

Clinical Implications of Potential Therapies for Diabetic Macular Edema

Several therapies have been investigated or are in use; none are approved specifically for DME.

**BY QUAN DONG NGUYEN, MD, MSC; DIANA V. DO, MD;
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INTRODUCTION

In an era in which multiple pharmacologic therapies are available and in use for the treatment of diabetic macular edema (DME), it may be surprising to realize that none of these therapeutic options are actually *approved* by the US Food and Drug Administration (FDA) for this indication. While many physicians are employing available devices and drugs off-label for the treatment of DME, clinical trials are ongoing to demonstrate the efficacy and safety of these agents for the condition. Other therapies await further clinical evaluation or are under consideration for approval by the FDA.

Retina Today asked leading retina clinicians and researchers to comment on the clinical potential of these agents, some of which are already in wide (off-label) use for the treatment of DME, others of which are eagerly awaited as additional options for DME management.

QUAN DONG NGUYEN, MD, MSC

Ranibizumab (Lucentis, Genentech) is a vascular endothelial growth factor (VEGF)-inhibiting pharmacologic agent that is FDA-approved as intravitreal injection for the treatment of patients with neovascular age-related macular degeneration (AMD) and macular edema following retinal vein occlusion.¹

Several years ago, my colleagues (Peter Campochiaro, Julia Haller, Diana Do, and other Wilmer Eye Institute investigators) and I published one of the very first papers investigating the use of ranibizumab for DME.² Our early work showed that ranibizumab was effective in reducing macular edema in DME and improving visual acuity. Since then, several randomized clinical trials have demonstrated that anti-VEGF blockade with ranibizumab is an

effective and safe treatment for DME. Although not yet FDA approved for DME, ranibizumab, along with other anti-VEGF agents, has become standard of care for patients with center-involved DME.

The 3-year outcome of the READ-2 study, which was an investigator-led clinical trial conducted across 14 sites in the United States, including 1 led by David Boyer, that we recently presented indicated that patients who were treated initially with laser and subsequently changed over to ranibizumab did not do as well at the 3-year follow-up as those who were treated with ranibizumab initially. The finding suggests that perhaps, if one plans to treat a patient with DME, and if ranibizumab or another antiangiogenic agent is available, one should consider using it, rather than laser, as the first line of therapy.

I also recently presented at the 2011 Congress of the American Society of Retina Specialists in Boston the 2-year primary outcomes of RISE and RIDE, the 2 phase 3 studies evaluating 2 different doses (0.3mg and 0.5mg) of ranibizumab compared to sham injection (those randomized to sham treatment could receive focal/grid laser) for the treatment of DME. The RISE and RIDE studies clearly demonstrated that monthly injection of ranibizumab was associated with significant improvement in visual acuity: 40% to 45% of patients gained 3 or more ETDRS lines of vision. In addition to the gain in visual acuity, patients who were treated with ranibizumab overall had fewer complications from their underlying diabetic retinopathy (DR) and less progression of the DR than those treated with sham injection. As the progression of DR lessens, fewer patients will lose vision from the diabetes, which could represent major socioeconomic benefits for our patients and society.

Another finding of the RISE and RIDE studies was that there were no statistically significant differences in side effects—serious systemic or ocular adverse events—between the groups treated with ranibizumab or those with sham injection.

Thus, the emerging data shows that anti-VEGF therapy for DME is overwhelmingly more beneficial than laser. Therefore, it may no longer be appropriate for patients with DME to have laser as first line, initial therapy, unless there are other relevant associated factors.

However, we also recognize from the RISE and RIDE results that patients should receive monthly injections of ranibizumab in order to achieve the highly successful outcomes. Such regimen may be a burden on patients. We continue to search for treatment options that can reduce the frequency of treatment or improve visual outcomes in patients with DME. The READ-3 study is an ongoing investigator-led multicenter study in the United States comparing 0.5 mg and 2.0 mg doses of ranibizumab in patients with DME. The results of this study, which will address the question of whether a higher dose of ranibizumab will provide either better outcomes or less frequency of treatments, will be forthcoming. I will be presenting the 6-month primary outcome of the READ-3 Study at the upcoming 2011 American Academy of Ophthalmology Convention in Orlando.

DIANA V. DO, MD

Aflibercept (Eylea, formerly VEGF Trap-Eye, Regeneron Pharmaceuticals) is an antiangiogenic agent formulated for intravitreal injection, a fusion protein specifically designed to bind all forms of VEGF-A and placental growth factor (PlGF).³

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.⁴ These positive results were seen both at the primary outcome of the study at month 6 and also at 1 year. The significance of the DA VINCI study lies with the dosing regimen of aflibercept. The study showed that, when aflibercept was administered every 2 months or on an as-needed (prn) basis, these regimens were just as effective as monthly treatment.

