Current Insights Into the Management of Diabetic Macular Edema

With
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STATEMENT OF EDUCATIONAL NEED

The effect of vision loss due to ocular manifestations of diabetes is a major public health burden facing our society, given the large aging population at risk for sight-threatening ocular conditions. Significant challenges lie ahead in addressing the needs of patients at risk for vision loss, as well as the effect on society that comes with an increasing population with impaired vision. Given the coincident systemic disease associated with diabetic retinopathy, the present and predicted burden and health care impact are substantial.

According to the 2012 Vision Problems in the US Report from the Prevent Blindness America foundation, diabetic retinopathy affects more than 7.6 million people age 40 years and older.1 This contributes significantly to the more than $50 billion in direct economic costs of vision problems in the United States.1

As new therapies enter the market, treatment options and dosing strategies can be impacted by the cost of treatment, which continues to be a major factor in treatment planning.2 Clinicians need to consider multiple treatment 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 increase to 324 million, including 35% of whom are expected to develop diabetic retinopathy.3 For nearly 20 years, diabetic retinopathy has been documented as the leading cause of blindness and decreased vision-related quality of life in working-age Americans.4-6 Diabetic macular edema (DME) is the leading cause of blindness and decreased vision-related quality of life, including 35% of whom are expected to develop diabetic retinopathy.7 This contributes significantly to the more than $50 billion in direct economic costs of vision problems in the United States.7

When not treated properly, which is often the case, DME progresses to proliferative diabetic retinopathy (PDR) and retinal neovascularization, hemorrhaging, and permanent loss of vision. Approximately 50% of untreated patients with PDR will become blind within 5 years of the initial diagnosis.8 Such outcomes can frequently be avoided, however. Both decreased vision and decreased vision-related quality of life may be modified by treatment, including new modalities that provide practitioners with the flexibility of customizing management based on each patient’s individual needs.

Focal macular laser photocoagulation (FML) has been the primary treatment for DME for more than 2 decades. The Early Treatment Diabetic Retinopathy Study (ETDRS) outcomes focused on the preservation of vision, finding a 50% reduction in the likelihood of severe vision loss with grid-style FML.9 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 subjects experienced progressive visual loss.10 Emerging therapies have recently shown promise, as both adjunctive and possibly first-line alternatives to laser therapy.

A study conducted by the DRCR.net showed that patients treated with 0.5 mg ranibizumab (Lucentis, Genentech) plus prompt laser (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).11 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 < .001) and in the ranibizumab plus deferred laser group (+9±12, P < .001), compared with those undergoing sham injections plus prompt laser (+3±13) treatments. Visual acuity was not significantly better compared with patients treated with triamcinolone plus prompt laser (+4±13, P = .3). Reduction in mean central subfield thickness was similar in all studied groups. Cataract progression and intraocular pressure (IOP) increases were more frequent in the triamcinolone plus laser group.

More recently, researchers revealed the 2-year primary outcomes of the RISE and RIDE studies, which also focused on the treatment of DME. These phase 2 and 3 studies evaluated 0.3-mg and 0.5-mg doses of ranibizumab compared with subjects who were randomized to sham treatments and focal/grid laser photocautogulation. The RISE and RIDE studies clearly demonstrated that monthly injections of ranibizumab were associated with significant improvement in visual acuity: 40% to 45% of patients gained ≥ 3 or more ETDRS lines of vision.12

Aside from the gain in visual acuity, patients who were treated with ranibizumab overall had fewer complications from their underlying diabetic retinopathy and less progression of diabetic retinopathy than those who were treated with sham injections. Another finding of the RISE and RIDE studies was that no statistically significant differences in side effects or serious systemic or ocular adverse events were associated with subjects treated with ranibizumab injections or sham injections.

In the READ 3 study, patients with DME were treated with multiple injections of either 0.5 mg or 2 mg ranibizumab. The mean increase in visual acuity was 8.7 letters for the 0.5-mg group and 7.5 letters for the 2-mg group. Visual acuity and central retinal thickness changes were maintained up to the 1-year evaluation.13

In 2011, the RESTORE study demonstrated superior gains in best-corrected visual acuity at 1 year with ranibizumab with or without laser vs laser monotherapy.14 In contrast to READ 2, the authors found greater reduction in foveal thickness in the anti-VEGF groups, as well as better vision-related quality of life. The number of total injections over the year for the injection-only group was 7.1 vs 4.8 in the combination therapy group.

