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Proliferative Diabetic Retinopathy

In this Issue...

Diabetic macular edema (DME) and other pathologies related to diabetic retinopathy remain leading causes of visual morbidity among the working-age population. Recently, several multicenter, randomized clinical trials reported data that have dramatically transformed the treatment paradigm for patients with these conditions, allowing us to now offer different therapeutic options with the potential for providing superior visual outcomes not previously experienced in patients with diabetes.

In this issue, we review the effects of panretinal photocoagulation on the development of DME, the effects of triamcinolone or antivascular endothelial growth factor (VEGF) intravitreal injections on the progression of diabetic retinopathy, and the impact of several newer treatment approaches for DME, including intravitreal ranibizumab, intravitreal triamcinolone in combination with focal/grid laser therapy, fluocinolone acetonide vitreous inserts, and intravitreal VEGF Trap-Eye.

LEARNING OBJECTIVES

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

- Discuss evidence supporting the use of various treatment modalities in patients with diabetic macular edema (DME)
- Describe the effects of triamcinolone and antivascular endothelial growth factor (VEGF) agents on the progression of diabetic retinopathy
- Explain the effect of panretinal photocoagulation (PRP) scatter laser therapy on DME administered in 1 sitting vs. 4 sittings in eyes without DME at the time of PRP

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THIS ISSUE

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Disclosure

Adrienne W. Scott, MD, discloses that she has no relevant financial relationships with commercial supporters.

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The author has indicated that there will be references to unlabeled/unapproved use of intravitreal triamcinolone and intravitreal ranibizumab for the treatment of diabetic macular edema.

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COMMENTARY

In 1985, the landmark Early Treatment Diabetic Retinopathy Study (ETDRS) defined clinically significant diabetic macular edema (DME) and established focal/grid laser as the gold standard of treatment.[1] Patients randomized to focal photocoagulation were half as likely (12% vs. 24%) to lose significant vision (≥ 15 letters) compared with DME eyes not treated with laser. Although the ETDRS reported that a small number of patients with visual acuity of 20/40 or worse experienced modest visual improvement (average gain of 6 letters over the 26-month follow-up), the key insight learned from the ETDRS was that

focal/grid laser therapy is indicated for the prevention of vision loss. A 2008 randomized clinical trial by the Diabetic Retinopathy Clinical Research Network (DRCR.net)[2] confirmed the benefit of focal/grid laser primarily as a vision-stabilizing treatment, and although one-third of focal/grid laser–treated eyes experienced a modest gradual increase in visual acuity (≥ 2 lines) over a 2-year follow-up, 20% of these laser-treated eyes actually worsened by 2 lines at 2 years. Focal/grid laser includes direct treatment to microaneurysms in areas of edema, along with grid treatment to all other areas of macular edema, with no treatment to areas without edema.

Although focal/grid laser photocoagulation has remained the mainstay of DME treatment, corticosteroid treatment has provided clinicians with another weapon in the DME treatment armamentarium. As inflammatory mediators and permeability factors have been implicated in the pathogenesis of diabetic retinopathy and DME, sound scientific rationale exists for the use of corticosteroids to combat these conditions. Intravitreal triamcinolone has the potential to provide a rapid reduction in macular thickness and a corresponding increase in visual acuity. The beneficial effects of corticosteroid use have not been shown to be prolonged. Treatment with intravitreal triamcinolone has demonstrated a reduction in the risk for progression of diabetic retinopathy vs. focal/grid laser therapy; however, in one randomized clinical trial, triamcinolone was not shown to be more effective than focal/grid laser in reducing the risk for visual acuity loss and was associated with a higher rate of adverse effects (with cataract progression and increased intraocular pressure being the most common) by the 2-year follow up, precluding clinicians from considering triamcinolone over focal/grid laser in most circumstances.[2] Longer-acting corticosteroids, such as dexamethasone and fluocinolone, have also been evaluated, with a favorable effect on visual acuity outcomes in DME noted; however, the ever-present concerns of cataract formation and steroid-induced glaucoma remain. In addition, these treatments have not been shown to provide visual acuity outcomes superior to those with focal/grid laser treatment, and have not demonstrated visual acuity outcomes equivalent or superior to intravitreal antivascular endothelial growth factor (VEGF) therapies.

