

The Future of CRVO, BRVO and DME Therapies

Most drugs for these diseases, when caused by macular edema, are currently under clinical trial for long-term efficacy.

BY MICHAEL S. IP, MD

Researchers 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. Three of the most common forms of retinal vascular disease are diabetic macular edema (DME), central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO).

Eighteen million people in the United States have diabetes, and the complications of diabetic retinopathy are a major cause of visual impairment.¹⁻³ 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 was 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.¹

SIMILAR TREATMENTS, DIFFERENT DISEASES

CRVO and BRVO occur less frequently than DME. CRVO and BRVO are the second most common retinal vascular disease. Loss of visual acuity frequently occurs in patients with CRVO due to macular edema.⁴⁻⁷ DME and retinal vein occlusion are different diseases, however, treatments for DME, CRVO and BRVO — when related to macular edema

— are similar (Table 1).

In addition to tight glycemic control,⁸⁻⁹ the only proven effective DME therapy is laser photocoagulation.¹⁰ 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 such patients. There have also been some issues with creeping of the scar and subsequent loss of visual acuity with laser photocoagulation.

SAFE, EFFECTIVE TREATMENT

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.

Therapies for retinal vein occlusion — in reference to the complication of macular edema — must be divided into CRVO and BRVO. Presently, there is not a proven effective therapy for macular edema due to CRVO. The Central Vein Occlusion Study (CVOS)⁵⁻⁷ evaluated laser photocoagulation as a treatment for macular edema from CRVO. Investigators determined that it did not effectively improve visual acuity. Photocoagulation did decrease leakage on the fluorescein angiograms, but because it is ineffective for visual acuity, we do not normally recommend laser photocoagulation for macular edema due to CRVO.

The Branch Vein Occlusion Study (BVOS)¹¹ showed that

TABLE 1. COMMON TREATMENTS FOR DME, BRVO AND CRVO**Diabetic Retinopathy/DME:**

- Laser photocoagulation
- Surgical approaches (eg, pars plana vitrectomy)
- Intravitreal/intraocular steroid injections
- PKC inhibitors
- Pharmacotherapy:
 - anti-VEGF treatments
 - growth factor suppression
- Nonbioerodable implant

Retinal Vein Occlusion (BRVO and CRVO):

- Laser photocoagulation (not for CRVO)
- Radial optic neurotomy
- Laser-induced chorioretinal anastomosis
- Corticosteroid treatment
- Anti-VEGF treatments
- Intravitreal steroid injections

visual acuity was improved with laser photocoagulation for patients who developed macular edema from a BRVO. There was a two-thirds chance of mild visual acuity gain following laser photocoagulation compared with a one-third chance of mild visual acuity gain without photocoagulation. Based on that study, the current standard therapy for many patients with BRVO is laser photocoagulation.

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

Medications for injection range from corticosteroids to antivascular endothelial growth factor (anti-VEGF) agents. An example of an anti-VEGF aptamers is pegaptanib (Macugen; OSI Eyetech, 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 yet received Food and Drug Administration (FDA) approval and/or are proven to be effective.

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

A recent search of the literature using the keywords *triamcinolone* (Kenalog; Bristol-Myers-Squibb, Princeton, NJ)

and *macular edema* revealed 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 triamcinolone use in patients with DME; a meta-analysis of five recently published articles on this topic showed that data from 135 patients are 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, endophthalmitis; and 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 trials network.

Bausch & Lomb (Rochester, NY) is looking at the Retisert, a technology platform that is similar to the FDA-approved Vitrasert (Chiron Vision, Emeryville, Calif) device. See *the CME activity, starting on page 42, for more information on the Retisert*. The Retisert is a nonbioerodable implant surgically placed in the eye to release fluocinolone acetonide over 3 years. The 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 such clinical trials.

DELIVERY APPROACHES

Allergan 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) was studied in several trials. 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,¹² in which DME patients 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 treatment. 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 did not 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 a few patients, although the number was too small to make definitive conclusions.

NOT REPLACEMENT THERAPIES

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

Retinal vein occlusion conditions (CRVO and BRVO) are also lacking efficient treatments. Just as for DME, there are some surgical procedures being tested; radial optic neurotomy and laser-induced chorioretinal anastomosis have been looked at for CRVO. Currently, there is a lack of significant case reports that show these are therapies that can reproducibly and reliably improve visual acuity in these patients. Until a randomized clinical trial is done — if ever — the majority of retinal specialists will not perform these on a routine basis.

CRVO, BRVO

Other promising approaches to CRVO treatment include corticosteroid treatment and anti-VEGF molecules. The intravitreal injection of triamcinolone for CRVO started in the late 1990s in the United States. Case reports and presentations on its use have increased over the last 6 years. An analysis of five studies in the literature, which included data from 47 patients, showed that almost all of the patients had anatomical improvements, and many had improved visual acuity. The treatment appears effective in the short-term, but we do not know long-term data, and therefore it is unclear if we should recommend this treatment to our patients. There are related side effects such as cataract and glaucoma. The National Institute of Health is funding a study called the Standard care versus Corticosteroid for Retinal vein occlusion study (SCORE) to look at triamci-

nolone use in these patients. We are hoping the trial gives us a definitive answer in terms of whether or not long-term use is appropriate.

Another phase 3 Allergan study (Posurdex trial; Irvine, Calif) is investigating the use of Posurdex for retinal vein occlusion. Investigators are currently enrolling and evaluating patients. Additionally, a phase 2 trial for the use of pegaptanib in CRVO patients has just been completed. It evaluated the role of pegaptanib in CRVO patients, but these data are not yet available.

Surgeons and specialists alike are using various therapies in an off-label fashion. For retinal vein occlusion and 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 manner, however.

Pegaptanib is FDA-approved for exudative age-related macular degeneration, but not for use in patients with DME or for retinal vein occlusion. We are not using this drug in an off-label fashion, and this is related to its cost as well as a lack of data supporting the use of pegaptanib in this fashion. Bevacizumab, because of its lower cost, is increasingly being used off-label for patients with macular edema due to retinal vascular disease (eg, DME, BRVO or CRVO).

There are additional drugs and therapies in the research pipeline for the treatment of the three most common retinal vascular diseases, DME, CRVO and BRVO. 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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