PERSPECTIVE

Management Paradigms for Diabetic Macular Edema

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• PURPOSE: To provide evidence-based recommendations for diabetic macular edema (DME) management based on updated information from publications on DME treatment modalities.

• DESIGN: Perspective.

• METHODS: A literature search for "diabetic macular edema" or "diabetic maculopathy" was performed using the PubMed, Cochrane Library, and ClinicalTrials.gov databases to identify studies from January 1, 1985 to July 31, 2013. Meta-analyses, systematic reviews, and randomized controlled trials with at least 1 year of follow-up published in the past 5 years were preferred sources.

• RESULTS: Although laser photocoagulation has been the standard treatment for DME for nearly 3 decades, there is increasing evidence that superior outcomes can be achieved with anti–vascular endothelial growth factor (anti-VEGF) therapy. Data providing the most robust evidence from large phase II and phase III clinical trials for ranibizumab demonstrated visual improvement and favorable safety profile for up to 3 years. Average best-corrected visual acuity change from baseline ranged from 6.1-10.6 Early Treatment Diabetic Retinopathy Study (ETDRS) letters for ranibizumab, compared to 1.4-5.9 ETDRS letters with laser. The proportion of patients gaining ≥10 or ≥15 letters with ranibizumab was at least 2 times higher than that of patients treated with laser. Patients were also more likely to experience visual loss with laser than with ranibizumab treatment. Ranibizumab was generally well tolerated in all studies. Studies for bevacizumab, aflibercept, and pegaptanib in DME were limited but also in favor of anti-VEGF therapy over laser.

• CONCLUSIONS: Anti-VEGF therapy is superior to laser photocoagulation for treatment of moderate to severe visual impairment caused by DME. (Am J Ophthalmol 2014;157:505–513. © 2014 by Elsevier Inc. All rights reserved.)

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DIABETES MELLITUS (DM) IS A GLOBAL EPIDEMIC with significant morbidity.[1] Although diabetic retinopathy (DR) affects 1 in 3 people with DM,[1] the leading cause of vision loss in this population is diabetic macular edema (DME),[2] which affects approximately 6.8% of the diabetic population.[3]

DME represents a spectrum of retinopathy signs characterized by edema and thickening of the central macula and surrounding noncentral macula that are not explained by the presence of an epiretinal membrane (ERM) at the macula. These symptoms are typically confirmed by slit-lamp biomicroscopy and, increasingly, with the aid of optical coherence tomography (OCT).

For nearly 30 years, focal/grid laser photocoagulation has been the mainstay of treatment for clinically significant DME (CSME).[4] However, there have been substantial advances in our understanding of DME since this method was first used. First, epidemiologic data indicate that DME, more than DR severity, is the most common cause of vision loss for patients.[5] Second, there is now better understanding that risk factors for DME (eg, serum lipids) may be different from those for DR, highlighting the importance of systemic management being targeted at DME.[6,7] Third, improved knowledge of the pathophysiology of DME has enabled the development of alternative therapies.[1,8] Fourth, the development of modern imaging techniques, such as OCT, has allowed assessment of early DME, including subclinical DME.[9] Last, the results from several large phase III randomized controlled trials (RCTs) for alternative therapies, namely anti–vascular endothelial growth factor (anti-VEGF) treatments, have now been reported.[10–14]

The treatment algorithm for the selection of patients, the initiation of anti-VEGF therapy, and the assessment and retreatment of DME using this group of therapies has not yet been established. This Perspective article summarizes major studies and RCTs examining DME treatment modalities with the aim of providing an initial set of evidence-based recommendations for DME management.

METHODS

WE CONDUCTED A LITERATURE SEARCH USING THE PubMed, Cochrane Library, and ClinicalTrials.gov

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databases with the terms "diabetes macular edema" or "diabetic maculopathy" to identify studies published from January 1, 1985 to July 31, 2013. This was followed by a manual search of references cited in selected major papers. Meta-analyses, systematic reviews, and RCTs with at least 1 year of follow-up published in the past 5 years were preferred sources. Recommendations for DME treatment were drafted by the Diabetic Macular Edema Treatment Guideline Working Group and graded for importance of clinical outcome and strength of evidence.[15]

SYSTEMIC MANAGEMENT

OPTIMAL MANAGEMENT OF SYSTEMIC RISK FACTORS IS A key component of the primary prevention of DR. Intensive control of hyperglycemia, hypertension, and possibly hyperlipidemia delay the onset and progression of DR. Whether the same is useful for DME is less clear, as there are fewer studies focused on DME alone. Because DME develops in a subset of patients with DR and the likelihood of developing DME increases with DR severity, control of systemic risk factors would be expected to have a major effect on DME. An overview of studies evaluating the effects of improving blood glucose levels, blood pressure, and lipid profile is available online (Supplemental References, available at AJO.com).