Since eyes with diabetic retinopathy have been shown to have elevated levels of VEGF in the vitreous and retina,[3] compounds targeting VEGF should be ideal agents for the treatment of DME. Ranibizumab binds all isoforms of VEGF-A and has demonstrated remarkable efficacy in reducing vascular leakage and thus decreasing DME. Another DRCR.net protocol[4] has significantly impacted the clinical management of DME, reporting rapid visual improvements and reduction in DME with serial intravitreal ranibizumab injections, as well as superior visual acuity outcomes vs. focal/grid laser therapy. Importantly, these superior visual outcomes seem to be sustained through at least 2 years of follow-up. Over time, less frequent ranibizumab injections are required, with a median of 6 injections within the first 6 months following treatment initiation, 2 to 3 injections in the second 6 months, and 2 to 3 injections in the second year. With a similar mechanism of action to ranibizumab, intravitreal bevacizumab has also shown promise in the treatment of DME in smaller studies and case series. Additionally, agents with a longer VEGF-binding half-life, such as VEGF Trap-Eye, are also attractive treatment options for patients with DME, as they may provide a visual benefit similar to that with ranibizumab, with the potential advantage of requiring fewer injections to maintain superior visual acuity in these eyes.

As more treatments become available for patients with DME-associated visual impairment, more questions remain:

- Is long-term pan-VEGF blockade safe? Although most studies to date have shown pan-VEGF blockade to carry a low risk for systemic and ocular adverse events, we do not know the long-term (decade-long) effects of serial treatments with these agents.
- Can treatment algorithms be generalized to all eyes with DME? Optimal long-term treatment algorithms are still unknown. There may not be one right therapeutic option for every patient with DME, and combination therapy with an anti-VEGF agent and focal/grid laser therapy, for example, may also be beneficial in some eyes to maximize visual gains. How does macular perfusion status influence response to treatment in these eyes? Even the timing of focal/grid laser treatment requires additional further clarification: Should eyes receive focal/grid laser first, with anti-VEGF therapy used later on as needed, or should focal/grid laser only be added after edema persists despite at least 6 months of treatment?
- What about the price of DME treatment? The cost-vs.-benefit ratio of these various therapeutic options must be taken into consideration. As the treatment paradigm shifts

away from focal/grid laser, the cost to the health care system rises. For example, 1 year of ranibizumab treatment for DME is estimated at $21,265 vs. $1326 for focal/grid laser therapy.[5]

It is an exciting time in the treatment of vitreoretinal diseases as we explore new pharmacotherapeutic options. Additional studies are warranted to determine the most advantageous therapeutic regimens for our patients with DME.

Commentary References

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3. Aiello LP, Avery RL, Arrigg PG, et.al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med.* 1994;331(22):1480-1487.
4. 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.e35.
5. Smiddy W. Economic considerations of macular edema therapies. *Ophthalmology.* 2011 Apr 19. [Epub ahead of print]

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EFFECT OF PANRETINAL PHOTOCOAGULATION ON DIABETIC MACULAR EDEMA

Diabetic Retinopathy Clinical Research Network, Brucker AJ, Qin H, Antoszyk AN, et al. Observational study of the development of diabetic macular edema following panretinal (scatter) photocoagulation given in 1 or 4 sittings. *Arch Ophthalmol.* 2009:127 (2):132-140.

