CURRENT AND FUTURE TRENDS IN THE TREATMENT OF MACULAR EDEMA

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ABSTRACT

Diabetic retinopathy and retinal vein occlusion are the most common causes of macular edema (ME). Both are associated with vision impairment, and both have major public health implications. Current treatment options for ME include laser photocoagulation and the off-label use of steroids and inhibitors of vascular endothelial growth factor (VEGF). Future treatments include the use of new lasers, long-acting intravitreal steroid implants, VEGF inhibitors, and other agents that inhibit specific pathophysiologic pathways. This article reviews data from several trials evaluating these treatment modalities, with an emphasis on laser therapy and new steroid delivery systems. (Adv Stud Ophthalmol. 2007;4(7):187-190)

Macular edema (ME), most commonly caused by diabetic retinopathy (DR), retinal vein occlusion (RVO), and uveitis, is associated with significant vision loss and has important public health implications.

The estimated prevalence of retinopathy and vision-threatening retinopathy among 10.2 million Americans older than the age of 40 years with known diabetes is 40.3% and 8.2%, respectively.1 Given the sharp increase in newly diagnosed cases of diabetes over the past decade, the aging of the US population, and the increasing age-specific prevalence of diabetes over time, future projections suggest that DR and vision loss will increase as public health problems.

With more than 130,000 new cases each year, RVO represents a similar order of magnitude.2,3 Although RVO is a less common cause of ME than DR, it is the third most common visually disabling retinal disorder, after DR and age-related macular degeneration.2,3 Based on published epidemiologic data, it can be inferred that branch RVO (BRVO) accounts for more than 95,000 of the new cases each year, whereas central RVO (CRVO) accounts for approximately 37,000 cases.2,3

In addition, RVO, particularly CRVO, has a relatively unfavorable natural history. Although 65% of patients in the natural history cohort of the Central Vein Occlusion Study who presented with good visual acuity (VA; ≥20/40) retained or improved VA at 1 year, only 19% of those with intermediate acuity (between 20/50 and 20/200) and 1% of those with poor VA (≤20/200) improved to 20/40 or better without intervention.4

CURRENT TREATMENTS

Current treatments for ME include laser photocoagulation, which is considered the gold standard, and the off-label use of corticosteroids and agents that inhibit vascular endothelial growth factor (VEGF).

Laser photocoagulation is fairly effective for ME resulting from BRVO,5 but less so for ME resulting from CRVO.6 In a study of patients with BRVO and VA 20/40 or better, 66% gained 2 lines or more after grid photocoagulation compared to approximately only 33% who were randomized to observation.7 In
addition, those receiving laser treatment were only 50% as likely as controls to experience a decline in VA. However, a study using a similar protocol in patients with CRVO and VA 20/40 or better demonstrated a reduction in ME in the laser group versus the controls, but without a concomitant improvement in VA.6

In contrast, focal photocoagulation is very effective in reducing diabetic ME and improving or stabilizing VA.7-9 A general strategy for focal treatment of diabetic ME is to treat areas of leaking microaneurysms with direct photocoagulation (taking care to avoid the center of the capillary-free zone and nearby areas), apply grid photocoagulation to areas with more diffuse leakage or capillary nonperfusion, and retreat at 3- to 4-month intervals for persistent ME or new onset of clinically significant ME, as indicated by VA on fluorescein angiography or retinal thickening on optical coherence tomography (OCT). The strategy is based on Early Treatment Diabetic Retinopathy Study (ETDRS) guidelines that have been modified over the years. The ETDRS has also demonstrated that treatment with a combination of direct and grid photocoagulation reduces vision loss in patients with clinically significant diabetic ME.10

To improve on existing paradigms for laser therapy, the Diabetic Retinal Clinical Research Network (DRCRN) compared 2 photocoagulation techniques in 263 patients with previously untreated diabetic ME—modified ETDRS direct/grid versus mild macular grid (MMG) photocoagulation.9 Modified ETDRS was slightly better than MMG photocoagulation in resolving edema for maximum retinal thickening (as measured by OCT) at all time points in the study (Figure 1). Given these findings, a larger long-term trial of the MMG technique is not justified.

**NEW AND FUTURE TREATMENTS**

Future treatments for ME include new lasers and laser delivery systems, long-acting intravitreal steroids, VEGF inhibitors, and other agents that inhibit specific pathways involved in the pathophysiology of ME.

**NEW LASERS**

The redesign and replacement of existing retinal laser delivery systems may result in improved patient outcomes and satisfaction with laser treatment.

One new system is the patterned scanning laser, which uses short-pulse durations (10–30 msec vs the traditional 100 msec) and a scanner for multiple, nearly simultaneous applications in a relatively short period of time.11 Another potential new advance is the application of short-pulse durations and low power to the same spot to localize retinal damage to specific layers, typically the retinal pigment epithelium, and minimize heat accumulation. In either system, shorter pulse durations result in higher spatial localization, less lateral spread, and potentially a greater likelihood that any retinal damage will be confined to the outer layers. Whether the efficacy is the same remains unknown.

