Practical Retina
Incorporating current trials and technology into clinical practice

The evolving paradigm for the treatment of diabetic macular edema

by David Telander, MD, PhD; Allan Hunter, MD

Drs. Telander and Hunter were asked to comment on the evolving paradigm for treating diabetic macular edema.

Nearly 1 year has passed since the approval of ranibizumab for the treatment of DME via the RISE/RIDE trials, which provided the first FDA-approved pharmacotherapy for the treatment of DME. The efficacy seen with ranibizumab is without compare.

Much discussion remains regarding the management of DME. For instance, given the availability of ranibizumab, is there a role for focal laser or intravitreal corticosteroids? Vitrectomy? Dosing ranibizumab in DME is also a topic of discussion because the monthly dosing used in RISE/RIDE can be challenging in certain circumstances for clinicians and patients.

The controversies will continue in the coming year as the fluocinolone and dexamethasone implants studied for DME are both slated for FDA consideration.

The insights and review of clinical trial data presented in this piece will prove to be very valuable.

Diabetic retinopathy remains the leading cause of vision loss in working-age adults. Diabetic macular edema (DME) is the leading cause of moderate vision loss in patients with diabetic retinopathy.\(^1,2\) The longer patients suffer from diabetic retinopathy, the more likely they are to be burdened with reduced vision. At 2 years, half of diabetic patients with clinically significant DME lost more than 10 letters of best corrected visual acuity. By 3 years, similar patients had a 25% rate of severe vision loss (at least three lines, equal to a doubling of the visual angle). New pharmacotherapy for DME has raised the bar for improved clinical outcomes, but surgical vitrectomy maintains its role for these patients.

Retina laser for DME

Since 1985, focal/grid macular laser photocoagulation has been the gold standard for treating DME. The Early Treatment Diabetic Retinopathy Study (ETDRS) showed clear evidence of the benefits of laser by reducing moderate vision loss approximately 50% in patients with clinically significant macular edema.\(^3,4\) While the findings were encouraging, clinicians were often disappointed by a subset of patients whose BCVA worsened despite laser therapy: 12% of ETDRS patients lost 15 or more letters at 3-year follow-up and few in this and other studies experienced any visual improvement. Additionally, laser is not without potential ocular harm, including loss of central vision from scarring.\(^5,6\)

Steroids for DME

With its introduction in 2001, intravitreal injection of triamcinolone acetonide (IVTA) demonstrated dramatic reduction of mac-
TABLE 1
Clinical Trials Examining Ranibizumab for Diabetic Macula Edema

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Study Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRCR.net</td>
<td>Ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema</td>
</tr>
<tr>
<td>READ-2</td>
<td>Ranibizumab for edema of the macula in diabetics</td>
</tr>
<tr>
<td>RESOLVE</td>
<td>Safety and efficacy of ranibizumab in diabetic macular edema</td>
</tr>
<tr>
<td>RESTORE</td>
<td>Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema</td>
</tr>
<tr>
<td>RISE/RIDE</td>
<td>Ranibizumab for diabetic macular edema</td>
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</tbody>
</table>

Anti-VEGF for DME

Ranibizumab was first approved for exudative age-related macular degeneration in 2006 and recently received FDA approval for DME in August 2012. A number of studies have demonstrated the drug’s improved efficacy over laser and IVTA for DME (Table 1). The RESOLVE, RISE, and RIDE studies have all shown the benefit of ranibizumab over sham injections for DME.7,9,10 RISE and RIDE deserve particular attention because the fixed monthly dosing regimen throughout the study afforded the highest BCVA gain among studies examining ranibizumab for DME (Table 2). Additionally, DRCR.net, READ-2, and RESTORE compared ranibizumab vs. laser and found ranibizumab therapy superior to laser monotherapy.11 But contrary to the notoriety of ranibizumab for DME, there is still a subpopulation of patients with refractory DME. In RISE and RIDE (despite standardized, fixed monthly injections), approximately 25% of patients in the 0.3-mg ranibizumab group had central foveal thickness of at least 250 µm on optical coherence tomography, and at least 70% of patients had fluorescein leakage on angiography. What alternative therapies do we have to offer such patients? To better understand, a review of vascular physiology and oxygen autoregulation is important.