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This multicenter, prospective, nonrandomized clinical trial by the Diabetic Retinopathy Clinical Research Network (DRCR.net) compared the effects of single-sitting vs. 4-sitting panretinal photocoagulation (PRP) on diabetic macular edema (DME) in patients with severe nonproliferative diabetic retinopathy (NPDR) or early proliferative diabetic retinopathy (PDR) with relatively good visual acuity and either no or mild center-involved macular edema. The Early Treatment Diabetic Retinopathy Study (ETDRS) established PRP (scatter laser placement) as an effective treatment in reducing the risk for severe vision loss in patients with PDR or severe NPDR. Tissue destruction from PRP treatment may lead to the release of inflammatory cytokines or cause oncotic fluid accumulation and subsequent fluid retention within the retinal tissues, however, and thus may trigger the development of retinal edema or worsen preexisting retinal edema. This theory is based on the observation of visual loss in some patients following PRP treatment and of macular edema on stereoscopic photographs taken 4 months after PRP treatment within the ETDRS. Depending on clinician preference, PRP may be administered in multiple sittings or in 1 sitting. It is unknown whether the risk for development of macular edema is higher in eyes treated with PRP in a single sitting vs. those treated in multiple sittings, and the investigators sought to address this question. Although a randomized design was considered, the participating clinicians had a strong pretrial bias for 1-sitting PRP vs. 4-sitting PRP; therefore, prior to initiation of the study treatment, clinicians indicated their preferences for 1-sitting PRP or 4 sitting-PRP. In this observational study, eyes without preexisting macular edema (confirmed by pretreatment optical coherence tomography [OCT] with central subfield [CSF] retinal thickness < 300 µm) and severe NPDR or PDR that required full-scatter PRP were included. Follow-up visits were performed for both groups after 3 days, 4 weeks, 17 weeks, and 34 weeks. At each of these visits, best-corrected visual acuity measurement and OCT were obtained. Seven-field fundus photographs were obtained at baseline and 3-field photographs were obtained at 34 weeks. The primary study outcome was OCT-measured CSF thickening at 34 weeks; the

main secondary outcome was visual acuity at 34 weeks. The protocol was designed to determine whether data trends were present and sufficiently significant to warrant further investigation in a randomized clinical trial.

The study enrolled a total of 155 subjects, none of whom had DME at the time of PRP initiation. Among 27 sites that declared, prior to participation, whether PRP would be performed in 1 sitting or 4 sittings (the subjects were not randomized), 84 eyes received single-sitting PRP (median, 1274 burns) and 71 eyes received 4-sitting PRP (median, 1260 burns). Each group had similar baseline characteristics. Mean baseline OCT CSF thickness measured 202 µm, and mean visual acuity at baseline was 20/25 (mean, 83 letters). At 3 days and at 4 weeks following PRP treatment, the OCT CSF thickness was slightly greater in the 1-sitting group than in the 4-sitting group (P =.01 at 3 days; P =.003 at 4 weeks). At the 34-week primary outcome visit, however, OCT CSF thickness was slightly greater in the 4-sitting group (P =.06). Visual acuity differences between the groups paralleled OCT trends, measuring slightly worse in the single-sitting group (-3 letters) compared with the 4-sitting group (-1 letter) at 3 days (P = .005). At 4 weeks and 17 weeks, each group exhibited a median change in baseline letter score of -1. By 34 weeks, the visual acuity score was slightly worse in the 4-sitting group (median change of -2 letters) than in the single-sitting group (median change of 0 letters; P = .06). No obvious correlation was found between an increase in retinal thickness by ≥ 25 µm and visual acuity loss (≥ 5 letters or ≥ 10 letters).

The results of this study suggest that although PRP administered in 1 sitting may transiently increase DME and decrease visual acuity 3 days post-treatment compared with PRP administered in 4 sittings, these differences appear to be transient, and by the 34-week follow-up, the retinal thickening was slightly greater with the 4-sitting regimen in eyes with no DME at the time of PRP initiation. Vision differences mirrored OCT differences. The authors concluded that no meaningful clinical differences occurred between the 2 groups, and that the use of single-sitting PRP may enhance patient convenience and compliance with the treatment. It is unclear how these differences may play out over longer follow-up periods. Also, since the subjects in this study were not randomized, it is possible that unknown disparities exist between the groups that might have biased the results one way or the other. A subsequent randomized trial by the DRCR.net suggested that PRP in the setting of DME (in which focal/grid therapy is administered at the time of the PRP) does not, on average, demonstrate a substantial decrease in edema or improvement in vision as is observed following focal/grid therapy administered for DME in the absence of PRP. Currently, it is unknown whether PRP administered in 1 sitting vs. 4 sittings in patients with DME who are receiving treatment would generate different outcomes.