**LONG-ACTING INTRAVITREAL STEROIDS**

Several studies have evaluated or are currently evaluating long-acting intravitreal steroids in diabetic ME and RVO.

In a controlled, double-masked trial, patients with persistent diabetic ME were randomized to receive intravitreal injections of triamcinolone acetonide or placebo.12 At 3 months, 24% of patients on active treatment gained 2 lines or more versus 9% of patients on placebo. However, there was a higher incidence of elevated intraocular pressure in the treatment group versus the placebo group (18% vs 3%).

![Figure 1. Resolution of Edema for Maximum Retinal Thickening in Patients Treated with Direct/Grid Photocoagulation or Mild Macular Grid Photocoagulation](image-url)
A sustained-release reservoir-style implant containing fluocinolone acetonide (FA) that is currently approved for the treatment of uveitis has also been evaluated in patients with diabetic ME.

In a study of 127 patients who received the FA implant and 69 patients who received the standard of care (SOC; macular grid laser or observation), 27.6% of those receiving FA gained 3 lines or more at 3 years versus 14.5% for SOC. The rates of decline in VA at 3 years were similar in both groups and due to cataract rather than ME. Separate measurements of central macular thickness demonstrated resolution of edema at 3 years in 51.2% of the FA group versus 37.7% for SOC.

At 3 years, intraocular pressure increased in 49% of FA-treated eyes versus 19.6% in fellow eyes, and filtering operations were required in 39.9% of treated eyes versus 1.8% of fellow eyes. In many cases, glaucoma was severe and unresponsive to standard therapy. In addition, 93% of treated eyes versus 19.9% of fellow eyes developed cataracts requiring surgery.

An intravitreous drug delivery system (DDS) containing dexamethasone has been evaluated in phase II studies; phase III trials are currently under way. Because dexamethasone is highly water soluble, the system was specifically formulated with polylactic-glycolic acid to prolong the effect of dexamethasone in the vitreous.

In a 6-month study, more than 300 patients with persistent ME (>90 days despite treatment) were randomized to a single treatment with dexamethasone DDS 700 µg, dexamethasone DDS 350 µg, or observation. The study population included patients with ME due to DR, RVO, Irvine-Gass syndrome, and uveitis.

Response to treatment with either dose was favorable compared to observation, with the greatest proportion of patients gaining 10 letters or more or 15 letters or more at 90 and 180 days being those who received the higher dexamethasone dose (Figure 2). The same dose response pattern was also seen with 2-line and 3-line improvements in VA at 90 and 180 days. In addition, improvements in VA were consistent across disease subtypes.

Improvements in VA were paralleled by decrements in fluorescein leakage on angiography and central retinal thickness measured by OCT, with patients receiving the higher dexamethasone dose showing the greatest reductions in leakage and retinal thickness.

The beneficial effects of dexamethasone DDS in a subset of patients with BRVO provided the impetus for a subsequent study that is now nearing completion.

In contrast to the high incidence of glaucoma requiring filtration surgery seen with intravitreal FA, intraocular pressure increases of 25 mm Hg or higher were seen in only 6% of eyes treated with the lower dexamethasone dose and 3% of eyes treated with the higher dose, with none of the eyes requiring filtration surgery.

VEGF INHIBITORS

Intravitreous ranibizumab has significant bioactivity in diabetic ME. In a small study, patients with chronic diabetic ME who received injections (0.5 mg) at baseline and again at 1, 2, 4, and 6 months had a mean increase of 10 letters, a mean decrease of 60% in macular volume, and a reduction in excess retinal thickness at 6 months. The drug appeared to be safe and well tolerated, with no ocular or systemic toxicity and no ocular inflammation at the dose given.

However, questions remain about the optimum dose of ranibizumab for diabetic ME, the dosing interval, length of administration, long-term risks, and the effects of the drug on eyes in persons with diabetes.

OTHER INHIBITORS

The mammalian target of rapamycin (mTOR) is a specific regulator pathway that is present in all mammalian cell types and is involved in a wide range of cellular processes. Inhibition of mTOR has been shown to have beneficial effects in various diseases, including diabetic macular edema.

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malian cells and involved with the hypoxia-inducible factor (HIF)-1α pathway.16 When stimulated by hypoxia, HIF moderates the production of VEGF. Conversely, mTOR inhibition downregulates the hypoxic response. Rapamycin, also known as sirolimus, inhibits the translation and activity of HIF-1α, decreases VEGF production, and inhibits VEGF-driven endothelial cell production.

Rapamycin is also a very potent inhibitor of VEGF-induced vascular hyperpermeability and may be a therapeutic option for ME in the future.17

CONCLUSIONS

Treatment options for ME are increasing. Although laser photocoagulation is the gold standard, new laser paradigms are likely to improve outcomes even further.

Off-label use of steroids and VEGF inhibitors are fast becoming a current reality, and studies by the DRCRN are under way to validate efficacy and safety. New compounds are also being tested.

Given the public health implications of diabetes and ME due to DR and RVO, cost effectiveness and treatment burden will become increasingly important considerations in evaluating treatment options.

REFERENCES
