Diabetic Macular Edema: Treatment Updates 2008

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The World Health Organization (WHO) estimates that 15 million people in the United States have diabetes, with half of these cases undiagnosed. In addition, about 50% of the 8 million patients diagnosed with diabetes do not receive appropriate eye care. Consequently, diabetic retinopathy (DR) continues to be a leading cause of new blindness in the United States. Blindness from DR usually results from non-resolving vitreous hemorrhage, traction retinal detachment or diabetic macular edema (DME).¹

Diabetic macular edema is the result of retinal microvascular changes that occur in patients with diabetes. Thickening of the basement membrane and reduction in the number of pericytes is believed to lead to increased permeability and incompetence of retinal vasculature. This compromise of the blood-retinal barrier leads to the leakage of plasma constituents in the surrounding retina, resulting in retinal edema. The hypoxic state achieved through this mechanism can also stimulate the production of vascular endothelial growth factor (VEGF). Macular edema affects approximately 29% of patients with diabetes who have disease duration of 20 years or longer and constitutes the primary cause of visual impairment in this population. For 30 years, the standard of treatment has been glycemic control, as demonstrated by the Diabetes Control and Complications Trial (DCCT)² and the United Kingdom Prospective Diabetes Study.³

In the DCCT, intensive glucose control reduced the risk of onset of DME by 23% compared with conventional treatment. Long-term follow-up of patients in the DCCT showed a sustained effect of intensive glucose control, with a 58% risk reduction in the development of diabetic macular edema for the DCCT patients followed in the Epidemiology of Diabetes Interventions and Complications Study.⁴

FOCAL/GRID LASER PHOTOCOAGULATION
Laser photocoagulation continues to be a well proven therapy to reduce the risk of vision loss from DME, as demonstrated by the Early Treatment Diabetic Retinopathy Study (ETDRS).⁵ In the ETDRS, laser photocoagulation reduced the risk of moderate visual loss from diabetic macular edema by 50% (from 24 to 12% 3 years after initiation of treatment). Focal laser treatment also increased the chance for visual improvement, with 16% of patients gaining more than one line of acuity.

The Diabetic Retinopathy Clinical Research Network reported results from a study comparing focal/grid photocoagulation and intravitreal triamcinolone for the treatment of DME. They concluded that over a 2 year period focal/grid photocoagulation is more effective and has fewer side effects than 1-mg or 4-mg doses of preservative-free intravitreal triamcinolone for most patients with DME.⁶

INTRAVITREAL TRIAMCINOLONE ACETONIDE
Intravitreal triamcinolone acetonide (IVTA) has been reported widely in the literature for the treatment of diffuse, refractory DME.⁷⁻¹¹ The rationale for the use of cor-
t corticosteroids in this condition stems from the observation that DME may be caused by VEGF, a 45 kda glycoprotein. Antonetti et al demonstrated that phosphorylation of tight junction proteins such as occludin and zonula occludens was regulated by VEGF-induced vessel permeability.

Corticosteroids have been demonstrated to inhibit the expression of the VEGF gene. In a study by Nauck et al, the platelet-derived growth factor-induced expression of the VEGF gene in cultures of human aortic vascular smooth muscle cells was inhibited by corticosteroids in a dose-dependent manner. A separate study by Nauck et al demonstrated that corticosteroids downregulate the induction of VEGF by the proinflammatory mediator platelet-derived growth factor and platelet-activating factor in a time- and dose-dependent manner.

Martidis et al reported results using IVTA injection in 16 eyes with macular edema due to diabetic retinopathy. All 16 eyes had persistent macular edema after having received multiple sessions of laser photocoagulation. Using OCT, it was demonstrated that the mean thickness of the central macula decreased from 540 µm before injection (at baseline) to 242 µm after injection (the normal average thickness of the central macula is 175 µm). Visual acuity improved by 2.4, 2.4, and 1.3 lines from the baseline value at the 1-, 3-, and 6-month follow-up intervals, respectively.