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EFFECT OF INTRAVITREAL TRIAMCINOLONE VS. FOCAL/GRID LASER ON PROGRESSION OF DIABETIC RETINOPATHY

Bressler NM, Edwards AR, Beck RW, et al; Diabetic Retinopathy Clinical Research Network. Exploratory analysis of diabetic retinopathy progression through 3 years in a randomized clinical trial that compares intravitreal triamcinolone acetonide with focal/grid photocoagulation. *Arch Ophthalmol.* 2009:127(12):1566-1571.

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In the Early Treatment Diabetic Retinopathy Study (ETDRS), panretinal photocoagulation (PRP) was shown to reduce the risk for severe vision loss in eyes with proliferative diabetic retinopathy (PDR) and high-risk characteristics. Although PRP has been an effective therapy, the laser treatment involves destruction of tissue and is inherently associated with undesirable treatment-related side effects, such as patient discomfort during laser administration, potential development or exacerbation of diabetic macular edema (DME), loss of peripheral or night vision, and possible complications from misdirected laser burns. Therefore, it would be beneficial to identify additional therapeutic options available for the prevention of PDR progression. A randomized clinical trial within

the Diabetic Retinopathy Clinical Research Network (DRCR.net) evaluated visual acuity in eyes with DME receiving laser vs. intravitreal triamcinolone 1 mg or intravitreal triamcinolone 4 mg. Progression of retinopathy was not a primary outcome in this trial. To this end, the investigators conducted an exploratory analysis of these same subjects. The main outcome measure evaluated in this trial was progression to PDR, as documented longitudinally by fundus photographs taken at baseline, and at 1, 2, and 3 years. A total of 840 eyes from 693 participants were randomized to receive either focal/grid laser treatment (n = 330), triamcinolone 1 mg (n = 256), or triamcinolone 4 mg (n = 254). Graders were masked with respect to treatment group assignment.

At 1 year, the cumulative probability of progression to diabetic retinopathy was 21% (*P* = .71) in the focal/grid-laser group, 19% (*P* = .03) in the triamcinolone 1-mg group, and 14% (*P* = .08) in the triamcinolone 4-mg group. After 2 years, the probability increased to 31% (*P* = .64), 29% (*P* = .005), and 21% (*P* = .03) in each of the groups, respectively. Up to 3 years, these probabilities increased to 37% (*P* = .73) in the focal/grid-laser group, 35% (*P* = .02) in the triamcinolone 1-mg group, and 30% (*P* = .07) in the triamcinolone 4-mg group. Within the subgroup analyses, the triamcinolone 4-mg dose was associated with decreased cumulative probability of progression to diabetic retinopathy at 1, 2, and 3 years with respect to level of retinopathy at baseline (nonproliferative PDR vs. PDR), pseudophakic status at baseline, and number of randomized treatments received.

Further evaluated within this exploratory analysis were patients with bilateral DME, with eyes randomized to focal/grid laser therapy in 1 eye and triamcinolone treatment in the other eye. Of the 72 patients with bilateral DME randomized to receive focal/grid photocoagulation in 1 eye and triamcinolone 1 mg in the contralateral eye, at 3 years, 13% exhibited progression of diabetic retinopathy in the laser-treated eye but not in the triamcinolone-treated eye, whereas 17% exhibited progression of diabetic retinopathy in the triamcinolone-treated eye and not in the laser-treated eye. A total of 75 patients were randomized to laser treatment in 1 eye and triamcinolone 4 mg in the other eye. In this group, at 3 years, 21% showed progression of diabetic retinopathy in the laser-treated eye and no progression in the triamcinolone 4 mg–treated eye, whereas only 7% showed progression of diabetic retinopathy in the triamcinolone 4 mg–treated eye and not in the laser-treated eye.

