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eOphthalmology Review
VOLUME 1, ISSUE 1

Diabetic Macular Edema

In this Issue...

Diabetic macular edema (DME) remains a common cause of visual impairment among working-aged adults. For more than 20 years, laser photocoagulation was the only proven form of treatment for patients with this disorder. Yet visual acuity results were limited, and patients' eyes were sometimes recalcitrant to laser therapy. Because of these poor results, investigators sought new treatments-namely, pharmacologic therapies targeted at the pathophysiology of DME. Since vascular endothelial growth factor (VEGF) and inflammatory cytokines have been implicated in the pathophysiology of DME, pharmacologic approaches have centered on anti-VEGF agents and corticosteroids. The efficacy and safety of these drugs have been investigated when used as monotherapy (compared with laser photocoagulation) and as combination therapy (with laser photocoagulation) in recent clinical trials. Studies also have examined extended drug delivery of some of these pharmacologic treatments.

In this issue, we review some of the recently published findings on pharmacologic therapy for patients with DME. The positive results of these studies have added new treatment options to our therapeutic armamentarium in the battle against DME.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Formulate a treatment plan for diabetic macular edema (DME) using intravitreal drug treatment
- Describe the efficacy and safety outcomes of clinical trials investigating the use of anti-vascular endothelial growth factor (VEGF) therapies and corticosteroid treatment for patients with DME
- Discuss potential drug-related adverse events to consider when selecting a treatment for patients with DME

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THIS ISSUE

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Guest Faculty Disclosures

Jennifer I. Lim, MD has indicated that she has received grants/research support from Regeneron, Genentech, Inc., and Allergan. She also has served as a consultant for Quark, as well as received honoraria from Genentech and Regeneron.

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The author has indicated that there will be reference to unlabeled/unapproved use of Avastin.

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COMMENTARY

The standard treatment regimen for patients with diabetic macular edema (DME) is currently undergoing major changes based on efficacy and safety results from recent clinical trials investigating pharmacologic treatment of the disease. The previously proven paradigm of laser photocoagulation has been compared with and used in combination with pharmacologic treatments for DME. The Diabetic Retinopathy Clinical Research (DRCR) Network recently published data showing that intravitreal ranibizumab—an anti-vascular endothelial growth factor (VEGF) agent—combined with either prompt or deferred (>24 weeks) focal/grid laser treatment was superior to focal grid laser therapy alone. This finding should substantially improve our management of DME.

How does one determine which treatment or combination of treatments to use for patients with DME? In applying these results, several factors must be considered.

First, when determining how to apply the results of recent clinical trials to clinical practice, one must know the inclusion and exclusion criteria used in the original study. In the DRCR.net study, which compared intravitreal ranibizumab (with prompt or deferred laser treatment) vs. intravitreal triamcinolone (with prompt laser therapy) with laser photocoagulation alone, only patients whose eyes had central macular thickening (confirmed on optical coherence tomography [OCT]) were enrolled. Thus, in patients with clinically significant diabetic macular edema (CSDME) without foveal involvement (e.g., 1 disc diameter of edema within 1 disc diameter of the center of the macula, but not involving the center of the macula, with visual acuity of 20/20), the DRCR Network results may not apply. In patients with CSDME without involvement of the center of the macula, but in which edema is near the center of the macula focal/grid laser treatment remains resonable treatment.

Second, although one does not usually consider visual acuity in the decision to treat CSDME with laser, visual acuity should be considered when deciding whether to use an intravitreal agent. The benefit of intravitreal therapy for DME is the greater possibility of improved visual acuity (vs. laser treatment). In the DRCR.net study discussed herein, ranibizumab-treated eyes (with prompt or deferred laser) improved, on average, 9 letters, including 50% that improved by ≥10 letters and <5% that deteriorated by ≥10 letters; laser-treated eyes improved, on average, 3 letters, including 30% that improved by ≥10 letters; and triamcinolone plus laser–treated eyes improved, on average, 4 letters at 1 year, including 30% that improved by ≥10 letters. In eyes with very good visual acuity—for example, 20/20 visual acuity—there is not much room for improvement (ceiling effect), and one should be circumspect about subjecting such patients to the potential risks associated with endophthalmitis, glaucoma, or cataracts.