Several pharmaceutical therapies for DME are currently in clinical development, including the anti-VEGF agent aflibercept (Eylea, Regeneron), and intravitreal corticosteroid delivery via the dexamethasone intravitreal implant (Ozurdex, Allergan) and the fluocinolone acetonide implant (Iluvien, Alimera).
The MEAD study was a sham-controlled trial assessing the safety and efficacy of 700-μg and 350-μg dexamethasone posterior segment drug delivery systems. Among patients who received the 700-μg implant, 22% experienced improvement of 3 lines or more of visual acuity; 85% had improvements of 4 lines or more. Among those receiving the 350-μg implant, 18% had improvements of 3 lines or more, and 11% had improvements of 4 lines or more. Among sham-treated patients, 12% had 3-line improvements and 4.6% had 4-line improvements. During the 3-year study, patients were evaluated for retreatment every 3 months after the sixth month. Patients assigned to the 700-μg regimen received an average of 4.1 implants over the 3-year period; patients assigned to the 350-μg regimen received an average of 4.4 implants.

Patients with either dose of dexamethasone implant saw an average decrease in central retinal thickness of 110 μm. All patients in the study had a baseline central retinal thickness of 300 μm or greater.

Cataracts developed due to long-term exposure to dexamethasone, hindered visual improvement for phakic patients in the implant groups. After cataract removal, the visual benefits of the dexamethasone treatment were restored. Ocular hypertension, also caused by long-term exposure to dexamethasone, was treated effectively with topical medication, with only 0.3% of patients requiring trabeculectomy to treat increased IOP.

The FAME study found that 2 doses of the fluocinolone implant significantly improved visual acuity in DME over 2 years. The implant can be administered in an outpatient procedure through a 25-gauge needle.

Although intravitreal corticosteroids have added benefit of targeting the inflammatory component of patients with DME, the clinical benefits have been less impressive. They may be an appropriate option with or without FML treatment in nonresponders who are pseudophakic or those who have had successful filtration surgery to control IOP.

The DA VINCI study, a phase 2 randomized clinical trial, showed that all doses and dosing regimens of aflibercept that were tested were superior to laser for centrally involved DME. A significant increase in BCVA from baseline was achieved at week 24 and maintained or improved at week 52 for all aflibercept dosing groups. When aflibercept was administered every 2 months or on an as-needed (prn) basis, these regimens were as effective as monthly treatments.

A 2013 report from the PLACID study demonstrated no significant between-group difference at 12 months for diffuse DME treatment in patients receiving dexamethasone intravitreal implant 0.7 mg combined with laser photocoagulation compared with laser alone.

Also of note in 2013, 2 phase 3 comparison studies (VIVID-DME and VISTA-DME) demonstrated positive 1-year results for treatment of DME comparing aflibercept with laser photocoagulation. 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 < .0001) and 1.2 letters in VIVID-DME (P < .0001). Ocular complications reported included 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 studies evaluating different therapies may lead to a better understanding of pathophysiology and to more efficacious treatments. Because of the continuation of research designed to investigate pathophysiology and the evolution of multiple clinical trials of emerging treatments, updated information on new diagnostic and treatment trends have 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. Finally, in the interest of providing more complete care to patients, arming clinicians with current insights into the management strategies for retinal therapeutics may assist in the reduction of treatment complications and further loss of vision.

**TARGET AUDIENCE**

This certified CME activity is designed for retina specialists and general ophthalmologists involved in the treatment and management of retinal diseases.

**LEARNING OBJECTIVES**

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

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

**ACCREDITATION AND DESIGNATION**

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**FACULTY/STAFF DISCLOSURE DECLARATIONS**

Dr. Eichenbaum states that he receives grant/research support from Genentech and Regeneron, is a consultant to Genentech and Allergan, and is on the speakers list for Genentech.

Dr. Albini states that he receives grant/research support from Genentech, and is a consultant to Allergan, Bausch + Lomb, Eleven, and Thrombogenics.

Dr. Fortun states that he is a consultant to Thrombogenics and Alcon.

Dr. Kitchens states that he has receives grant/research support from Genentech and Regeneron, and is a consultant for Allergan, Genentech, Regeneron, Synergetics, and Thrombogenics.

Dr. Reichel states that he is a consultant to Genentech and Thrombogenics, and is on the speakers list for Regeneron and Thrombogenics.

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**Current Insights Into the Management of Diabetic Macular Edema**

**David Eichenbaum, MD:** Since intravitreal anti-VEGF agents were US Food and Drug Administration (FDA)-approved for the treatment of age-related macular degeneration (AMD), the indications and labels for their use have expanded to additional disease states including retinal vein occlusion (RVO) and diabetic macular edema (DME). Currently, there is only 1 anti-VEGF agent that is FDA-approved for DME, which is ranibizumab (Lucentis Genentech); however, bevacizumab (Avastin, Genentech) is also used off-label. We will most likely have additional agents for DME available in the not-too-distant future, including aflibercept (Eylea, Regeneron), the dexamethasone intravitreal implant (Ozurdex, Allergan), and the fluocinolone acetonide implant (Iluvien, Alimera), so it is important to review our practice patterns, preferences, and interpretation of the evidence related to DME treatments.

