involvement, I do not necessarily feel that the patient will need an angiogram before initiating anti-VEGF therapy. It is just not critical. I have actually stopped getting baseline angiograms on these patients. The exception to that rule is when I am concerned that there might be occult retinal neovascularization. Generally, I will use the OCT and vision information to make that kind of determination.

**Dr. Ho:** Do you use OCT for every patient?

**Dr. Sadda:** Yes, without a doubt, because all the clinical trials are based on OCT-determined foveal involvement.

**Dr. Singh:** This is good point. You need to consider the population of patients with featureless retinas in whom there does not appear to be severe peripheral nonperfusion.

**Dr. Ho:** These are young adult juvenile diabetics with featureless fundi, meaning relatively little hemorrhage or exudation and no obvious neovascularization.

**Dr. Singh:** This applies to African American patients especially. It is in that subset of patients that I most often find a featureless retina. I like to choose a patient with center-involving DME and no neovascularization. That is why I use widefield angiography on those patients at baseline.
Widefield angiography aids in determining the state of the patient’s retinopathy, whether there is peripheral nonperfusion, and if this patient is at risk of developing neovascularization. I do not, however, get subsequent angiograms because if I initiate anti-VEGF therapy, I assume the treatment will alleviate the risk of neovascularization. On the other hand, if or when I see something on an initial angiogram, then I am going to treat the patient with panretinal photocoagulation earlier than I would have otherwise.

Dr. Ober: I also have a large percentage of African American patients and also see a significant number of featureless retinas. In my experience, there is an increased incidence of anterior segment neovascularization. So I do get a widefield angiogram on every new patient who requires treatment. If they have center-involving DME or if they are new patients with noncentral DME, I will generally get an angiogram on the initial visit. Subsequent angiograms are always driven by changes in disease or examination. They are not something I do routinely.

Dr. Ho: There is a particular angiographic pattern with DME that we thought was important to distinguish between focal retinal leakage versus diffuse leakage, where there may be incompetence of the outer blood/retina barrier. It was thought that steroids worked better for diffuse edema. Any thoughts on whether there is value to classifying angiographic patterns in DME?

Dr. Sadda: Yes, this concept of focal leakage from microaneurysms as opposed to telangiectatic retinal capillary-driven diffuse leakage is interesting. This concept emerged in part from data on focal laser for DME in the ETDRS study. Even though both patterns of leakage responded to treatment, patients with diffuse telangiectatic capillary leakage and cystoid macular edema did not do as well. I think that is where that concept came to be.

I have not seen any data from any of the anti-VEGF studies or the steroid trials, to suggest that there is a differential effect. I have not seen any trial data to suggest that patients with focal leakage and microaneurysms respond better to anti-VEGF therapy than to laser. From my perspective, it is not so useful, but I do understand that people use that as a reason to use combination therapy with laser in some patients, such as those with primarily microaneurysm-driven leakage.

Dr. Ho: We appear to be split on angiography with Drs. Ober and Singh routinely performing baseline widefield FA and Drs. Sadda and myself doing this less frequently. If there is unexplained vision loss, then I almost always consider FA, but I find myself doing less angiography at baseline or follow-up in general. Currently, I am performing frequent OCTA (OCT dyeless angiography with the Optovue Avanti system) to better understand DME and more generally diabetic maculopathy.

PATIENT FOLLOW-UP—WHAT NEXT?

Dr. Ho: After you have your diagnostic information, given an anti-VEGF injection, your patient comes back for a follow-up visit 1 month later. There’s a little less edema, but vision is still 20/50. I presume you do an examination and OCT. Another anti-VEGF results in some anatomic response, but no visual response. The patient returns at month 3, but still, there is no change in visual acuity (20/50 vision). There is center-involving DME and the macula is still 400 μm with cystic changes. What do you do then?

Dr. Ober: Depending on whether the patient has a history of glaucoma and what the baseline IOP is, I would either change the anti-VEGF class or provide steroids.