Third, when planning treatment, clinicians should realize that laser photocoagulation might still be indicated with anti-VEGF therapy. In the DRCR.net study, one-third of eyes in the ranibizumab-with-deferred-laser group received laser photocoagulation after 24 weeks.

Location of edema, visual acuity, and potential side effects all must be considered when selecting a treatment for patients with DME. Laser photocoagulation still has value in specific groups of eyes with CSDME and in combination with pharmacologic treatments.[1,2] Anti-VEGF agents and sustained-release corticosteroids also play a role in managing DME, as discussed in the reviews that follow.

Commentary References

1. Nguyen QD, Shah SM, Heier JS, et al; READ-2 Study Group. Primary end point (six months) results of the Ranibizumab for Edema of the mAcula in Diabetes (READ-2) Study. *Ophthalmology*. 2009;116(11): 2175-2181.e1.
2. Nguyen QD, Shah SM, Heier J, et al; READ-2 Study Group. Two-year outcomes of the Ranibizumab for Edema of the mAcula in Diabetes (READ-2) Study. *Ophthalmology*. 2010;117(11):2146-2151.

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INTRAVITREAL TRIAMCINOLONE IS INFERIOR TO LASER THERAPY IN TREATING DIABETIC MACULAR EDEMA

Diabetic Retinopathy Clinical Research Network (DRCR.net), Beck RW, Edwards AR, Aiello AP, et al. **Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema**. *Arch Ophthalmol*. 2009;127(3):245-251.

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The DRCR network initially conducted a randomized clinical trial to compare outcomes with intravitreal injections of 1-mg and 4-mg doses of preservative-free triamcinolone vs. laser/grid photocoagulation in treating DME. At 2 years, the primary study results showed that the triamcinolone-treated group of eyes fared worse (worse mean visual acuity and thicker OCT results) than did the laser/grid photocoagulation group. This study was designed to determine whether visual acuity and OCT findings at 2 years were sustained through 3 years.

Of the original 840 eyes studied, 306 had 3-year follow-up data available at the conclusion of the clinical trial. This group represents about 80% of the eligible patients with 3-year follow-up data (others had either withdrawn or were lost to follow-up). These eyes were equally represented in the 3 treatment groups: triamcinolone 1 mg, triamcinolone 4 mg, and laser photocoagulation. The mean number of treatments at 3 years was 3 in the laser group and 4 in the triamcinolone groups. Among the 3-year completers, 6% in the laser group received triamcinolone 4 mg; moreover, 23% in the

triamcinolone 1-mg group and 20% in the triamcinolone 4-mg group received laser/grid photocoagulation at some point during the study. All patients' eyes showed improved visual acuity at the end of the study. The primary outcome of visual acuity at 3 years was similar to that at 2 years. Visual acuity results were slightly better in laser-treated vs. triamcinolone-treated eyes. More eyes in each group had better vision and thinner OCT readings at 3 years than at 2 years. Intraocular pressure (IOP) increased by ≥10 mm Hg at any time during the 3-year study in 3% of eyes in the laser-treatment group, 17% in the triamcinolone 1-mg group, and 31% in the triamcinolone 4-mg group. The 3-year rates of IOP-lowering medication usage were 3%, 2%, and 12% in the laser, triamcinolone 1-mg, and triamcinolone 4-mg treatment groups, respectively. No eyes required glaucoma surgery between years 2 and 3. The 3-year cumulative probability of cataract surgery was 31% (27% if excluding eyes that had received some triamcinolone) in the laser treatment group, 46% in the triamcinolone 1-mg group, and 83% in the triamcinolone 4-mg group (P <.001 for all pair-wise comparisons).

Overall, continued treatment of the eyes in all 3 treatment groups resulted in improved visual acuity and OCT outcomes between years 2 and 3. Although the visual acuity results are similar for the 3 groups, the complication rates are disparate. In particular, the rate of cataract severity requiring cataract surgery was significantly greater (p<0.001) in the triamcinolone 4-mg group and triamcinolone 1-mg group, compared with the laser-treatment group. Complications requiring surgery are associated with increased patient morbidity and higher health care costs—both of which are results that cannot be ignored. It appears, therefore, that no benefit is associated with the use of intravitreal triamcinolone, with its accompanying higher complication rates, is not superior to the use of laser photocoagulation in the treatment of DME.