Jonas et al described the results of IVTA injection in 26 eyes with macular edema due to DR. These patients showed decreased fluorescein leakage following intravitreal injection in all patients. Visual acuity improved from a mean of 20/165 at baseline to a mean of 20/105 at the end of follow-up. In comparison, 16 patients followed in a control group who received laser photocoagulation showed no improvement in visual acuity.

**INTRAVITREAL DEXAMETHASONE**

Following the same mechanism of action as other corticosteroids, many physicians favor the use of intravitreal dexamethasone (IVD) over IVTA because of the reduced incidence of floaters with this therapy.

Wang et al reported that dexamethasone may inhibit retinal accumulation, leukostasis accumulation and vascular permeability through its blockage of VEGF and ICAM-1 expression, thereby exerting the same effects as other corticosteroids.

**INTRAVITREAL ANTI-VEGF AGENTS**

Vascular endothelial growth factor increases retinal vascular permeability, causes breakdown of the blood-retinal barrier, and results in retinal edema. VEGF is upregulated in diabetic retinopathy and is present in increased levels in the aqueous and vitreous humors of patients with PDR. At least five isoforms of VEGF are known. Three currently available anti-VEGF agents are pegaptanib, bevacizumab, and ranibizumab.

**Pegaptanib sodium.** Pegaptanib sodium (Macugen, OSI/Eyetech) is a pegylated aptamer directed against the VEGF-A165 isoform. It was the first US Food and Drug Administration (FDA)-approved ophthalmologic anti-VEGF agent for the treatment of choroidal neovascularization (CNV) from age-related macular degeneration (AMD). In a phase 2 prospective clinical trial, pegaptanib appeared to improve anatomic and visual outcomes in patients with DME. Retrospective analysis of these data demonstrated some efficacy on retinal neovascularization as well. Phase 3 trials of pegaptanib for DME are currently being conducted.

**Bevacizumab.** Bevacizumab (Avastin, Genentech), a full-length recombinant humanized antibody, is active against all isoforms of VEGF-A. It is FDA-approved as an adjunctive systemic treatment for metastatic colorectal cancer. Although off-label systemic bevacizumab has demonstrated some efficacy against exudative AMD, the agent has shown greater promise as an intravitreal medication. Case reports and small observational series have been reported using off-label intravitreal bevacizumab to treat exudative AMD, macular edema from nonischemic central retinal vein occlusion, iris neovascularization, pseudophakic cystoid macular edema, and other diseases. Small, nonrandomized pilot studies have documented some efficacy against diffuse DME and various complications of PDR. The Diabetic Retinopathy Clinical Research Network (DRCR.net) has completed enrollment in a phase 2, prospective, randomized, multicenter clinical trial to determine the safety and possible benefits of this agent. Plans for a phase 3 trial of two doses of an intravitreal anti-VEGF agent versus modified ETDRS grid laser photocoagulation for DME are under discussion.

Arevalo et al reported that primary intravitreal bevacizumab at doses of 1.25 to 2.5 mg seems to provide stability or improvement in visual acuity, optical coherence tomography (OCT), and fluorescein angiography (FA) in eyes with DME at 6 months.

**Ranibizumab.** Ranibizumab (Lucentis, Genentech), a recombinant humanized antibody fragment, is active against all isoforms of VEGF-A. Intravitreal ranibizumab is FDA-approved for the treatment of exudative AMD. Two pilot studies of ranibizumab demonstrated some efficacy in the treatment of DME. DRCR.net is planning two phase 3, prospective, randomized, multicenter trials of ranibizumab for DME. In the first trial, patients with DME and no PDR will be randomized to modified ETDRS grid...
laser photocoagulation; photocoagulation before ranibizumab; photocoagulation plus IVTA; or ranibizumab before photocoagulation. In the second trial, patients with DME and PDR will be randomized to modified ETDRS grid laser photocoagulation plus scatter photocoagulation; modified ETDRS grid laser photocoagulation plus scatter photocoagulation plus ranibizumab; or modified ETDRS grid photocoagulation plus scatter photocoagulation plus IVTA.

