HOT TOPIC

Advances in the Treatment of **Diabetic Macular Edema**

Mary Beth Yackey, OD
Cincinnati Eye Institute

Can you believe that 34.2 million people who reside in the United States have diabetes? Overall crude estimations show that 13.0 percent of adults in the US have diabetes according to the Centers for Disease Control and Prevention. The percentage of adults with diabetes increases with age, reaching 26.8 percent among those 65 years and older. (1)

With a disease that is so prevalent, it is no surprise that diabetic retinopathy is the leading cause of blindness in the working-age population in the United States and one of the leading causes of blindness worldwide. (2) Since the 1980's, laser photocoagulation was really the only option for effective treatment of diabetic macular edema. Fortunately, however, over the past several years we have seen other treatment options emerge for those with diabetic macular edema. It is important to remember that diabetic macular edema (DME) can occur at any stage of retinopathy from very mild to severe proliferative disease.

Diabetes is a complex disease requiring many healthcare disciplines to work together as a team to best care for a patient with diabetes. The first step to managing a diabetic patient is to identify the disease. Educating the patient about diabetes is vitally important so that systemic control occurs. The diabetic patient must understand the importance of lifestyle choices and the effect of each on their overall health. A few of the modifiable factors that influence the patient's overall well-being include smoking, overweight and obesity, physical activity, daily blood sugar levels and A1C, hypertension, and high cholesterol. (1) Landmark clinical studies, such as the Diabetes Control and Complications Trial, have demonstrated the benefit of increased glycemic control with respect to diabetic retinopathy, and follow-up studies have highlighted that continued glycemic control remains this reduced risk. (3,4,5). Proper treatment and management of patients who have diabetes and its comorbidities are integral into the prevention, treatment, and management of diabetic retinopathy.

For decades, laser therapy was the gold standard treatment for those with sight-threatening eye disease secondary to diabetic macular edema. The Early Treatment Diabetic Retinopathy Study (ETDRS) found that focal laser photocoagulation for clinically significant DME was superior to observation. Grid and focal laser treatment seals leaking capillaries and aneurysms, decreasing the accumulation of fluid and exudates in the retina. Patients in the ETDRS who received macular laser treatment had 50% less risk for moderate vision loss than those that did not receive laser treatment. (6) Laser therapy is effective at reducing progressive loss of vision, but only 3% of eyes undergoing laser treatment gained 3 or more lines of vision. (6) For this reason it is important to counsel patients with DME that the goal is to stabilize vision and reduce the likelihood of further loss, not necessarily to improve visual function. (3) Another complication of focal/grid therapy is that it can leave the patient with small central scotomas which can enlarge over time due to a phenomenon known as laser "creep" in which the laser lesions can expand with time. (6) If the focal or grid laser is accidentally applied to the papillomacular bundle, vision will adversely be affected.

Fortunately, new paradigms have emerged yielding more treatment options for DME. One class of newer treatment modalities for DME is Anti-VEGF. In most cases today, intravitreal anti-VEGF is given as the first line of treatment for DME. Anti-VEGF medications can stabilize and even improve vision overtime. They also have favorable safety profiles. The RISE and RIDE trials proved over a 2-year period that patients gained 12 letters of vision when treated with ranibizumab (Lucentis, Genetech). This effect was maintained with continued treatment of ranibizumab. (7) The FDA has approved both ranibizumab (Lucentis, Genetech) and aflibercept (Eylea, Regeneron) to treat diabetic retinopathy in patients with DME.(8,9,10, 11) Bevacizumab (Avastin, Genetech) is used off-label in retinal care. All three anti-VEGF's are unique in their molecular structure and pharmacokinetics. (12) Ranibizumab is a monoclonal antibody fragment. Aflibercept is a fusion protein that combines the binding domains of VEGF receptors 1 and 2 with an antibody fragment. Bevacizumab is full length, bivalent monoclonal antibody against VEGF-A, and was originally produced for use in oncology. The DRCR Retina Network's Protocol T study found compared the safety and efficacy of all three and found that they all worked well. After 1 year of treatment with aflibercept, patients with poor baseline vision achieved more substantial improvements in vision. Also, greater macular thinning was obtained with 1 year treatment of aflibercept than the other two Anti-VEGFs. However, at 2 years, aflibercept was no more effective than ranibizumab for the treatment of eyes with DME and more severe visual impairment. (12)