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RANIBIZUMAB PLUS PROMPT OR DEFERRED LASER VS. TRIAMCINOLONE PLUS PROMPT LASER IMPROVED OUTCOMES IN PATIENTS WITH DME

Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, Beck RW, et al. **Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema**. *Ophthalmology*. 2010;117(6):1064-1077.

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This clinical trial compared the visual acuity and safety outcomes in 854 eyes with DME (visual acuity 20/32 to 20/320) randomized to 1 of 4 treatment groups: (1) sham injection plus prompt laser photocoagulation (n=293); (2) intravitreal ranibizumab 0.5 mg plus prompt laser (within 3 to 10 days; n=187); (3) intravitreal ranibizumab 0.5 mg plus deferred laser (≥24 weeks; n=188); or (4) intravitreal triamcinolone 4 mg plus prompt laser (n=186). The objective of the study was to determine whether the use of combination therapy is associated with improved outcomes compared with the use of laser photocoagulation alone. Intravitreal injections were administered every 4 weeks after baseline, up to and including week 12. From week 16 to week 24, an extensive web-based, live algorithm was used to establish a patient's need for injection. At 24 weeks to 1 year, the investigators were free to determine whether to retreat.

In this study, 94% to 96% of all patients in the 4 treatment groups completed the 1 year endpoint. More eyes in the sham-injection-plus-laser group than in the other groups received alternative therapies, and no eyes in the ranibizumab-plus-deferred-laser group received alternative treatments. At 1 year, the mean change (± standard deviation [SD]) in the visual acuity letter score from baseline was significantly greater in both the ranibizumab-plus-prompt-laser group (+8 ± 11 letters; P<.001) and the ranibizumab-plus-deferred-laser group (+9 ± 12 letters; P<.001), but not in the triamcinolone-plus-prompt-laser group (+4 ± 13 letters; P<.31), compared with the sham-injection-plus-prompt-laser group (+3 ± 13 letters). More eyes gained >10 letters (50% and 47%) and >15 letters (30% and 28%), and a lower proportion of eyes had a substantial worsening of >10 letters

(4% and 3%) and >15 letters (2% and 2%), in the 2 ranibizumab groups compared with the sham-injection-plus-prompt-laser group (28% and 15% for >10 and >15 letter gain, respectively, and 13% and 8% for >10 and >15 letter loss, respectively). The triamcinolone-plus-prompt-laser group of eyes showed an initial increase in visual acuity, followed by a decline, and the sham-injection-plus-prompt-laser group experienced a gradual improvement in visual acuity over 1 year. In contrast, both ranibizumab groups showed visual acuity gains, which were most rapid by 8 weeks and continued to improve through 1 year. Interestingly, progression of retinopathy, development of vitreous hemorrhage, or need for panretinal photocoagulation laser treatment occurred less often in both ranibizumab groups and the triamcinolone group than in the sham-injection-plus-prompt-laser group.

Complications of IOP elevation (IOP >10 mm Hg from baseline, IOP >30 mm Hg, or initiation of IOP-lowering medications not in use at study entry at ≥1 visits) during 2 years of follow-up occurred more frequently in the triamcinolone-plus-prompt-laser group (50%) than in the ranibizumab groups (9%) or the sham-injection-plus-prompt-laser group (11%; P<.001). Rates of cataract surgery were 59% in the triamcinolone group vs. 14% each in the laser or ranibizumab groups (P<.001). No systemic safety signals were observed. Progression of tractional retinal detachment was a rare event, which was reported in 1 eye only.