**INTERPRETING SAFETY DATA**

**Dr. Eichenbaum:** What are your opinions on the relative safety of anti-VEGF agents when treating disease states such as AMD, RVO, and now DME?

**Thomas A. Albini, MD:** There has been a lot of concern regarding the safety of anti-VEGF agents in DME and close scrutiny of the trial data, but even the most recently announced studies on aflibercept for DME revealed no serious adverse events SAEs. There are few definitive data from prospective randomized control trials that raise safety concerns for cardiovascular events or cerebrovascular events with these drugs. Although it makes sense from a scientific point of view to worry about safety with VEGF suppression, from the limited data we have it seems that patients with diabetes do well with these intravitreally administered drugs.

**John Kitchens, MD:** I have not seen a trend toward systemic SAEs related to VEGF suppression, either in the CATT study or the various studies from which we have data. Diabetic patients are probably our most fragile patient population and the most prone to potential systemic issues, but none of the DME studies have shown any significant increase in systemic SAEs with anti-VEGF agents.

**Jorge A. Fortun, MD:** I agree. Although prospective data are limited, our overall clinical experience shows that these antiangiogenic drugs are well tolerated, particularly in patients with diabetes who are most at risk for potential vasculopathic events.

**Elias Reichel, MD:** Retina specialists have administered millions of these injections over a very long period of time—8 years—and, given the number of physicians and patients using these drugs, if there were safety signals we would have detected them. Also, the clinical studies, while small, suggest that complications from antiangiogenic drugs are rare.

**Dr. Eichenbaum:** What about local safety? We have all heard reports and had experience with inflammation in the eyes when we inject these different drugs into the back of the eye. Do you believe there is a local safety difference between agents that is detectable in the clinic?

**Dr. Fortun:** No. I have had experience with some local effects such as sterile inflammation when using intravitreal injections, but I believe this is related to the injection process itself, not the actual drugs. There may be different characteristics in inflammation between agents, but no one agent has seemed to produce sterile inflammation more than another. The differences I have seen may just be a result of the handling of the drug, or myriad other factors that can apply to any of these agents.

**Dr. Eichenbaum:** When aflibercept was first FDA-approved for AMD, we saw a cluster of sterile inflammation cases. However, the cases were localized geographically and, to some extent, by practice. Data from the VIVID and VISTA trials did not reveal this kind of inflammation. Do you think that this was a fluke or that aflibercept may be more immunogenic than bevacizumab or ranibizumab?

**Dr. Reichel:** I have not had any cases of sterile inflammation with any of these agents. Any cluster cases that have been reported are most likely related to storage and handling of the drugs.

**Dr. Fortun:** I have not had any issues with aflibercept, but it is something that I am worried about because I have heard anecdotal reports regarding sterile inflammation. I have seen sterile inflammation with bevacizumab and ranibizumab, but I have been using those drugs longer.

**Dr. Albini:** I have not had any issues with aflibercept, but it is something that I am worried about because I have heard anecdotal reports regarding sterile inflammation. I have seen sterile inflammation with bevacizumab and ranibizumab, but I have been using those drugs longer.

**Dr. Kitchens:** I agree that any incidence of sterile inflammation with these drugs is not related to the molecules, but to how the drugs are handled and stored. We had some inflammatory issues with aflibercept in some patients in the first year of using it after it was approved for AMD. We had 10 cases compared with 1 case with ranibizumab and no cases with bevacizumab over the same time period, so it was a considerably higher incidence.

**Jon Prenner, MD:** suggested during the American Society of Retina Specialists meeting last year that keeping the vials cold, not subjecting them to fluctuations in temperature, and keeping them from warming over a period of time may help reduce the incidence of inflammation. We now have a “keep it cool” policy in which the vials are stored in a refrigerated environment.
erator until we are ready to inject. This has brought our rate of inflammation to zero.

**Dr. Eichenbaum:** Patients with DME inherently suffer from vasculopathy. Does this cause you to have more worry regarding systemic safety than you might with patients with AMD? Additionally, many patients with DME present bilaterally, as opposed to patients with RVO and AMD presenting unilaterally most of the time. Does bilateral exposure to these agents cause any concerns?