These data suggest that eyes with DME treated with triamcinolone 4 mg may exhibit decreased progression of diabetic retinopathy at 3 years, compared with both triamcinolone 1 mg–treated eyes and focal/grid laser–treated eyes. These results point to a sustained effect of the corticosteroid treatment over the 3-year time period, as most eyes did not receive triamcinolone injections every 4 months and < 50% received any corticosteroid treatment in the third year. It is unlikely that focal/grid laser therapy or treatment with triamcinolone 1 mg was associated with an increased risk for diabetic retinopathy progression. Even though treatment with triamcinolone 4 mg appears to decrease the risk for progression to diabetic retinopathy in eyes with DME, the authors caution that corticosteroid treatment is still not a superior treatment to PRP for the prevention of diabetic retinopathy progression, given the known increased risk for both cataract formation and steroid-induced glaucoma in susceptible steroid-treated eyes. Similar results at 1 year after study entry were noted in eyes with DME treated with ranibizumab, however, without the complications of cataracts or adverse events related to increased intraocular pressure,[1] suggesting a role for antivascular endothelial growth factor agents in the management of PDR.

References

1. 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.e35.

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RANIBIZUMAB OR TRIAMCINOLONE PLUS FOCAL/GRID LASER VS. FOCAL/GRID LASER ALONE FOR THE TREATMENT OF DIABETIC MACULAR EDEMA

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.e35.

Diabetic macular edema (DME) is a multifactorial disease whose pathophysiology is not yet completely understood. Elevated glucose within retinal blood vessels may damage endothelial cells, compromising the blood-retinal barrier and facilitating vascular leakage and macular edema. The Early Treatment Diabetic Retinopathy Study (ETDRS) established focal/grid laser photocoagulation as the gold-standard treatment for eyes with center-involving DME. Visual outcomes with focal/grid laser are primarily favorable, with the greatest visual benefit realized over 2 years. Prior studies, however, have demonstrated a risk for decreased visual acuity in a small number of eyes following focal/grid laser treatment. Although intravitreal triamcinolone has been shown to reduce vascular leakage and macular edema in eyes with DME, the long-term visual results have not demonstrated superiority to focal/grid laser. Cataract and glaucoma are commonly reported side effects associated with the use of ocular corticosteroids. Additionally, increased levels of vascular endothelial growth factor (VEGF) have been found in the eyes of individuals with diabetes. Intravitreal antiVEGF therapy has demonstrated success in the treatment of vascular leakage and resultant macular edema. Other potential treatment strategies include combination therapy with intravitreal triamcinolone or intravitreal ranibizumab, to rapidly reduce macular edema, followed by focal/grid laser photocoagulation. Combination therapy may, theoretically, provide the rapid reduction in macular edema and corresponding improvement in visual acuity observed with triamcinolone and ranibizumab treatment, while prolonging the duration of this effect by adding focal/grid laser. The current phase 3, multicenter, randomized, prospective clinical trial by the Diabetic Retinopathy Clinical Research Network (DRCR.net) was designed to compare visual outcomes and safety of antiVEGF therapy with ranibizumab in combination with prompt or deferred focal/grid laser, intravitreal triamcinolone in combination with prompt focal/grid laser, and focal/grid photocoagulation alone. Eyes with DME-associated retinal thickening of > 250 μm in the central subfield (CSF), based on optical coherence tomography [OCT]) measurements, were randomized to 1 of 4 treatment groups: (1) sham injection plus prompt laser (n = 293); (2) ranibizumab 0.5 mg plus prompt laser (n = 187); (3) ranibizumab 0.5 mg plus deferred (≥ 24 weeks) laser (n = 188); or (4) triamcinolone 4 mg plus prompt laser (n = 186). A preestablished uniform retreatment regimen was followed. The main outcome measures included best-corrected visual acuity and safety at 1 year.

At 1 year, the improvements in visual acuity letter score from baseline were significantly greater in the ranibizumab-plus-prompt-laser group (+ 9 ± 11; $P < .001$) and ranibizumab-plus-deferred-laser group (+ 9 ± 12; $P < .001$), compared with the sham-injection-plus-prompt-laser group (+ 3 ± 13). The triamcinolone-plus-prompt-laser group did not exhibit greater visual acuity improvement from baseline compared with the sham-injection-plus-prompt-laser group (+ 4 ± 13; $P = .31$). Visual benefits at 2 years were similar. Each of the ranibizumab treatment groups exhibited the greatest mean increase in visual acuity from baseline by the 8-week study visit. Alternatively, the triamcinolone-plus-prompt-laser group initially demonstrated improvement in visual acuity through the 24-week visit, but this improvement was not sustained. The sham-injection-plus-prompt-laser group demonstrated gradual improvement in the first year, with stabilization of vision thereafter. Within the pseudophakic subset of eyes in the triamcinolone-plus-prompt-laser subgroup, improvements in visual acuity were similar to those in both ranibizumab groups; however, elevated intraocular pressure and cataract progression were reported more frequently in the triamcinolone group. OCT thickness paralleled visual acuity results, with both ranibizumab treatment groups showing sustained reduction in CSF thickness from the 1-year to the 2-year visit. The triamcinolone-plus-prompt-laser group demonstrated an increase in mean CSF from the 1-year to the 2-year visit and mirrored the slight decline