The advantage of aflibercept is that it behaves differently from the current monoclonal antibodies, ranibizumab and bevacizumab (Avastin, Genentech). Aflibercept is a fusion protein, specifically designed to have a higher binding affinity for VEGF. Therefore, theoretically, it is more durable and has a longer duration of action in the eye. Clinical trials in both DME and neo-

vascular AMD have demonstrated this durability, showing that aflibercept's biologic activity appears to extend for at least 2 months. Aflibercept therefore has an advantage over current anti-VEGF treatments, with excellent bioactivity and excellent visual acuity results.

Clinically, if this compound is approved, it will allow patients with AMD to be seen every 2 months instead of every month without sacrificing efficacy. In DME as well, the DA VINCI data suggest that patients can be seen or treated every 2 months instead of every month and still maintain excellent visual acuity results. This is a potentially very positive aspect of aflibercept, and it will make the follow-up of patients with these chronic diseases less burdensome for both patients and their families.

Over the past 2 years, more and more evidence has emerged showing that anti-VEGF agents are superior to laser for center-involved DME. As retina specialists become aware of this data, they will increasingly use anti-VEGF therapy as their first-line treatment for center-involved DME. Aflibercept will fit well into this clinical armamentarium; it has been both efficacious and safe in clinical trials to date, and it has a longer duration of action than other available anti-VEGF agents.

At this time, it appears that most anti-VEGF agents work best as monotherapy. There is no clinical trial evidence data to suggest that combination therapy, either with laser or a steroid, is more efficacious than anti-VEGF therapy alone. Until we have that data, I would recommend using the anti-VEGF agents alone, because that appears to be the most efficacious and safe way to treat patients.

Based on the positive results of the DA VINCI study, a phase 3 study of the drug in patients with DME has been initiated. One-year results of this study may be available next year.

DAVID S. BOYER, MD

The dexamethasone implant (Ozurdex, Allergan) is a corticosteroid intravitreal implant containing dexamethasone 0.7 mg in the Novadur solid polymer drug delivery system. It is indicated for the treatment of macular edema following branch or central retinal vein occlusion and noninfectious posterior uveitis.⁵

In studies evaluating anti-VEGF treatments for DME, patients respond very well, but there is still residual fluid in some patients. I think we will find that steroids, delivered long-term with devices such as the dexamethasone implant, will be a good adjunct to treatment with anti-VEGF therapy, and also as an alternative therapy in certain patients who do not respond well to anti-VEGF therapy.

In clinical practice, most retina specialists will proba-

Phase 1 Trial Shows Promise for Antisense Drug

iCo-007 works by a different mechanism than anti-VEGF drugs.

BY QUAN DONG NGUYEN, MD, MSC; AND DAVID S. BOYER, MD

A pharmaceutical agent in development for the treatment of retinal diseases has shown promise in a phase 1 clinical trial in patients with diabetic macular edema (DME).¹ iCo-007 (iCo Therapeutics, Inc. Vancouver, Canada) is of great interest to retina specialists because it uses a novel, different mechanism from the existing therapies that target inhibition of vascular endothelial growth factor (VEGF).

iCo-007 is an oligonucleotide, a second-generation antisense inhibitor targeting C-raf kinase messenger ribonucleic acid (mRNA). Multiple growth factors, not only VEGF, seem to be implicated in the etiology of DME. iCo-007 has the potential to inhibit neovascularization and decrease vascular permeability by binding to the mRNA molecule and decreasing the production of C-raf kinase, a pathway through which multiple growth factors signal.

The phase 1 study of iCo-007 indicated that the compound is safe and that it seems to have a long duration of action, with a period of several months before retreatment is needed. A question of great interest is whether the combination of the mechanisms of action of a C-raf kinase inhibitor and an anti-VEGF molecule will be more efficacious than either agent alone. If that is found, the use of two different approaches would give patients with DME the maximum opportunity for benefit.

Based on the encouraging data from the phase 1 study, the phase 2 investigator-led study, iDEAL, is currently being planned and will be a collaborative effort among the investigators, iCo Therapeutics, and the Juvenile Diabetes Research Foundation, which has funded the READ, READ-2, and READ-3 studies. The iDEAL study, which is a large multicenter study at 27 centers across the United States, will be launched in Q4 of 2011. The study will evaluate two doses of iCo-007 and combination of iCo-007 with ranibizumab or laser photocoagulation.

