

# The Future of DME Therapies

Most drugs for this disease are currently under clinical trial for long-term efficacy.

BY MICHAEL S. IP, MD

**R**esearchers are looking for new and effective therapies for retinal vascular disease, as not many existing treatments produce profound improvements in visual acuity. New treatments are not only being studied in clinical trials, they may also be used for off-label indications where appropriate. One common form of retinal vascular disease is diabetic macular edema (DME).

Eighteen million people in the United States have diabetes, and the complications of diabetic retinopathy are a major cause of visual impairment.<sup>1-3</sup> The two most common complications of diabetic retinopathy are proliferative retinopathy and DME, the latter of which is widely known to be the most common cause of retinal vascular disease. Most patients with diabetic retinopathy have moderate vision loss due to DME. DME is a common condition affecting working-age adults, with longer diabetes duration signifying a greater chance of having diabetic retinopathy and DME. It is estimated that 20% of patients with type 1 diabetes (diabetes duration 15 years) have DME; 25% of type 2 diabetes patients with the same duration taking insulin and 14% not taking insulin also have DME.<sup>1</sup>

## LASER PHOTOCOAGULATION

In addition to tight glycemic control,<sup>4-5</sup> the only proven effective DME therapy is the use of laser photocoagulation.<sup>6</sup> The Early Treatment Diabetic Retinopathy Study (ETDRS) showed a reduction in moderate vision loss when patients with DME received photocoagulation. There are some caveats to laser photocoagulation; only 17% of patients with reduced vision at baseline who received photocoagulation had improved visual acuity. Another caveat is that leaking microaneurysms may be close to the center of the retina, and this makes it difficult to photocoagulate. There have also been some issues with creeping of the scar and subsequent loss of visual acuity with laser photocoagulation.

By and large, laser photocoagulation is a safe procedure. It is relatively effective at maintaining a patient's visual acuity, although it does not consistently improve visual acuity. We are looking for new and better treatments.

Where are we going in the future with these therapies? There are a myriad of new treatments. Investigation into surgical approaches using pars plana vitrectomy, injections, protein kinase-C (PKC) inhibitors and pharmacotherapy for macular edema is currently underway.

## PHARMACOTHERAPEUTIC APPROACHES

The types of medication for injection range from corticosteroids to antivascular endothelial growth factor (anti-VEGF) agents. Anti-VEGF aptamers include pegaptanib (Macugen; Eyetech Pharmaceuticals, Melville, NY/Pfizer, New York, NY). Antibody approaches against VEGF include such molecules as ranibizumab (Lucentis; Genentech, San Francisco) and bevacizumab (Avastin; Genentech). Growth factor suppression is another option and this approach is still in clinical trials. At this time, none of these pharmacotherapeutic approaches have received Food and Drug Administration (FDA) approval and/or have been proven effective.

Corticosteroids may be delivered in a number of ways: topically, peribulbarly, injected and implanted as biodegradable or sustained-release devices (nonbiodegradable intravitreal). We started using intravitreal corticosteroids in the United States in 1999.

A recent search of the literature using the keywords triamcinolone (Kenalog; Bristol-Myers Squibb, Princeton, NJ) and macular edema, reveals that there were no publications with these terms prior to 2001. In the past 2 years, 61 articles concerning the use of intravitreal steroids have been published, specifically for Kenalog use in patients with DME; a meta-analysis of five recently published articles on this topic showed that data from 135 patients is available. The overwhelming majority of patients in this analysis had significant anatomical improvement both on clinical examination and on optical coherence tomography (OCT). There was also a beneficial effect on visual acuity, however not quite as dramatic. The lack of long-term follow-up data is a limitation of these studies, as are the side effects related to this treatment (both injection-related complications such as detachment of the retina, vitreous hemorrhage, endoph-

thalmitis, as well as drug-related complications including cataract and glaucoma). This treatment appears to have significant promise, but larger clinical trials are needed to test the long-term effects. One current clinical trial is being done within the auspices of the Diabetic Retinopathy Clinical Research Network, which is a National Eye Institute-sponsored clinical trial network.

Bausch & Lomb (Rochester, NY) is looking at Retisert, a technology platform that is very similar to the FDA-approved Vitrasert (Chiron Vision, Emeryville, Calif) device. Retisert is a nonbioerodable implant surgically placed in the eye to release fluocinolone acetonide over 3 years. Retisert appears to have potential efficacy based on phase 1 and 2 data. Again, we have to compare results with long-term side effects such as cataract and glaucoma. We are awaiting results of these clinical trials.

Additional drugs in the pipeline for the treatment of DME may produce safe and effective treatments.

Allergan (Irvine, Calif) is studying intraocular steroids in the Posurdex studies. Bioerodible dexamethasone implants are injected into eyes with DME. Phase 3 results are needed before we can use that treatment as a widespread intervention, however this approach is promising. In summary, a number of corticosteroids and delivery approaches are under evaluation for DME. We have to weigh the potential efficacy of earlier studies against the long-term side effects.

Another promising approach is Eli Lilly and Company's (Indianapolis, Ind) PKC inhibitor. The oral administration of ruboxistaurin (awaiting FDA review) has been studied. Patients were given 32 mg/day of ruboxistaurin compared with placebo. In a number of clinical trials, no safety effects have yet been noted and ruboxistaurin compared with placebo was associated with less overall visual loss.

A phase 2 study testing the efficacy of pegaptanib,<sup>7</sup> where patients with DME were injected every 6 weeks for 36 weeks, determined that mean visual acuity change from baseline to week 36 favored patients who received 0.3 mg of pegaptanib compared with patients who received sham.

The overall difference was slightly more than 5 lines of mean visual acuity. On OCT, a statistically significant difference was seen in patients; those who received pegaptanib had a greater chance of having an absolute decrease of  $\geq 75 \mu\text{m}$  retinal thickness. Essentially, this trial showed that patients who received pegaptanib compared with those who didn't receive it had better visual acuity. They were also more likely to show anatomical benefit on OCT. It also

appeared that there was some regression of retinal neovascularization in some subjects, although the number was too small to make any definitive conclusions.

Other anti-VEGF agent trials (bevacizumab and ranibizumab) will most likely be conducted in the future. We are not, though, looking to replace laser photocoagulation, it is an effective and safe treatment. Patients with certain presentations of DME are always going to be good candidates for initial laser photocoagulation (eg, a patient presenting with relatively good visual acuity but some visual loss due to focally leaking microaneurisms that are outside the foveal vascular zone). Many treatments mentioned are going to serve as essentially useful adjuncts to laser photocoagulation rather than a replacement.

Surgeons and specialists alike are using various therapies in an off-label fashion. For DME, it is common to use triamcinolone off-label. Triamcinolone is FDA-approved for intramuscular and intrabursal use but not for intravitreal injection. Retina specialists have been using it for some years in this fashion, however. Pegaptanib is FDA approved for exudative age-related macular degeneration, but not for use in patients with DME. We are not using pegaptanib off-label, and this is related to its cost as well as a lack of data supporting its use in this fashion. Bevacizumab, because of its lower cost, is increasingly being used off-label for patients with DME.

There are additional drugs and therapies in the research pipeline for the treatment of DME. Current research, evaluating the pharmacotherapies outlined above, is in progress and will hopefully identify at least one and possibly several new treatments for these conditions that will be efficacious and have a favorable safety profile. ■

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