It is not surprising that multiple studies have shown that Anti-VEGF injections are superior to laser therapy in decreasing DME and improving vision. (13-16) The BOLT study looked at patients with persistent DME who had been previously treated with laser, and compared bevacizumab (Avastin, Genetech) injection versus more laser therapy to control DME. The bevacizumab group gained 8 letters of vision on average and an average decrease in central macular thickness of 130 mm, while the repeat laser group lost an average of 0.5 letters and central macular thickness decreased by 68mm on average. (13) The RESTORE study compared three arms of treatment: ranibizumab (Lucentis, Genetech) alone, ranibizumab injections plus laser treatment, and laser only. At 12 months, both the amount of vision gained and the decrease in central macular thickness proved superior in the anti-VEGF treatment, ranibizumab, alone compared with laser only treatment at 12 months. (14,15)

Why do we still do laser treatment if anti-VEGF proves to be so much more efficacious? The answer is found in the REVEAL study. What this study shows is that patients who were treated with ranibizumab alone received on average 7.8 injections in the first 12 months compared to the laser

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alone patients who received an average of 1.9 treatments. (16) Anti-VEGF therapy is more effective than laser in the management of DME but it requires several more office visits for treatment. Laser therapy remains a reasonable treatment option for those who are not able to travel to the office easily or have a history of poor compliance with follow-up care. There are some patients that simply do not respond well to anti-VEGF therapy which makes laser treatment a better choice. Finally, the cost of treatment is cheaper with laser compared to anti-VEGF for DME control.

Given the above benefits of laser treatment, it is easy to understand that laser therapy for DME is yet a relevant option. MicroPulse laser therapy has evolved the way laser treatment can be performed. First, the hardware has changed from water-cooled, tube-based energy sources to smaller solid-state photocoagulators. Treatment has changed from thermal laser burns to low-intensity laser burns to nonvisible, sublethal protocols that result in no laser burn during or after treatment, such as MicroPulse laser therapy (IRIDEX). There is no thermal necrosis, but rather a stress response to induce a biological effect. MicroPulse is gentle enough to be applied safely to mild foveal edema or juxtafoveal edema of any thickness. The beauty of MicroPulse laser treatment is that it does not leave laser scars and can be used safely and repeatedly. MicroPulse laser treatment may be used by itself or combined with anti-VEGF to help control DME. (17)

In addition to Anti-VEGF and laser treatment for DME, let us not forget about the benefits of steroid therapy. Corticosteroids inhibit the activity of VEGF and suppress other inflammatory cytokines that are involved in the pathophysiology of DME. (18, 19) Another benefit of corticosteroids is that they restore patency to retinal vessels and decrease vascular leakage. In addition, steroid therapy is beneficial when anti-VEGF is not effective at reducing DME. Unfortunately, steroid therapy can cause cataracts to develop and may cause ocular hypertension.

The newest way to deliver steroid is via sustained release formulations. The MEAD trial showed dexamethasone intravitreal implant 0.7mg (Ozurdex, Allergan) to be efficacious and safe and gained FDA approval for the treatment of DME. (20) Another FDA approved sustained-release steroid is fluocinolone acetonide intravitreal implant 0.19mg (Iluvien, Alimera). The FAME trial proved the safety and efficacy of fluocinolone acetonide. (21) It is important to notice the differences between these two sustained-release medications. The benefit of sustained-release formulas is that there is a decreased injection burden. Dexamethasone intravitreal implant 0.7mg is a biodegradable device releases medication over 4-6 months, while fluocinolone acetonide intravitreal implant 0.19mg is not biodegradable and has a 3-year duration of effect. Moreover, fluocinolone acetonide intravitreal implant 0.19mg is injected through a smaller needle than the dexamethasone device. Before proceeding with the treatment using fluocinolone acetonide, a steroid challenge must be done to prove safety of use of steroids without responding ocular hypertension.