1. Safety study of iCo-007 intravitreal injection to treat diabetic macular edema. <http://clinicaltrials.gov/ct2/show/NCT00886808>. Accessed September 30, 2011.

bly use anti-VEGF therapy as the first line of treatment for patients with DME, and if we do not see the response we want after a certain number of injections we can add a steroid implant to see if we can improve the patient's vision and response.

The duration of action of the dexamethasone implant seems to be between 2 and 4 months. Patients receiving the currently available anti-VEGF agents for DME will have to be seen regularly, so the addition of an implant will not increase the frequency of their visits. In fact, this addition may allow us to lengthen the period of time between visits and injections for some patients. Diabetes is a disease of the inner retina, whereas AMD is in the outer retina and the photoreceptors are negatively affected very quickly. In DME, hopefully a sustained delivery treatment will allow us to achieve a good therapeutic response even if patients are not seen exactly at 4-week intervals. Still, I think we get the best results in DME the more promptly we treat patients when they begin to develop fluid.

The treatment paradigm for DME is still evolving. Studies so far have demonstrated that ranibizumab injected intravitreally gives better results than laser in patients with DME, but these studies enrolled only patients with center involvement. In addition, many

patients enrolled in these trials were not newly diagnosed, but had previously been treated with laser. Patients with extrafoveal areas of leakage often respond well to laser, and they may not need laser again for a long time. At the present time, therefore, each physician will adopt his or her own paradigm for each patient depending where the leaks are, how acute they are, what the visual acuity is, how cooperative the patient is, and so on, and will establish different paradigms for treatment.

If patients are doing well with anti-VEGF treatment, we can add laser and possibly reduce the frequency of injection; however, even though optical coherence tomography findings may improve with laser, visual acuity results do not necessarily parallel this response. The benefit of adding laser, or of adding steroids, whether fluocinolone or dexamethasone or triamcinolone, is still subject to debate.

Patients with previous vitrectomy often do not have a good long-term response to anti-VEGF therapy. The CHAMPLAIN study⁶ showed that a single injection of the dexamethasone implant in previously vitrectomized eyes resulted in a 2-line improvement in visual acuity in roughly 30% of patients. The safety profile was also good. For the eyes in this study, many of which had

received numerous previous treatments, the dexamethasone implant is a wonderful adjunct that seems to give an additional improvement that we could not achieve with intravitreal anti-VEGF or steroid injections.

JULIA A. HALLER, MD

The fluocinolone acetonide implant (Iluvien, Alimera Sciences), an intravitreal insert containing 0.19 mg of the corticosteroid, is a proposed treatment for DME currently under review by the FDA and 7 European health authorities.⁷ Fluocinolone has a history of ophthalmic use, being the active ingredient in Retisert (Bausch + Lomb), a corticosteroid implant indicated for the treatment of chronic noninfectious posterior uveitis.⁸

The FAME Study, in which our center participated, found that 2 doses of the fluocinolone implant significantly improved visual acuity in DME over 2 years.⁹ The insert can be administered in an outpatient procedure through a 25-gauge needle.

As with any steroid, the questions regarding incorporating this device into clinical practice involve the balance of safety and efficacy, considering the potential risks of cataract and glaucoma with intraocular administration of a steroid. In the FAME Study, the risk-benefit ratio was superior for the lower dose of the implant. Subjects requiring cataract surgery were more frequent in the insert groups than the group that received sham injections. The visual benefit for these patients was similar to that of subjects who were pseudophakic at baseline. Glaucoma requiring incisional surgery occurred in 3.7%, 7.6%, and 0.5% of the low-dose, high-dose, and sham groups, respectively, according to the 2-year published data from the study.

We know that the pathogenesis of diabetes includes an inflammatory component, so the use of steroids, with their multifactorial antiinflammatory activity, makes theoretical sense in the management of the ocular complications of diabetes. Other studies have shown that steroids not only help reduce the vascular permeability that produces DME but also can stabilize and even decrease the level of retinopathy in these diabetic eyes. Therefore, steroids have considerable potential as an effective therapy for diabetic retinopathy and DME. The clinician's job is to maximize the upside and minimize any potential downside of the therapy. With the fluocinolone implant designed to provide a therapeutic effect for up to 36 months, the clinician must evaluate the risks and benefits of a longer-acting drug vs a shorter-acting drug that might have a better safety profile. These decisions must be made on an individual basis, as every patient is different.

The availability of steroid implants and anti-VEGF drugs has already changed our treatment paradigm in DME. Instead of monotherapy with laser alone, often leaving patients with significant scars in their retinas, we can now offer the option of pharmacologic therapy, and inject with steroids and anti-VEGF agents. That has been a real sea-change for practicing clinicians. ■

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