Dr. Ho: If there are no ocular comorbidities or systemic comorbidities that drive you one way or another between classes, what do you do on month 3?

Dr. Ober: I would switch to steroids.

Dr. Sadda: Now that we have 2 FDA-cleared anti-VEGF agents for DME, I am going to try the other anti-VEGF agent. And I would not do the 1-week challenge, because it would not be informative at this stage. I would still want to have tried both agents first. If I were not happy with a response early on, I would switch. What is the harm in finding out how the other agent works?

Dr. Singh: I would continue with the anti-VEGF drug because the visual acuity responses can be slow. But if 1 anti-VEGF agent does not give the patient a response, then I, too, would switch treatments.

Dr. Ho: I would practice similarly. At month 4, if there is a slight improvement, the OCT shows the lesion to be 380 μm, and visual acuity is 20/40 instead of 20/50, what do you do?

Dr. Sadda: If there were improvement, I would continue. I am fine with therapeutic response being slow or gradual. As long as there is some improvement, I would like to see what happens with another treatment. I would continue that second anti-VEGF.

Dr. Singh: I, too, would continue. You have had 3 months of moderate response with this agent. It could be possible that you had an anomaly in month 2. Maybe you got into the subconjunctiva or there was egress after the injection of the agent where your technique failed. If a
In my experience with the dexamethasone 0.7-mg implant, I would expect a substantial response 80% of the time. I would not necessarily expect all of the edema to be resolved with a single injection, but I would expect a significant reduction. If there is no response to the steroid, I would be suspicious of other confounding factors such as vitreomacular traction or cystoid degeneration from chronic edema.

**Dr. Singh:** There are a few patients who might only need 2 or 3 injections. But there are many other patients who are up to 6, 7, or 8 injections a year for recurrent DME. That is when I migrate to the dexamethasone 0.7-mg implant. I would agree with Dr. Sadda; I think that it is hard to quantify who will respond well and when. Not many studies have looked at population-based numbers of anti-VEGF treatments. I think it would be very helpful to have cut points based on clinical experience, because I do believe there is probably not a significant bell curve. I think it is more like a molehill, where we see patients following a variety of roads based on their individual VEGF loads.

**Dr. Ho:** Burden of treatment is also a driver for switching to another class of drugs and potentially corticosteroids.

**Dr. Singh:** I am not sure if there is a benefit within a particular class of drug. The bigger cut point for me is going to another agent.

**THE FUTURE OF DME TREATMENTS**

**Dr. Ho:** Where do you see the treatment of DME going in the next 5 to 10 years?

**Dr. Ober:** I think for your average patient with mild to moderate disease, anti-VEGF agents will drive the treatment course. As we get newer and longer-term treatments for AMD, it will filter in to our DME armamentarium. For patients with severe DME, combination therapy is going to rule the marketplace.

**Dr. Sadda:** I think we are getting a good handle on dealing with leakage. Our interests will lie in patients who do not have a good anatomic response. Diabetic neuropathy that occurs in the retina may occur almost independently of the vasculopathy. Neuroprotection might become an important strategy. Products might also be developed for dealing with ischemia. I think that attacking the nonperfusion aspect of ischemia and neuroprotection will become important, as will combination therapy. But its focus will remain on dealing with vision loss.

**Dr. Singh:** I agree that combination treatment will be developed in keeping with providing a personalized approach. Some patients will do well on an anti-VEGF. Others
will need a more individualized approach to determine possible biochemical factors. Ultimately, the goal will remain the same: to dry the retina. But how we get there will differ for each patient.

Dr. Ho: Several experts on this leading cause of blindness in adults, working Americans have given their thoughts on the prevalence and growing incidence of the disease and the real responsibilities we bear as retina specialists. Because patients value vision, and it is likely that some people with diabetes mellitus will continue certain behaviors until they lose their vision, treatment options alone will not suffice.