The industry has come a long way for providing treatment options for those with DME. Lasers are becoming safer with less side effects with the advent of MicroPulse treatment. Injectable Anti-VEGF options remain first-line therapy for DME, but do not always work alone and may be combined with laser or steroid treatment. Injectable corticosteroids provide yet another measure for treating DME. Sustained-release steroid options allow for less number of treatments and decrease patient burden. Overall, these newer treatment options for DME will allow for the patient to have a better quality of life and yield safer and effective treatment options.

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Advances in the Treatment of **Diabetic Macular Edema** | The Surgical Perspective

MIDWEST COMMENTARY

Haroon Chaudhry, MD

Specializing in Vitreoretinal Diseases & Surgery

Cincinnati Eye Institute

Many optometrists have an OCT but don't have OCT-A. Is this something they should invest in?

While our patients benefit greatly from having access to OCT in your offices, I don't think OCT-A is at an investment stage. It provides non-invasive details about the vasculature but is cumbersome data to interpret which doesn't add much until treating. OCT, fundus photos and/or dilation are more useful in detecting disease and that won't change in the near future.

Other than telling patients that we are referring them to a retina specialist for diabetes, do you have any patient recommendation tips on what to expect for that visit and treatment? What can optometrists share with retinal specialists to make the patient transition as smooth as possible?

I find diabetic patients range from strict compliance with referrals to dangerous non-compliance. Tell them they'll be dilated and have imaging but most important is to take this seriously. They should be educated that diabetic retinopathy is a leading cause of vision loss but preemptively discussing injections and lasers may scare the ones who need it most from showing up. I bring this up after explaining the disease differently for different personalities. For some it's 'this is your only chance don't miss it' and for others it's 'treatment is what we want to avoid with lifestyle changes.'

MID-ATLANTIC COMMENTARY

Kori Elkins, MD

Specializing in Age-Related Macular Degeneration, Diabetic Retinopathy and Retinal Surgery.

Tidewater Eye Centers

Any comments on electrodiagnostics for diabetic retinopathy?

Electrodiagnostic testing includes electroretinography (ERG), visual evoked potential (VEP) and electo-oculogram (EOG). While VEPs and EOGs are commonly used to help differentiate neuro-ophthalmic conditions, an ERG is a direct measure of photoreceptor function. In particular interest for diabetic patients are abnormalities on multifocal ERG (mfERG) testing with a machine like the Diopsys. Several studies have confirmed a decrease in amplitude for diabetic patients, even before they have visible retinopathy. These findings suggest that neurodegeneration is occurring early in these patients and would serve as a tool to monitor for progressive damage as well as patient education.

How do you decide on when to use on-label (Lucentis, Eylea) vs. off-label treatments (Avastin)?

According to data published by the Organisation for Economic Co-operation and Development (OECD), which comprises 30 countries including the majority of Europe, the US, Canada and Japan, there are twice as many Avastin injections performed in the U.S. than both Lucentis and Eylea combined. Personally, I start my patients on Avastin even though it is off-label. We have a frank discussion regarding its usage as an off-label medication and my rationale for why I think it is a good choice for them. Our knowledge regarding the safety of all three treatments is excellent and there is little difference in their safety and side-effect profile. If a patient has a history of using a different medication and is new to me, then I continue them on their previous treatment. If there has been no significant response after 3 injections then I am quick to switch to Eylea or consider an intravitreal steroid like Triesence or Ozurdex (for DME or RVO patients).