**Dr. Albiní:** Although I worry about the systemic health of all my patients with diabetes, the benefits of anti-VEGF agents far outweigh the risks, based on data from the clinical trials. Anti-VEGF agents are the best treatment, in my opinion, for DME.

**Dr. Eichenbaum:** The trials looked at unilateral exposure, however, not bilateral exposure.

I believe that Genentech elected to recommend approval of the ranibizumab 0.3 mg dose rather than the 0.5 mg dose by the FDA because of concerns associated with systemic exposure with bilateral dosing and similar efficacy between the doses.

**Dr. Fortun:** Patients with DME are certainly different from those with AMD. Our experience with anti-VEGF across several disease processes has been so favorable clinically, however, that even in a population at a higher risk for vasculopathic effect from systemic anti-VEGF the benefits still outweigh the risks. There is a hypothetical concern, but it is nothing that would keep me from using anti-VEGF agents for DME.

**Dr. Albiní:** The other thing to consider is that we may be able to inject every 8 weeks when aflibercept is approved—but we still have data on aflibercept dosed every 4 weeks that show the drug is safe.

**Dr. Reichel:** This issue is interesting. When we started using bevacizumab for DME, dosing was not considered much—we just used the standard dose that we were using for AMD. RISE and RIDE evaluated both the 0.5 mg dose approved for AMD and the 0.3-mg dose of ranibizumab, and, because of safety concerns, Genentech went for FDA approval with the lower dose.

With aflibercept, Regeneron is not altering the dose for treating DME; theoretically, there could be a slight safety concern. However, I believe that this will not be an issue in clinical practice because we monitor patients’ blood pressures and overall systemic health carefully.

**Dr. Eichenbaum:** I have a lot of confidence in the systemic safety of these drugs, even in patients who are vasculopathic or who have a history of vasculopathic events—even within 90 days of infarction. If I have a patient with acute vasculopathic events or risk factors, particularly a patient with diabetes, I inform him or her about the risks, but I will not routinely withhold a dose, especially if the patient is monocular or has aggressive disease.

**TREATMENT STRATEGIES FOR DIABETIC MACULAR EDEMA**

**Dr. Eichenbaum:** The VISTA and VIVID trials provide the most recent pivotal data regarding aflibercept for DME. It is likely that, based on these data, aflibercept will be approved for DME at a 2-mg dose.1 Do you think that aflibercept will be a game-changer if approved, and how will you use it for DME?

**Dr. Fortun:** The main difference with aflibercept is every-8-week dosing. Looking beyond VISTA and VIVID to the DA VINCI data,6 patients in the as-needed (prn) dosing arm had results comparable with those in the other 2-mg arms. Granted, it was a smaller study, but some participants gained 10 or 11 letters at the endpoint of the study. Given those results, the dosing schedule and the reduced treatment burden makes aflibercept an interesting option.

**Dr. Reichel:** I am enthusiastic about aflibercept for a number of reasons. I like the possible prolonged dosing of the drug, which is critical for patients with diabetes because they are younger, working patients for whom multiple visits are burdensome. Also, in my experience, aflibercept has proved most effective for central retinal vein occlusion (CRVO) when compared with ranibizumab and bevacizumab. This is important because the vitreous levels of VEGF in CRVO are highest, followed by DME and then AMD. Based on this, the better response may be mirrored when using aflibercept for DME, so I will most likely choose aflibercept.

I am not sure at this point what my treatment strategy will be. For AMD I am a believer in prn dosing, and I will probably apply a similar approach to DME. I believe that to achieve the best sustained response, early, aggressive treatment is probably more critical for patients with DME than those with AMD.

**Dr. Fortun:** I agree that early treatment is important, and we saw that in all of the trials; the crossover arms never caught up in terms of visual acuity to the treatment arms.

**Dr. Kitchens:** I think that 2014 is going to be a pretty exciting year for diabetes, with many new options available to us. I am looking forward to the FDA approval of the intravitreal dexamethasone implant for DME soon, which will be an important tool in our armamentarium. The fluorocinolone acetonide implant may be available, albeit with a limited indication. I also am positively anticipating the approval of aflibercept.

I will use aflibercept for patients who have not had a fully drying effect with ranibizumab or bevacizumab injections. I will be very interested to see how some of these patients...
who have been receiving injections for a long period of time will respond to aflibercept.