**PARS PLANA VITRECTOMY**

It is widely recognized that there have been recent advancements in small gauge retinal and macular surgery. The advent of better instrumentation, adjuncts to help visualize the structures of the retina, and decreased surgical times help explain why diabetic macular edema is now being treated surgically. These studies suggest that vitreomacular traction, or the vitreous itself, may play a role in increased retinal vascular permeability. Removal of the vitreous or relief of mechanical traction with vitrectomy may, in some patients, be followed by substantial resolution of macular edema and corresponding visual rehabilitation. However, this treatment may be applicable only to a specific subset of eyes with DME.

Another theory involves the removal of the internal limiting membrane (ILM). Ducournau et al propose that ILM removal would work beyond simply removing adherent collagen fibers (responsible for metamorphopsia and edema); it also induces a cellular response at the Muller cell level (gliosis). This gliosis is believed to play an important role in the repair and regeneration of injured neural tissue.

**COMBINATION THERAPIES**

Recent studies focus on the combination of two or more of aforementioned discussed treatments. Their main objective is to study whether there is a cumulative effect to these treatments.

**Intravitreal bevacizumab with triamcinolone.** Ahmadieh et al reported that three consecutive intravitreal injections of bevacizumab had a beneficial effect on refractory DME in terms of central macular thickness reduction and vision improvement. Addition of triamcinolone in the first injection seemed to induce earlier visual improvement. Addition of triamcinolone in the first injection seemed to induce earlier visual improvement.

**Intravitreal triamcinolone or dexamethasone and focal laser photocoagulation.** Kang et al concluded that macular grid laser photocoagulation maintained improved visual acuity and reduced the risk of recurrent macular edema after IVTA. This treatment also did not appear to increase the risk of complications.

Busquets et al assessed the effectiveness of intravitreal dexamethasone with thermal laser photocoagulation for DME in a 12-month retrospective analysis of 20 eyes with clinically significant DME. Dexamethasone was followed by thermal laser within 2 weeks. Dexamethasone retreatment was based on OCT central thickness >250 µm. At 12 months, mean pre-treatment Snellen (VA) was 20/393; mean final VA was 20/70. Mean VA change was +4.5 lines. Mean reduction in foveal thickness was 103 µm. They concluded that therapy with corticosteroids and thermal laser may improve vision in DME patients.

**FUTURE THERAPIES**

The RIDE study (A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus) is an ongoing placebo-controlled trial evaluating the efficacy and safety of intravitreal ranibizumab 0.5 mg injection every 4 weeks for 24 months in patients with DME.

The CAPTURE trial (Combined Approach to Treatment Using Ranibizumab and Efalizumab for Diabetic Macular Edema) is studying the combined administration of ranibizumab and efalizumab (Raptiva, Genentech) for DME. It is assessing the role of Raptiva, which inhibits the binding leukocyte function associated antigen-1 (LFA-1) to intercellular adhesion molecule-1 (ICAM-1), thereby inhibiting the adhesion of leukocytes to other cell types.

VEGF-Trap Eye (Regeneron) is a soluble VEGF receptor fusion protein that binds all forms of VEGF-A and related placental growth factor (PGF). When administered as a single 4.0 mg intravitreal injection in a phase 1 study, a marked decrease in central retinal thickness and mean macular volume was noted.

The phase 3 FAME (Fluocinolone Acetonide in DME) trial is evaluating the Medidur (Alimera Sciences) fluocinolone-based implant. A phase 3 trial of the Posurdex (Allegan Inc.) biodegradable implant (sustained delivery formulation of dexamethasone) for the treatment of DME is currently under way. Another steroid implant, Retisert (Bausch & Lomb), was evaluated in patients with DME with good results but a concerning side effect profile (90% of patients developed cataracts, and 40% required glaucoma surgery within 3 years).

**CONCLUSION**

Multiple therapeutic options are currently available for the treatment of DME, and many more are on the horizon. It is up to the clinician to determine which therapies or combinations thereof are most appropriate on a case-by-case basis. Optimal patient care will ultimately result from the evolution of new technologies and effective recruitment and enrollment in randomized prospective clinical trials.
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