FOCUS ON DIABETIC MACULAR EDEMA*

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ABSTRACT

The current state of treatment for diabetic macular edema (DME) is focused on slowing the rate of vision loss through assessment of retinal function and therapies that prevent DME progression. Recently developed pharmacologic agents have been shown to reduce the risk of vision loss as a result of DME and diabetic retinopathy. In clinical studies, the protein kinase C-β inhibitor ruboxistaurin reduced the risk of DME progression and moderate vision loss, and the vascular endothelial growth factor inhibitor pegaptanib also showed short-term early promise for DME. Bevacizumab is currently under investigation. Early Treatment Diabetic Retinopathy Study-type laser photocoagulation has been shown to improve long-term visual outcomes and is still the mainstay of therapy. Subsequent clinical trials are needed to determine the most effective role of pharmacologic agents and other interventions in preventing vision loss from DME.

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D iabetic retinopathy (DR) progressively damages retinal blood vessels, resulting in the breakdown of the blood-retina barrier and increased vascular permeability. Diabetic macular edema (DME) occurs when fluid and proteins leak from compromised vessels into the surrounding retinal tissue and collect within the macula. In the United States, clinically significant DME develops in 6% of people with type 1 diabetes and 2% to 4% of people with type 2 diabetes. Ten-year incidence rates for clinically significant DME are 20.1% for people with type 1 diabetes and 13.9% for people with type 2 diabetes. DR, a microvascular complication of diabetes, is the leading cause of blindness among US adults aged 20 to 74 years, resulting in 12,000 to 24,000 new cases of blindness each year.

In addition to fluorescein angiography and funduscopy, ophthalmologists need reliable and reproducible methods for assessing DME. Although optical coherence tomography (OCT) is very good at measuring retinal thickness, questions remain as to whether it is an effective means of assessing visual function. Further studies on OCT as a tool for assessing DME are needed.

When a patient develops DME, ophthalmologists typically intervene with photocoagulation to slow vision loss. New pharmacologic agents, such as protein kinase C-β (PKC-β) inhibitors and vascular endothelial growth factor (VEGF) inhibitors, are currently being studied in clinical trials and have shown evidence of benefit with regards to visual outcomes. These agents may in the future prove to be first-line therapies for the prevention of vision loss as a result of DME. Further study will determine their efficacy as monotherapy and their potential role in combined therapies.
therapies to prevent or slow vision loss. This article reviews novel therapeutic approaches to DME.

**Assessing Diabetic Macular Edema**

*Optical Coherence Tomography*

Optical coherence tomography is a reproducible measurement of retinal thickness and is therefore valuable in the assessment of DME. Despite individual day-to-day and diurnal variations in retinal thickening, and some instrument-dependent variation, OCT is a reliable means of measuring retinal thickness, perhaps even better than photographic assessment. However, it remains unclear if diminished retinal thickness as determined by OCT will equate with functional improvement or improvement in visual acuity.

The Diabetic Retinopathy Clinical Research Network (DRCR Network), a collaborative network that facilitates multicenter clinical research on DR, DME, and associated conditions, is conducting a 3-year pilot study which, among other outcomes, will examine the correlation between OCT measurements and visual acuity. This randomized, multicenter clinical trial will compare standard laser photocoagulation therapy to the mild macular grid method for the treatment of DME. Patients enrolled in the study must be at least 18 years old, have clinically significant DME, visual acuity of 20/400 or better, and no prior laser therapy. Results are expected to be published in 2006.

**Treatiing Diabetic Macular Edema**

*Novel Therapeutic Approaches*

There is a growing body of evidence to support several therapeutic approaches to DME, including PKC-β inhibitors, anti-inflammatory approaches, vitrectomy, and growth hormone inhibition. The use of these novel medical approaches in combination with standard photocoagulation therapy is also under examination. The use of combination therapies may offer treatment advantages, particularly when the therapies approach the disease through different pathways.

The Protein Kinase C-β Inhibitor Diabetic Macular Edema Study (PKC-DMES) demonstrated that ruboxistaurin, a selective PKC-β inhibitor, did not have a significant effect on the progression of DME. However, if patients with very poor glycemic control at baseline were excluded, the risk of DME progression was reduced by 31% (Figure 1). In the Protein Kinase C-β Inhibitor Diabetic Retinopathy Study (PKC-DRS), treatment with ruboxistaurin did not slow the progression of DR, although some loss of treatment effect could be attributed to an abbreviated follow-up period. However, PKC-DRS showed a 30% or more reduced risk for the development of moderate vision loss in patients treated with ruboxistaurin compared to patients who received placebo (Figure 2).

![Figure 1. Ruboxistaurin Treatment Reduced the Risk of DME Progression](image1)

![Figure 2. Ruboxistaurin Treatment Reduced the Risk of Moderate Vision Loss](image2)
is an effective therapy for the prevention of vision loss in DME and DR.

Intravitreal VEGF inhibitors are another novel therapeutic approach to DME. A recently published phase II study showed that patients treated with pegaptanib had better visual acuity, were more likely to show a reduction in central retinal thickness, and were less likely to need photocoagulation at follow-up compared to patients receiving placebo. In another small unpublished series, patients injected with bevacizumab experienced decreased neovascularization of the iris, of the disc, and elsewhere, in addition to decreased DME. Studies of ranibizumab for DME are ongoing. Although these preliminary results are promising, the long-term outcomes from treatment with these agents remain unknown. For instance, data have shown that neovascularization appears to recur when pegaptanib is no longer present in the eye, suggesting that there may be a role for concomitant therapy with other modalities.