**Dr. Eichenbaum:** Dr. Reichel touched on a couple of important things. First, the ACCORD trial showed that the vitreous levels of VEGF in DME are high\(^8\)—similar to what is seen in CRVO. Second, he mentioned the every-8-week dosing. I think that many of us do not treat on-label with ranibizumab for DME, and I think that over time, the treatment burden is reduced with all of the anti-VEGF agents. I do not think aflibercept will be dosed at a reduced frequency just because it is stated in the label. Especially after the first 12 to 24 months of treatment, it may be dosed at a reduced frequency because regular treatment is less necessary with any agent in DME, unlike wet AMD, once disease control is obtained. However, I do think that the potency of aflibercept will come into the discussion, just as it has in CRVO. Having another choice of agent will enhance our ability to treat the disease.

**Dr. Albini:** In my opinion, aflibercept is the agent with the biggest therapeutic bang across the board. It is already my go-to agent for the conditions for which it is approved. Once it is approved for DME, I will use it, especially because of the reduced injection burden.

However, for many patients, particularly those with bilateral DME, even aflibercept’s injection burden will be unsustainable. For these patients I will use sustained-release treatments, such as the dexamethasone intravitreal implant.

**Dr. Eichenbaum:** I agree that early, intense treatment is important to control DME. In patients with anything approaching a reasonable glycemic state, antiangiogenic drugs probably have a real disease-modifying effect.

Dr. Albini, you mentioned the potential of dexamethasone approval, which is anticipated based on the MEAD trial results.\(^9\) Do you think dexamethasone could be used in conjunction with other agents, or do you think it will be used primarily on its own? The MEAD data indicate that, although dexamethasone could reduce the burden of frequent anti-VEGF injections, it probably does not have the same benefits of the antiangiogenic drugs, particularly in phakic patients.

**Dr. Albini:** I think the majority of retina specialists who are considering using the dexamethasone implant will most likely use it in combination with anti-VEGF treatments. For me, however, it is difficult to see what my treatment strategy would be using the dexamethasone implant as a combination therapy, so initially, I will use it as monotherapy for patients who really require a lower injection burden. In my opinion, this is the clear niche of this drug. In the MEAD trial, patients had good results with only 2 injections per year of the implant per eye, as opposed to 6 injections with anti-VEGF agents.

One of the problems with combination therapy is that we do not have the clinical trial data to guide us.

**Dr. Fortun:** Out of all of the diseases we treat, DME lends itself least to a “cookbook approach” because it is so varied from patient to patient. Steroids do not suppress VEGF, but they do address the inflammatory component in diabetic retinopathy, so I believe that the dexamethasone intravitreal implant will find its niche as an adjuvant.

**Dr. Eichenbaum:** We have a wealth of experience using intravitreal triamcinolone acetonide (IVTA; Kenalog, Bristol-Myers Squibb) injections for DME, but I believe that dexamethasone will be a better agent overall to use as monotherapy or in combination. The specific benefits of the time-release dexamethasone as a steroid and delivery system include its better safety profile over IVTA and the duration of efficacy in sustained release.

**THE ROLE OF LASER**

**Dr. Eichenbaum:** There is still a role for thermal laser in DME. For noncentral DME, circinate exudates, extrafoveal disease, and other disease that meets the definition of classic clinically significant DME, laser is a reasonable first-line treatment.

We now have a large amount of data, however, emphasizing the superiority of anti-VEGF agents and steroids over laser for visual improvement in patients with center-involved DME. Findings from the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I suggest that the burden of these injections is likely reduced over time, even without laser. In your day-to-day practice, what is the role of thermal laser for your center-involved DME patients?

**Dr. Albini:** If there is a focal leaking microaneurysm responsible for central fluid I will still use 1 round of prompt laser. I inject with an anti-VEGF agent for diffuse DME.

**Dr. Fortun:** For diffuse DME, I mainly inject. I will use laser only for clusters of leaky vessels if they do not respond to an injection.

**Dr. Reichel:** Laser definitely has an added effect, although I am not sure if its use relieves the treatment burden of injections. For focal DME, I apply laser alone. In the case of diffuse edema with a focal leak that is extending to the fovea, I will inject anti-VEGF to dry the leakage and then apply deferred laser. The DRCR.net Protocol I defined deferred as more than 6 months after the initiation of anti-VEGF injections.\(^1\) In my opinion, this is too long, but I do not think prompt laser is a good idea either. I would most likely apply laser after 3 or 4 anti-VEGF injections. I do not know if I would use laser in cases in which the retina is significantly edematous.

I have used micropulse laser with good results for DME, and I believe it to be important that the DRCR.net perform...
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Studies using this technology in combination with anti-VEGF therapy.