Pathogenesis of DME

DME is based on water accumulation in the macula. Starling’s law describes the steady state of water between vessels and extracellular tissue. Hydrostatic pressure drives water out from vessels, and oncotic/osmotic pressure works in the opposite direction. In DME, these forces are out of balance. The main deterrent to hydrostatic pressure is the arterioles of the retina. It has been shown that prior to the development of DME, the retinal arterioles and venules undergo dilation.12 The vessels have been shown to constrict after laser for DME13 or branch retinal vein occlusion macular edema.14 The hypothesis of how laser works is relatively straightforward. Laser causes the RPE scar with improved oxygen flux from the choroid into the retina with secondarily decreased consumption from a reduced photoreceptor concentration. Oxygen is then free to passively diffuse to the inner retina. The increased oxygen tension in the inner retina causes arterial constriction by autoregulation and decreases hydrostatic pressure to the fourth power of the vessel’s radius. Steroids and anti-VEGF pharmacology work by suppressing the permeability effect of VEGF165 (either directly or through upstream mechanisms) on retinal endothelial cells that also contribute to DME.15

Vitrectomy of DME

The thought that vitreomacular traction and adhesion contribute to the development of DME is supported by the observation that the prevalence of posterior vitreous detachment is lower in eyes with DME than in those without DME.16 Epiretinal tensile forces were initially postulated to be involved based upon clinical observations.17 Laboratory investigations have confirmed that capillary stretching increases thymidine uptake and VEGF production in capillaries.18-21 Therefore, the mechanical effects of a taut hyaloid certainly can cause or contribute to the development of severe DME and DME that is unresponsive to anti-VEGF or steroid therapy. No large, multicenter, randomized, controlled trial has been conducted for this issue. Of the studies showing positive effect on thinning the retina, the extent of treatment effect was greater in eyes with signs of macular traction on OCT.22 The DRCR.net prospective study found 38%
of patients gained at least 10 letters 6 months after vitrectomy, and most eyes had more than a 50% reduction in macular thickening. In addition, they found greater visual improvement with epiretinal membrane removal and worse baseline visual acuity. Although there is general acceptance that vitrectomy has a role in a subset of DME patients, which patients would most benefit remains in debate. In addition, the role of ILM peeling during vitrectomy also remains controversial. Many small studies have shown improved outcomes with ILM peeling, but this may simply be the result of more complete removal of all tractional membranes.

As early as 1985, pars plana vitrectomy surgery was shown to slow the progression of retinal neovascularization in diabetic retinopathy. Half a decade later, vitrectomy was shown to reduce DME. The similar benefit of laser, pharmacotherapy, and vitrectomy for DME is easily explained by retinal oxygenation. Stefánsson et al showed that vitrectomy in cat eyes with an induced bilateral branch retinal vein occlusion had an increased epiretinal oxygen tension when compared to the non-vitrectomized contralateral eye. Vitrectomy appears to reduce focal retina hypoxia due to vascular ischemia plausibly due in part to improved “oxygen fluid currents” in the vitreous cavity. In addition to decreasing hypoxia of the retina, multiple authors debate the additional contribution of epiretinal traction on DME.

Conclusion
In sum, the many recent studies for DME have given retinal specialists new tools to better treat patients. While focal macular laser can still be effective in reducing macular thickening, pharmacologic therapy (ie, anti-VEGF and steroid) has been shown to improve visual outcomes but requires many more treatments. Surgical vitrectomy certainly continues to play a role in treatment for the many patients with a tractional component of DME. Undoubtedly, in the future we will find that patients may need various combinations of these therapies to obtain the best outcome, and many studies are already beginning to address this.

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**REFERENCES**