Early phase studies of novel pharmacologic agents for the treatment of DR and DME show that these therapies are effective. Ruboxistaurin has been shown to substantially reduce the risk of DME progression and moderate vision loss. Pegaptanib treatment has been associated with improved visual acuity, lower rates of retinal thickening, and reduced need for further treatment at follow-up. Bevacizumab and ranibizumab injections also have shown promising early results. Further study will determine the long-term effects of pharmacologic therapies for DME and their potential utility as preventive treatments for this condition.

Steroids

Intravitreal steroid use is widely gaining acceptance as a treatment for DME. In animal studies, corticosteroids have been shown to reduce the breakdown of the blood-retinal barrier that occurs as a result of retinal photocoagulation. Corticosteroids also downregulate the production of VEGF. Case series of intravitreal triamcinolone acetonide use in patients with DME by Martidis et al, Jonas et al, and Massin et al (4 mg, 25 mg, and 4 mg, respectively) each reported improvement in mean visual acuity at endpoint. The safety and efficacy of intravitreal triamcinolone acetonide in the treatment of diffuse DME has been retrospectively studied in a clinical case series by Chieh et al. The study involved 210 eyes of 174 patients who received an intravitreal injection of 1 mg or 4 mg of triamcinolone acetonide, and found a significant improvement in visual acuity ($P < .001$) in the study group at 6 months. Cardillo et al compared the safety and efficacy of intravitreal versus posterior sub-Tenon’s capsule injection of triamcinolone acetonide for diffuse DME in a prospective, double-masked, randomized controlled trial involving 12 patients (24 eyes). This study randomized 1 eye of each patient to receive 4-mg triamcinolone acetonide intravitreal injection and the fellow eye to receive a 40-mg triamcinolone acetonide posterior sub-Tenon’s capsule injection. Both intravitreal and sub-Tenon’s capsule injections resulted in significant but transient improvements in central macular thickness, with the intravitreal injection demonstrating significantly thinner central macular thickness than that obtained with the sub-Tenon’s capsule injection. The mean visual acuity was significantly better than in the sub-Tenon’s capsule-injected eyes at 3 months after injection. Studies delineating the possible role of steroids in DR are ongoing. A DRCR Network randomized multicenter trial that began enrolling patients in 2005 seeks to compare intravitreal triamcinolone acetonide injections at doses of 1 mg or 4 mg to macular laser photocoagulation for DME. Another DRCR Network-sponsored phase II randomized clinical trial of peribulbar triamcinolone acetonide to treat DME is currently recruiting patients.

Photocoagulation Treatment

Studies published before the development of photocoagulation showed that approximately 50% of patients with proliferative diabetic retinopathy (PDR) were blind within 5 years of onset. With intensive treatment and careful follow-up, as demonstrated by the Early Treatment Diabetic Retinopathy Study (ETDRS) Report 9, only 4% of patients with PDR who received active treatment progressed to severe vision loss within 5 years. The long-term effectiveness of pan-retinal photocoagulation in DR also has been demonstrated. In one series, 15-year repeat procedure rates for argon laser and xenon photocoagulation were not significantly higher than 5-year rates. Of the patients randomized to photocoagulation, 5% of the argon-treated patients and 3% of the xenon-treated patients had received additional laser treatment, 58% of the argon-treated patients and 41% of the xenon-treated patients had 20/40 or better visual acuity, and 95% of argon-treated patients and 82% of xenon-treated patients had 20/200 or better visual acuity. Photocoagulation also remains the principal treatment for DME. ETDRS Report 1 showed that focal
Photocoagulation for clinically significant DME substantially reduced the risk of vision loss, increased the chance of visual improvement, and decreased the frequency of persistent macular edema. However, approximately 12% of eyes lost lines of vision even with treatment (Figure 3).26,27 Findings from the ETDRS Report 19 support photocoagulation for patients with clinically significant DME, particularly when the center of the macula is involved.28 The group of ETDRS patients at the highest risk for vision loss from DME had definite involvement of the macula center at baseline. Nevertheless, patients receiving immediate focal photocoagulation had improved visual outcomes compared to patients who were assigned to deferred photocoagulation treatment. These studies suggest that focal photocoagulation was effective in slowing the vision loss associated with DME.

The results from scatter photocoagulation studies suggest that more intense scatter photocoagulation may have detrimental effects on the macula. The ETDRS Report 3 showed that full scatter treatment increased the risk of losing 3 full lines of vision compared to no treatment, and the incidence of vision loss was twice as high within the first 4 months of treatment. Patients in the mild scatter group had a high initial event rate that decreased over time (Figure 4). The high initial rates could be partially attributed to the mild scatter photocoagulation being administered in 2 treatments (600–800 burns at baseline followed by another 600–800 burns). The difference between full scatter and mild scatter was highly statistically significant, whereas there was no difference between vision loss rates for patients receiving full scatter photocoagulation compared to those not receiving treatment.29

Focal photocoagulation also has been shown to be effective treatment for PDR and DME, although further studies are needed to determine optimal photocoagulation strategies and the role of photocoagulation in combination therapy.

**Conclusions**

Diabetic retinopathy is a common microvascular complication, which is a factor in the development of DME, that contributes to blindness in patients with DR. Photocoagulation is currently the primary intervention to slow vision loss in DME. Clinical trials of pharmacologic agents also have shown benefit for visual outcomes. Patients treated with ruboxistaurin had reduced risk for DME progression and reduced risk for moderate vision loss, and preliminary studies and case reports of pegaptanib, ranibizumab, and bevacizumab treatment have shown improved visual outcomes. Areas of current and future investigation include photocoagulation, intravitreal steroid injection, vitrectomy, peribulbar and retrobulbar steroids, combination therapies, and medical and surgical procedures. Further study will determine the role of structural assessments, photocoagulation techniques, and pharmacologic agents in an optimized treatment strategy for patients with DME.
REFERENCES