**Combination Therapy**

**Dr. Eichenbaum:** What is the role of combination therapy for DME?

**Dr. Reichel:** Going back to the topic of steroids, I agree with Drs. Fortun and Albini—there is no cookbook for using steroids in combination therapy, but there also is no cookbook approach to treating DME. Approximately 10% to 15% of patients with diabetes have 400 µm to 600 µm of retinal thickness that will not respond to any anti-VEGF therapy or laser. The dexamethasone implant will play an important role for these patients. We have 3 years of data showing that the dexamethasone implant is safer than any other steroid that we have had available.9

Regarding the issue of dexamethasone implant and IOP, fortunately, only about 1 out of 300 patients had to undergo an incisional glaucoma procedure; the rate of cataracts in the MEAD study was about 23%,9 which in patients with chronic DME is not a significant issue. These data provide retina specialists the confidence to go ahead and inject multiple dexamethasone implants.

**Dr. Eichenbaum:** This is an important point. Patients with chronic and later-stage DME, such as those with central thickness of 600 µm and visual acuity of 20/200, are similar to our patients with acute CRVO. I use multiple types of treatments in combination on the patients with acute CRVO: antiangiogenic, dexamethasone, and, sometimes, peripheral scatter laser. Patients with advanced diabetes and thick edema may need combination therapy as well.

**Dr. Reichel:** The MEAD study was interesting because the average duration of the participants’ disease was 18 months.9 Diabetic macular edema was chronic and the edema was thick. For these patients we have to be aggressive—often, 1 or even 2 types of therapy will not work.

**Dr. Albini:** I think another thing to point out about the MEAD study is that participants received only 2 injections of the dexamethasone implant per year.9 In reality, many of these patients require more than that. We know from CRVO and other diseases that the effect of the dexamethasone implant starts to diminish after about month 3 or 4. There is a possibility that patients may have better visual acuity outcomes in a real-world setting than what we saw in MEAD.

**Dr. Eichenbaum:** With any injectable therapy, patients can be injected more frequently in the clinic vs the clinical trials when necessary, especially early in the treatment course. In VIVID and VISTA, for example, after the protocol converted from the initial monthly loading doses of aflibercept to every 8 weeks after 3 injections, there was a slight increase in retinal thickness on optical coherence tomography (OCT) at the first 8-week timepoint. This shows that some participants were not staying dry early on with the every-8-week dosing regimen.

Based on this information, would you inject patients more with either monotherapy aflibercept or whatever combination you are using, or at least as frequently as is enough to keep them dry throughout that first year of DME treatment?

**Dr. Albini:** Systemic safety is the only factor that I would weigh against injecting aflibercept more frequently. If the patient has bilateral disease, and I am injecting 2 eyes with aflibercept every 2 weeks, I may worry about the long-term systemic effects. If efficacy were the only concern, more frequent injections make sense. However, there would still be the issue of injection burden.

**Patient Compliance and Counseling**

**Dr. Eichenbaum:** What are the main issues surrounding patient compliance with DME?

**Dr. Kitchens:** I think patients with diabetes have a different threshold of compliance than our patients with AMD. Patients with diabetes tend to be younger, so they may be more able to get themselves to their appointments. They are used to living with a chronic disease, unlike patients with acute CRVO, who are often overwhelmed when the event occurs. Also, the treatments they have received for DME often have not worked, so when we are able to achieve anatomic results, these patients are more likely to comply with a treatment regimen.

**Dr. Albini:** My patients with diabetes in Miami are very different from Dr. Kitchens’ diabetic patients.

**Dr. Eichenbaum:** I wish I had a population more like Dr. Kitchens’ patients! I often worry about my patients with DME not coming in for follow-up and eventually having to deal with severe disease progression such as proliferation, vitreous hemorrhage, and tractional retinal detachments (TRDs). The patients are inherently noncompliant, which is how their diabetes has progressed enough to develop DME.

**Dr. Albini:** Exactly. Because these patients are in the workforce, it is not easy to get them to take off time for an appointment with me every 2 weeks.

**Dr. Kitchens:** Do you have Saturday clinics?

**Dr. Kitchens:** No, we do not. Patient counseling at the outset is critical. For example, if you tell a patient that he or she is going to get monthly injections over the next year and that you are going to do everything you can to save his or her vision, I do not think that is a convincing message. Rather, it is the same message they have heard before. If you
say to them, however, “Hey, guess what, I am going to tell you something that you probably never hear—I will make you better. All you have to do is come back 12 times over the next 12 months, and be willing to do whatever it takes to save your vision,” I find that patients buy into this.