OCULAR MANAGEMENT

• **LASER PHOTOCOAGULATION:** The use of laser photocoagulation has been the mainstay of treatment for CSME since the landmark Early Treatment Diabetic Retinopathy Study (ETDRS) in 1985.[4] However, laser photocoagulation mostly does not improve vision, and a significant proportion of patients experience progressive worsening of vision despite laser photocoagulation (Supplemental Table 1, available at AJO.com). Furthermore, long-term use of this treatment is limited by significant risks and adverse effects, such as central and paracentral scotomata, loss of color vision, progressive enlargement of laser scars ("laser creep"), and occasional secondary choroidal neovascularization.[16] The subthreshold micropulse diode laser and the patterned scan laser are 2 innovations developed to minimize scar formation. However, long-term experience is needed to define their precise roles in DME treatment.

• **ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS:** VEGF is a potent factor in the pathogenesis of DME that is upregulated in hypoxic and hyperglycemic states. Elevated VEGF levels in the intraocular fluid correlate with vascular hyperpermeability and DME severity. Current evidence shows that anti-VEGF therapies reverse visual impairment, in addition to stabilizing and preventing future vision loss.[5–13] Four VEGF-binding drugs are currently used for ophthalmic conditions: ranibizumab, bevacizumab (off-label), aflibercept, and pegaptanib. Evidence for DME treatment with anti-VEGF therapies is largely based on data from phase II and phase III RCTs for ranibizumab, including Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE):[17] Two-year Outcomes of the Ranibizumab for Edema of the mAcula in Diabetes (READ-2);[18,19] A 12 Month Core Study to Assess the Efficacy and Safety of Ranibizumab Intravitreal Injections (RESTORE);[10] Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I;[11–13] and A Study of Ranibizumab Injection in Subjects with CSDME with Center Involvement Secondary to Diabetes Mellitus (RISE and RIDE).[14,20]

Ranibizumab. RESOLVE was a phase II, double-masked, sham-controlled RCT evaluating the efficacy and safety of ranibizumab compared with sham treatment over 12 months.[17] Patients (n = 151) with visual acuity (VA) 20/40-20/160 and central retinal thickness (CRT) ≥300 μm were randomly assigned to ranibizumab 0.3 mg or 0.5 mg, or to sham injections. Dose doubling and rescue laser treatment were permitted according to predefined criteria. At the end of the study, a mean average change in best-corrected VA (BCVA) of +7.8 letters from baseline was observed in the ranibizumab groups compared with -0.1 letters in the sham group ($P < .0001$). Mean CRT reduction was parallel to mean BVCA improvement. More than 3 times the proportion of patients who were treated with ranibizumab gained ≥10 and ≥15 letters compared with those receiving sham injections.

READ-2 was a phase II, multicenter, interventional RCT comparing ranibizumab with focal laser treatment and a combination of both in DME among patients with type 1 or 2 DM. Patients (n = 126) with VA 20/40-20/320 and CRT ≥250 μm were randomized to receive 0.5 mg ranibizumab injections at baseline and at months 1, 3, and 5 (Group 1); laser treatment at baseline and then at month 3 as needed (Group 2); or ranibizumab injections and laser treatment at baseline and at month 3 (Group 3).[18] This was followed by a maintenance regimen of 0.5 mg ranibizumab every 2 months and/or laser treatment every 3 months for residual edema. Mean BVCA change from baseline to month 24 was +7.7 letters for Group 1, +5.1 letters for Group 2, and +6.8 letters for Group 3, although the mean differences were not significantly different among all groups. Patients in Groups 2 and 3 who received ranibizumab injections on top of laser treatment required less frequent injections without compromising visual outcomes at 2 years than those who received ranibizumab only in Group 1. More aggressive treatment with ranibizumab from year 2 to year 3 demonstrated that mean BCVA could be further improved by