We must also leverage change through modifications in patients’ eating habits, exercise, cardiovascular activity, and compliance with other medical regimens they may be assigned. Several new treatment options, however, have expanded our choices in finding the best therapeutic strategy for individual patients. Although the future looks bright, many questions and challenges remain, not the least of which is the ever-growing number of those afflicted with diabetes mellitus.


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City _______________________________________________________________  State _________________________________

CURRENT INSIGHTS INTO RETINAL DISEASE MANAGEMENT:
FOCUS ON DME AND INTRAVITREAL CORTICOSTEROIDS

1 AMA PRA Category 1 Credit™  Expires March 1, 2016

1. RIDE and RISE
   a. Compared ranibizumab to bevacizumab for the treatment of diabetic macular edema
   b. Compared ranibizumab to sham injection for the treatment of diabetic macular edema
   c. Compared ranibizumab to aflibercept for the treatment of diabetic macular edema
   d. Compared ranibizumab to photocoagulation for the treatment of diabetic macular edema

2. VIVID and VISTA
   a. Allowed patients in either treatment arm to receive rescue treatment
   b. Allowed only patients in the aflibercept arm to receive rescue treatment
   c. Allowed only patients in the focal laser group to receive rescue treatment
   d. Allowed only patients in the sham treatment group to receive rescue treatment

3. A majority of studies show a substantial and clinically significant advantage
   a. In using focal laser treatment alone in the treatment of diabetic macular edema
   b. In using anti-VEGF therapies alone in the treatment of diabetic macular edema
   c. In using a combination of anti-VEGF therapies and focal laser in the treatment of diabetic macular edema
   d. There is not yet enough evidence to suggest one treatment is substantially more effective than another

4. Steroid use in diabetic macular edema
   a. Is often not recommended in cases with chronic inflammation
   b. Can be advantageous in cases of chronic inflammation and epithelial cell changes
   c. Should only be considered after other treatments have failed
   d. Should be used in cases of extrafoveal involvement

5. Treatment failure in diabetic macular edema should be defined as
   a. No anatomic response, but with a visual acuity improvement
   b. No visual acuity response, but with an anatomic improvement
   c. Neither an anatomic nor a visual acuity response
   d. Either an anatomic or visual acuity response but without the corresponding component response

6. In eyes that have undergone vitrectomy
   a. The anti-VEGF drugs fill a niche that steroids do not
   b. Panretinal photocoagulation remains the treatment of choice
   c. Steroids fill a niche the anti-VEGF drugs do not
   d. None of the above

7. The MEAD studies on dexamethasone suggest
   a. Optimal dosing is probably less than every 6 months for most patients
   b. The implant shows efficacy out to 12 months with no IOP spikes
   c. Treatment is most efficacious in phakic patients
   d. Steroids do not elevate intraocular pressure in a diabetic patient population
**ACTIVITY EVALUATION**

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<thead>
<tr>
<th>Did the program meet the following educational objectives?</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
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<td>Understand the current and anticipated public health burden attributed to diabetic eye disease and DME</td>
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<td>Differentiate existing DME therapy options from recent primary and secondary treatments</td>
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<td>Interpret clinical research data comparing laser therapy to new DME treatment protocols</td>
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<td>Review the use of intravitreal steroids as single and combined approaches to DME</td>
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<td>Define complications and strategies to minimize vision loss with intravitreal steroids</td>
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<td>Educate patients about treatment regimens and risks associated with DME</td>
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<td>Improve practice management issues encountered with retinal therapies</td>
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Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME). Please complete the following course evaluation and return it via fax to (610) 771-4443.

Name and email  
______________________________________________________________________________________________________

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

Comments regarding commercial bias:
_______________________________________________________________________________________________________________
_______________________________________________________________________________________________________________

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

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

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

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

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

If no, please identify the barriers to change.
_______________________________________________________________________________________________________________
_______________________________________________________________________________________________________________

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

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Supported through an unrestricted educational grant by Allergan.