Eyes treated with ranibizumab plus either prompt or deferred laser fared significantly better than did those receiving triamcinolone plus prompt laser or laser therapy alone. Bear in mind, however, that two-thirds of ranibizumab-treated eyes did receive additional treatment after week 16, and about one-third of ranibizumab-treated eyes in the deferred-laser group did receive laser photocoagulation. Thus, it appears that laser is still needed in an era of anti-VEGF therapy for DME, although at this time it is not possible to predict a priori who will require combination therapy. The optimal timing for laser therapy in combination with ranibizumab has not yet been determined in this study. The use of triamcinolone plus laser could be considered in pseudophakic eyes, although the risk for elevated IOP still exists, and the treatment is not superior to anti-VEGF treatment. Ranibizumab plus prompt or deferred laser is superior to laser photocoagulation alone for the treatment of patients with DME. Since this study used ranibizumab as a comparator agent, the results are not necessarily applicable to treatment with bevacizumab.

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MILD MACULAR GRID LASER HAS NO ADVANTAGE OVER MODIFIED EARLY TREATMENT DIABETIC RETINOPATHY STUDY GRID

Writing Committee for the Diabetic Retinopathy Clinical Research Network, Fong DS, Strauber SF, Aiello LP, et al. **Comparison of the modified Early Treatment Diabetic Retinopathy Study and mild macular grid laser photocoagulation strategies for diabetic macular edema**. *Arch Ophthalmol*. 2007;125(4):469-480.

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The objective of this study was to determine whether eyes treated with modified macular grid (MMG) therapy (using mild, widely spaced burns throughout the macula, avoiding the foveal area) have an added benefit over and better visual acuity outcomes than eyes treated with Early Treatment Diabetic Retinopathy Study (ETDRS) laser therapy. With the MMG technique, burns are distributed throughout the macula in areas of both thickened and unthickened retina, and microaneurysms are not directly treated.

A total of 263 subjects (mean age, 59 years) with previously untreated DME underwent laser therapy using either the modified ETDRS (162 eyes) or MMG (161 eyes) technique. Visual acuity, fundus photographs, and OCT measurements were obtained at baseline and at 3.5, 8, and 12 months. Patients underwent retreatment if DME persisted. The main outcome measure was change in OCT at 12 months. Mean visual acuity was 20/32 (mean ± SD, 74 ± 13 letters) and mean ± SD OCT central subfield retinal thickness was

340 ± 123 µm. Overall, 19% of eyes had a central subfield thickness of <250 µm but were still eligible, because at least 1 of the 4 inner subfields had a thickness of ≥300 µm.

At 12 months, among eyes with a baseline central subfield thickness ≥250 µm, the adjusted mean difference was 33 µm (95% confidence interval [CI], 5 to 61 µm; P=.02). Resolution of central subfield thickening, maximum zones of thickening, weighted inner zones of thickening, and retinal volume occurred in both groups, with ETDRS-treated eyes showing a slightly greater resolution than did MMG-treated eyes. At 12 months, the mean change in visual acuity was 0 letters in the modified ETDRS group and 2 letters worse in the MMG group (adjusted mean difference, 2 letters; 95% CI, -0.5 to 5 letters; P=.10).

Eyes treated with the MMG technique did not achieve a better outcome than did those receiving modified ETDRS treatment. The theoretical advantages of MMG were not confirmed in this study. In fact, the opposite was true, with the MMG group showing a slightly lower reduction in retinal thickening and a trend toward a slightly worse visual acuity outcome. Thus, the power of clinical trials is again demonstrated in deciphering treatment benefit. This study also precluded the need for a larger, more costly phase 3 clinical trial. It should be noted, however, that both the MMG and EDTRS methods resulted in OCT decreases in retinal thickening, and that there was no untreated control group, thus preventing determination of how the observed changes in retinal thickening would have differed from the natural history of DME.

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FACTORS ASSOCIATED WITH VISUAL ACUITY OUTCOMES FOLLOWING LASER TREATMENT

Aiello LP, Edwards AR, Beck RW, et al; Diabetic Retinopathy Clinical Research Network. **Factors associated with improvement and worsening of visual acuity 2 years after focal/grid photocoagulation for diabetic macular edema**. *Ophthalmology*. 2010; 117(5):946-953.

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The purpose of this study was to determine the factors associated with visual acuity outcomes in the group of eyes randomized to focal laser vs. triamcinolone therapy. Only the eyes that received laser treatment in the laser vs. triamcinolone study (330 eyes) were included. The inclusion criteria for these eyes were 20/40 to 20/320 visual acuity and OCT central subfield thickness of ≥250 µm. The main outcome of the study was ETDRS visual acuity.