Dr. Fortun: Early and aggressive treatment is a requirement to improve DME. The drier the retina is in any disease process, the better the outcomes will be. That said, a dry retina in DME is probably less important than it is in AMD. Patients with DME can probably tolerate a little bit of edema for a couple of weeks if they are entering a rebound period. The common thinking is that if we cannot control DME with treatments every 3 months, we are not treating the patient appropriately. DME is more of a systemic disease than AMD, yet somehow we find it acceptable to give monthly injections for AMD but not for DME.

To promote better compliance with my patients who have DME, I present the treatment as dialysis for the retina. I tell my patients the vessels in the eye are the same as the small blood vessels in their kidneys. When you sell treatment to patients as one for a chronic disease that will stabilize or improve their condition, I think you get better compliance.

Dr. Eichenbaum: I agree. I do not think I can overemphasize to my patients that their systemic disease control affects the overall outcome with the eye. I like the message that we are going to make patients better with frequent treatments, but I do not feel confident telling that to a patient who comes in with a history of an HbA1c level of 10 or 12. I tell my patients that without good systemic control I can probably buy them time, but if they cannot control their blood sugar level the diabetes will eventually win and they will lose their vision. I feel it is important to be compassionate but frank about how aggressive diabetic eye disease can be.

Dr. Kitchens: I agree with you on being frank, but I have that talk with patients on their second visit. After I have gives patients a message of hope I relay my strategy for treatment and ensure that they understand what they need to do systemically to help save their vision.

I also think having a widefield angiogram to show patients helps drive home the gravity of their disease. If a patient has significant peripheral nonperfusion, I am able to show them a normal widefield angiogram and then show them theirs and say, “Look, this is the damage that has happened.” I have found that this can spur a patient to make a lot of lifestyle changes.

Dr. Eichenbaum: The advanced imaging that we now have is a very powerful tool, and we should be using it for educating our patients more than we currently do. An image of a diabetic retina drives the message home that patients need to be making changes to improve their condition, particularly for younger patients.

When you see peripheral nonperfusion, what do you do about it? Do you consider using scatter laser treatment, or is there not enough data to support using it for DME patients?

Dr. Albini: I have never used scatter laser for peripheral nonperfusion.

Dr. Fortun: I have used scatter laser treatment for CRVO, and I have also used it for DME, particularly in patients for whom I wish to reduce the treatment burden of frequent injections. I am unaware, however, of any solid data showing that scatter laser plays a role in reducing the overall VEGF load.

Dr. Reichel: We do not have a widefield angiography system, so I do not have much experience with scatter laser; however, I have tried it in desperation and have been unimpressed.

PREVENTING PROGRESSION OF DIABETIC RETINOPATHY

Dr. Eichenbaum: What do you see as being the next big development in the area of DME?

Dr. Fortun: I think that if we prevent diabetic retinopathy from progressing the DME, that would be a big advantage for our patients. There are some secondary data from VIVID and VISTA that show that anti-VEGF may have a role in reducing in the progression of diabetic retinopathy.1

Dr. Albini: These data could represent a revolution for our diabetic patients if monthly or bimonthly injections in those patients prove to be successful in treating moderate to severe diabetic retinopathy. This will definitely change our treatment patterns.

Dr. Kitchens: If I have a patient with moderate or mild DME but good visual acuity, 20/20 or 20/25, I consider whether I want to commit this person to monthly injections for the next 3 months to 1 year to get rid of macular edema that is not of significant consequence to visual acuity. However, if a patient have severe nonproliferative changes, or maybe even early proliferative changes, I will inject an anti-VEGF agent because, not only am I going to make their edema better, I will also make the retinopathy better.

Dr. Eichenbaum: We have evidence from DRCR.net Protocol I3 and the subgroup analysis that shows these patients with good vision get worse over the course of 3 to 6 months if they are not treated. Thirty percent of these patients lost 5 letters of vision or more if they were untreated. Protocol V is looking at center-involved DME in patients with very good vision (20/25 or better) prospectively and randomizing them to prompt laser and deferred anti-VEGF, observation and...
deferred anti-VEGF, and prompt anti-VEGF. I believe these data may push us all to treat retinopathy even earlier, even when the patient is not significantly symptomatic.

Dr. Kitchens: The DRCR.net looked at subclinical DME and found that many of these patients will not progress over the course of a few years. Is it difficult to know whether anti-VEGF injections will produce results for these patients. This is why it is important to take everything into consideration when you start to think about committing these patients to the burden of monthly injections.

Dr. Albini: If aflibercept does get approved with an indication for retinopathy without DME, would you try treating based on that?

Dr. Kitchens: We have all seen the dramatic changes that bevacizumab and ranibizumab can make in proliferative disease, and even in very severe nonproliferative disease. I may treat with aflibercept, depending on the severity of the retinopathy.