in visual acuity from the 1-year to the 2-year visit. Individuals in the sham-injection-plus-prompt-laser group did not exhibit parallel OCT and visual acuity results, as their mean change in visual acuity did not continue to rise from year 1 to year 2. Both the ranibizumab and triamcinolone treatment groups were less likely to exhibit progression of diabetic retinopathy or experience a vitreous hemorrhage from baseline to the 1-year visit. No systemic adverse events were attributed to any of the study treatments, although 3 eyes (0.8%) in the ranibizumab treatment group developed injection-related endophthalmitis.

Intravitreal ranibizumab plus prompt or deferred laser proved to be a more effective treatment for patients with center-involving DME than either triamcinolone plus prompt laser or focal/grid laser alone, and ranibizumab injections seem to convey a low risk for both systemic and ocular adverse events. Interestingly, the superior visual acuity results and reduction in OCT thickness were maintained through the 2-year visit in the ranibizumab groups, even as fewer injections were required to treat the DME. An added benefit appeared to be decreased progression of diabetic retinopathy in ranibizumab-treated eyes. Moreover, although pseudophakic eyes may benefit from intravitreal triamcinolone injections, patients receiving this treatment may exhibit an increased likelihood of intraocular pressure elevations compared with those treated with ranibizumab plus prompt or deferred laser or focal/grid laser therapy alone. Furthermore, in this study, the results with intravitreal triamcinolone in pseudophakic eyes are not superior to those with ranibizumab, and the results with intravitreal triamcinolone represent a beneficial subgroup analysis in which the entire group (main outcome measure) did not derive benefit from treatment, resulting in less confidence in the validity of the results than those noted with intravitreal ranibizumab.

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EFFECT OF FLUOCINOLONE ACETONIDE INTRAVITREAL INSERTS IN PATIENTS WITH DIABETIC MACULAR EDEMA

Campochiaro PA, Brown DM, Pearson A, et al; FAME Study Group. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology.* 2011;118(4):626-635.e2.

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Diabetic macular edema (DME) is a frequent cause of morbidity among patients with diabetes. Although focal/grid laser photocoagulation has historically been the gold standard of treatment for DME, visual improvement results are modest in treated eyes, and a small percentage of laser-treated eyes actually lose vision. Antibodies to vascular endothelial growth factors (VEGF), such as intravitreal ranibizumab, have also proven successful in the treatment of DME, with more rapid reduction in macular thickness and corresponding visual improvement than that previously observed following focal/grid laser photocoagulation. VEGF inhibition may not be the most comprehensive therapeutic target for this condition, however, as many inflammatory mediators that promote vascular leakage, in addition to VEGF, are also at play in the pathogenesis of DME. In contrast, ocular corticosteroid treatment does target the inflammatory component of DME. Intravitreal triamcinolone has also been shown to rapidly reduce macular edema and to improve vision. This effect has not been sustained, however, and repeated intravitreal injections may be required as often as every 3 to 4 months. Thus, use of a longer-acting corticosteroid may be more desirable for sustained DME treatment.