Worse baseline visual acuity was the only factor associated with more frequent improvement in visual acuity (P< .001). More frequent worsening in visual acuity was observed in the eyes with greater baseline OCT retinal volume (P<.001) and better baseline visual acuity (P<.009). There was no difference in outcomes between eyes with or without prior macular or panretinal photocoagulation laser treatment. The visual acuity outcome at 4 months was not generally indicative of the final visual outcome.

It would be helpful to know a priori if certain clinical findings are associated with better or worse visual acuity outcomes. The authors of this study sought to determine whether systemic or ocular factors were associated with visual acuity outcomes. Their finding that neither factor was associated with visual acuity outcomes is interesting, as it suggests that focal/grid laser is beneficial in all patients (despite glycosylated hemoglobin or blood pressure levels). In addition, it also indicates that continued focal/grid laser therapy is advantageous, as the percentage of eyes with improved visual acuity increased over time. Last, the lack of a correlation between the final visual outcome and the 4-month outcome also supports this notion of continued treatment.

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SUSTAINED-RELEASE DEXAMETHASONE FOR PATIENTS WITH PERSISTENT DIABETIC MACULAR EDEMA

Haller JA, Kuppermann BD, Blumenkranz MS, et al; Dexamethasone DDS Phase II Study Group. **Randomized controlled trial of an intravitreous dexamethasone drug delivery system in patients with diabetic macular edema**. *Arch Ophthalmol*. 2010;128(3):289-296.

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The study evaluated the use of a dexamethasone intravitreous drug delivery system (DDS) in eyes with persistent DME of ≥90 days' duration following laser treatment (20/40 to 20/200 visual acuity). Patients were randomized to observation or treatment with 350 µg or 700 µg of dexamethasone DDS. The primary outcome measure was the proportion of eyes achieving an improvement in best-corrected visual acuity of ≥10 letters at the 90-day follow-up visit. Key secondary outcome measures included the proportion of eyes that achieved a 15-letter improvement in best-corrected visual acuity, the proportion of eyes that achieved at least a 2- or 3-grade improvement in fluorescein angiographic leakage (standardized 9-grade scale), change in central retinal thickness using OCT (performed at selected investigational sites), and safety parameters.

In 171 eyes with DME, the mean baseline visual acuity was 20/100. The primary outcome was achieved in 33% of the dexamethasone DDS 700-µg group vs. 12% of the controls; P=.007. There was no significant difference in the primary outcome between treatment with dexamethasone DDS 350 µg and observation. At day 60, a statistically significant difference was reported between the dexamethasone DDS 700-µg group and the observation group (P=.01), and between the dexamethasone DDS 350-µg group and the observation group (P=.04), in the proportion of eyes that achieved at least a 15-letter improvement in best-corrected visual acuity. There were also improvements (p<0.001) in both central retinal thickness (OCT) and fluorescein leakage in eyes treated with dexamethasone DDS 700 µg. Fluorescein leakage, but not OCT thinning, was decreased (p=0.01 for 2 or more step improvement and p=0.03 for 3 or more step improvement in leakage) in the dexamethasone DDS 350-µg group at day 90. The number of eyes with an increase in IOP of ≥10 mm Hg from baseline at any time through day 180 was 8 of 53 (15%) in the dexamethasone DDS 700-µg group, 8 of 55 (15%) in the dexamethasone DDS 350-?g group, and 1 of 56 (2%) in the observation group.

This study is interesting for several reasons. First, it comprises a group of patients who failed conventional therapy and had persistent DME of ≥90 days' duration. Second, this study involves a sustained-release delivery mechanism for administering therapy for 90 days after a single injection. Third, the investigators used dexamethasone because of the theoretical benefit of lower complications associated with the agent. A lower rate of elevation in IOP was indeed observed. One must bear in mind, however, that the results were short-term (6 months); the results of focal/grid laser or anti-VEGF therapy in these eyes is unknown, since the control group was observed; and the rate of cataract development needs to be determined at ≥1 years. It would be interesting to compare this treatment with anti-VEGF treatment or with combination therapy.

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