Dr. Fortun: My threshold for injecting aflibercept would depend on the optimal dosing interval for that indication, which we do not currently know.

Dr. Kitchens: I think the dosing interval would be based on the VIVID and VISTA trials—monthly dosing for the first 3 months and then every 8 weeks.

Dr. Fortun: I would consider injecting aflibercept for severe nonproliferative or early proliferative diabetic retinopathy, most likely using a prn regimen.

Dr. Eichenbaum: It would be nice to have the option of using aflibercept or ranibizumab in the setting of diabetic retinopathy (instead of only DME) because it would open up the treatment of proliferation without DME to these agents. At this point, I have restricted treatment of proliferation to bevacizumab. I believe that ranibizumab is more potent and potentially safer than bevacizumab for DME; I believe that if we had more potent agents for retinopathy, most likely using a prn regimen.

Dr. Albini: I am somewhat wary about using aflibercept to treat proliferative retinopathy. If the data prove a benefit, I may do so.

Dr. Kitchens: I agree. It is a difficult decision to commit a patient who has 20/20 vision to frequent injections.

Dr. Albini: We are accustomed to observing these patients for at least 3 months until they develop high-risk characteristics.

Dr. Eichenbaum: In the setting of proliferation, treating with aflibercept, ranibizumab, or bevacizumab could provide a benefit. I have made the mistake in the past of not treating non–high-risk proliferation and then having a patient non-compliant with follow-up come back in 18 months with an opaque vitreous hemorrhage and traction. At the very least, non–high-risk new retinopathy should be followed closely. A lot of my treatment recommendations for new cases of non–high-risk PDR are made by trying to determine the reliability of the patient—and that is difficult to do.

Dr. Reichel: The most vexing patient for me is the patient with reasonably good vision—20/30 or 20/40—who has had 3 anti-VEGF injections that have resolved most of the edema but who has a central foveal cyst. The photoreceptors look good on OCT, he or she does not have vitreomacular traction. What would you do in this scenario? Do you continue injecting, or do you watch and wait?

Dr. Fortun: I wait and watch.

Dr. Eichenbaum: I will treat until there is no change in the OCT for at least 2 or 3 injections. Then, I may stretch out the treatment or skip 1 month and see if the cyst gets worse. In my experience, the vast majority of patients with central foveal cysts will not worsen for several months.

Dr. Fortun: In DME, unlike AMD where we worry about the catastrophic bleed, there is some wiggle room, in that you can observe to see how a patient responds to treatment.

Dr. Eichenbaum: That is an important point. You can try to customize the treatment as we do for everything, and there is more latitude in DME. You look at the patient’s specific needs, at his or her tolerance of the treatment burden, the cost, and the frequency of follow-up, and you can do that in the context of your knowledge of this growing database of clinical trial results.
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CME QUESTIONS

1. The RISE and RIDE studies found that:
   a. Ranibizumab is associated with improved visual acuity for patients with DME.
   b. Between the 2 doses of ranibizumab evaluated, the 0.5-mg dose was associated with higher rates of adverse events than the 0.3-mg dose.
   c. Ranibizumab was not associated with a significantly higher rate of adverse events compared to sham injection.
   d. All of the above.

2. If left untreated, diabetic macular edema (DME) can progress to:
   a. hemorrhaging
   b. nonproliferative diabetic retinopathy
   c. transient visual acuity loss
   d. retinal neovascularization
   e. a and c
   f. a and d

3. In the VIVID and VISTA trials, aflibercept was found to be effective and safe for the treatment of DME.
   a. true
   b. false

4. The ACCORD trial demonstrated that VEGF levels in patients with DME are:
   a. higher than in age-related macular degeneration (AMD)
   b. lower than in AMD
   c. no different than AMD
   d. none of the above

5. The recommendations from the DRCR.net Protocol I include:
   a. six month deferral of laser after anti-VEGF injections
   b. three month deferral of laser after anti-VEGF injections
   c. prompt laser
   d. none of the above
### Did the program meet the following educational objectives?

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<th>Objective</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
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<td>Describe the current epidemiology of major retinal diseases, including AMD, RVO and DME</td>
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<td>Assess pivotal clinical studies involving new approaches to treat DME</td>
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<td>Utilize expert case examples to differentiate between clinical study dosing protocols and alternative dosing schedules</td>
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<td>Interpret retinal imaging case examples describing the treatment of DME</td>
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<td>Educate patients on ophthalmic implications of systemic diabetes management</td>
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Do you feel the program was educationally sound and commercially balanced? □ Yes □ No

Comments regarding commercial bias: __________________________________________________________________________________

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

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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.

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If no, please identify the barriers to change.

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