Campochiaro and colleagues sought to assess the efficacy and safety of intravitreal inserts of low-dose fluocinolone acetonide (0.2 µg/day) vs. high-dose fluocinolone acetonide (0.5 µg/day) in eyes with DME in 2 parallel, prospective, randomized, sham injection–controlled, double-masked, multicenter clinical trials. In an outpatient clinic, fluocinolone acetonide inserts were injected into the vitreous with a 25-gauge needle. A total of 956 subjects with persistent DME after at least 1 focal/grid laser treatment were

randomized to receive sham injections (n=185), low-dose inserts (n=375), or high-dose inserts (n = 393) in a 1:2:2 ratio. The main outcome measure of the study was the percentage of patients with improvement in vision of ≥ 15 letters above their baseline visual acuity letter score at 24 months. Secondary outcome measures included other parameters of visual function and foveal thickness (FTH). Patients were assessed at screening, baseline, 1 week, 6 weeks, and 3 months after initial study treatment and every 3 months thereafter. Subjects were allowed rescue focal/grid laser treatment for persistent edema after the week 6 evaluation. Retreatment with the initially assigned study drug was permitted after month 12 if a patient experienced a loss of ≥ 5 letters in visual acuity or an increase in FTH of 50 µm above their best status during the previous 12 months.

Overall, 28% of patients in each of the fluocinolone acetonide insert groups met the primary outcome of ≥ 15 letters of visual acuity improvement over baseline, compared with 16% in the sham-injection group (*P* = .002). A rapid, favorable treatment response to fluocinolone acetonide insert was observed, as 10% of patients in each of the treatment groups met the primary outcome within 1 month. The letter gains achieved in patients in each of the treatment groups were superior to that reported in the sham group at every time point. Mean visual acuity improvement between baseline and month 24 measured 4.4 and 5.4 in the low-dose and high-dose fluocinolone acetonide treatment groups, respectively, compared with 1.7 in the sham-injection group (*P* = .02 and *P* = .016 in the low-dose and high-dose groups, respectively). Phakic eyes in each treatment group demonstrated an initial increase in visual acuity of 3 letters between baseline and week 6 that was stable through month 9, but then showed a gradual decline in visual acuity letter score, with a mean reduction in letter score of 5 letters (high-dose group) and 9 letters (low-dose group) at month 24. Reduction in FTH on optical coherence tomography was observed in both treatment groups vs. the sham-injection group at all time points. After month 12, in the sham-injection group, 2 (19.5%), 3 (2.7%), or 4 (1.6%) study treatments were administered for eyes with reduced vision or recurrent DME; this was in contrast to 21.3%, 1.9%, and 0.3%, respectively, in the low-dose group and 22.%, 2.5%, and 0.3%, respectively, in the high-dose group. A total of 7.6% of eyes in the high-dose fluocinolone acetonide group required incisional glaucoma surgery, compared with 3.7% in the low-dose fluocinolone acetonide group and 0.5% in the sham injection–treated group.

Fluocinolone acetonide intravitreal injections appear to be a beneficial treatment option for eyes with DME. A favorable risk-to-benefit ratio was seen at 24 months, particularly in the low-dose treatment group, compared with the sham group. Low-dose and high- dose fluocinolone acetonide groups appear to be comparable in their efficacy, with the higher-dose treatment carrying the increased risk for elevated intraocular pressure necessitating incisional glaucoma surgery. Given the relatively low requirement for repeated injections in each of the treatment groups, the authors suggest that fluocinolone acetonide injections may compare favorably with intravitreal ranibizumab with respect to need for repeated intravitreal injections. Regular monitoring of intraocular pressure is suggested for eyes receiving intravitreal fluocinolone acetonide treatment. Limitations of the study include the adverse events with respect to cataract surgery in phakic patients, the adverse effects associated with elevated intraocular pressure in all patients, the lack of comparison with focal/grid laser therapy (standard of care at the time of the trial), and superior vision outcomes using anti-VEGF injections compared with a different corticosteroid preparation

(but a corticosteroid preparation nevertheless) in a randomized trial.

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VEGF TRAP-EYE VS. FOCAL/GRID LASER IN PATIENTS WITH DIABETIC MACULAR EDEMA

Do DV, Schmidt-Erfuth U, Gonzalez VH, et al. The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. *Ophthalmology.* 2011 May 4. [Epub ahead of print]

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Vascular endothelial growth factor (VEGF) has been implicated as an important mediator in the pathogenesis of diabetic retinopathy and diabetic macular edema (DME), and elevated VEGF levels have been reported in eyes with DME. Thus, inhibition of VEGF has

been an important target in the treatment of DME. Repeated intravitreal injections of ranibizumab, a humanized, monoclonal antibody that binds all isoforms of VEGF-A, and bevacizumab, the complete antibody to the VEGF-A molecule, have both been shown to have a beneficial effect in patients with DME, with improvement in visual acuity and reduction of foveal thickness observed. One theoretical disadvantage of both ranibizumab and bevacizumab is the potential need for intravitreal injections every 4 weeks. VEGF Trap-Eye (Regeneron Pharmaceuticals, Inc.; Tarrytown, New York) is a recombinant fusion protein consisting of the VEGF-binding domains of human VEGF receptors 1 and 2. The binding affinity of VEGF Trap-Eye to VEGF is 10 times higher than that of either ranibizumab or bevacizumab. In a phase 1 study, intravitreal VEGF Trap-Eye yielded favorable results in reducing retinal thickness and improving vision in patients with DME. The current multicenter, randomized, double-masked, phase 2 clinical trial compared intravitreal VEGF Trap-Eye with standard macular laser therapy over a 24-week period in eyes with DME. Patients with DME were randomized in 1 eye only in a 1:1:1:1:1 ratio to receive 1 of the following 5 treatment regimens: (1) VEGF Trap-Eye 0.5 mg every 4 weeks; (2) VEGF Trap-Eye 2 mg every 4 weeks; (3) VEGF Trap-Eye 2 mg for 3 initial monthly doses and then every 8 weeks; (4) VEGF Trap-Eye 2 mg for 3 initial monthly doses and then on as-needed (prn) basis; or (5) macular laser photocoagulation plus sham injection. All patients in each of the VEGF Trap-Eye groups received sham laser treatment at the week 1 visit. The purpose of this trial was to determine whether any of these different doses and regimens of VEGF Trap-Eye are superior to the gold-standard DME treatment—macular laser photocoagulation—with respect to the main outcome measure of mean change in visual acuity and central retinal thickness at 24 weeks. The follow-up schedule for all groups was every 4 weeks through the 24-week primary endpoint.

A total of 200 patients completed the study. Subjects in all 4 VEGF Trap-Eye treatment groups demonstrated a statistically significant mean visual acuity increase from baseline to week 24 (from 8.5 to 11.4 letters), compared with an increase of only 2 letters in the laser therapy group (P = .0085). No statistically significant differences among each of the VEGF Trap-Eye treatment groups were detected, although the study was not powered to detect differences among these groups. At week 24, up to 34% of the VEGF Trap-Eye–treated patients gained ≥ 15 letters from baseline, 64% gained ≥ 10 letters, and 93% gained 0 to 10 letters, compared with only 21% gaining ≥ 15 letters, 32% gaining ≥ 10 letters, and 68% gaining 0 to 10 letters in the laser treatment group. Overall, 4.5% of patients in the VEGF Trap-Eye 0.5-mg group lost ≥ 15 letters at 24 weeks, compared with 9.1% in the laser treatment group. Patients in the 2-mg prn group received a mean of 1.5 of 3 possible prn injections. No patients in any of the VEGF Trap-Eye 2-mg treatment groups had lost ≥ 15 letters at the primary endpoint. Among patients in the VEGF Trap-Eye–treated groups, 2 patients developed endophthalmitis (1.1%) and 1 patient experienced a retinal tear (0.6%).

Injections of intravitreal VEGF Trap-Eye were well tolerated, with all dose groups superior to the macular laser group at 24 weeks with respect to improved visual outcomes and decreased macular thickness in eyes with DME. The rate of injection-related ocular adverse events was comparable to that reported in other clinical trials. Interestingly, in the 2-mg group treated every 8 weeks and the 2-mg prn group, visual gain seemed to be maintained after the initial loading phase without sacrificing efficacy of the agent. Although this trial is a phase 2 study with a small sample size and a limited follow-up period, additional evidence has shown that VEGF inhibition may be an ideal treatment modality for maximizing visual outcomes in eyes with DME. While promising, definitive results from an adequately sized phase 3 trial are needed to demonstrate the superiority of VEGF Trap-Eye to focal/grid laser therapy or the noninferiority or equivalency to ranibizumab.

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