EARLY INTERVENTION IN DIABETIC MACULAR EDEMA

Earlier seems to be better in terms of visual acuity improvement in DME.

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The diabetes epidemic continues unabated, and it has become an urgent societal problem requiring global attention. According to a study by the World Health Organization, the international incidence of diabetes increased from 108 million in 1980 to 422 million in 2014.[1] Diabetes affects approximately 8% of the population in the United States.[2] Diabetic retinopathy (DR) is a leading cause of blindness worldwide, and diabetic macular edema (DME) contributes greatly to this vision loss.[3] Therefore, early detection of and prompt intervention in DME are essential in order to preserve vision in diabetic patients. This article reviews treatment options for DME and explains why early intervention is imperative to successful management of these patients.

VISION LOSS IN DME

All patients with diabetes are at risk of developing DME. The onset of DME is usually insidious and painless. It often does not present until after the disease is advanced and vision loss occurs. Vision loss in DME is a result of vascular exposure to high glucose levels over extended periods of time. Hyperglycemia destroys retinal endothelial cell tight junctions and incites the accumulation of subretinal and intraretinal fluid, leading to the development of macular edema.[4]

Although DME is reversible in its early stages, chronic edema may lead to irreversible changes in the retina and become debilitating for the patient. If the disease is untreated, 20% to 30% of patients with DME will lose at least 3 lines of vision within 3 years.[5] The long-term prognosis for DME is poor, and treatment is recommended immediately, once a patient is diagnosed.[6]

DIAGNOSIS OF DME

To initiate prompt intervention, a multidisciplinary approach and novel strategies to detect DME in its early stages are necessary. The American Academy of Ophthalmology recommends annual eye examinations for all diabetic patients to screen for the development of DR and DME.[7]

The most well-established primary examination technique to diagnose DME is biomicroscopy under stereopsis with high magnification. Optical coherence tomography (OCT) and fluorescein angiography (FA) are also useful as ancillary tests in the evaluation of DME.[4] Indeed, OCT is more sensitive in detecting retinal thickening than biomicroscopy, and it provides quantitative information regarding central retinal thickness. FA identifies leaking microaneurysms, and ultra-widefield angiography can now identify areas of retinal ischemia that were not previously appreciated on conventional FA.[8]

OCT angiography (OCTA) is an emerging imaging modality that can provide novel information in regard to retinal and choroidal vascular diseases. OCTA is a fast, noninvasive tool to examine retinal structures microscopically, and it facilitates the identification of subsequent disorders such as DR and DR-associated complications.[9]

Improvement of all of these diagnostic techniques in recent years has allowed earlier diagnosis of DME.

OVERVIEW OF DME TREATMENT

Historically, treatment of DME has been based on the definition of clinically significant macular edema (CSME). CSME is defined as (1) retinal thickening within 500 µm of the foveal center; or (2) hard exudates within 500 µm of the foveal center, if associated with thickening of the adjacent retina; or (3) retinal thickening greater than one disc area in size, part of which is within 1 disc diameter of the center of the fovea.[4]

AT A GLANCE

- Although treatments for DME have shown great promise in clinical trials, the translation of these results into clinical practice remains challenging.
- In clinical trials of anti-VEGF agents, there is a subset of patients who do not achieve the excellent outcomes seen in the overall study population.
- A post hoc study suggests that early response to anti-VEGF treatment may predict long-term response.

TABLE 1. STUDIES OF ANTI-VEGF AGENTS AND CHANGES IN BCVA IN PATIENTS WITH DME[14,15,16,21]

Study	Year	Anti-VEGF Agent	Number of Injections in 1 Year	BCVA Letter Improvement
Protocol I	2010	ranibizumab + prompt laser	8	9.0
Protocol I	2010	ranibizumab + deferred laser	9	9.0
BOLT	2010	bevacizumab	9	8.6
RISE and RIDE	2012	ranibizumab	13	11.7
VIVID and VISTA	2013	aflibercept	9	11.5

Abbreviations: BCVA, best corrected visual acuity; DME, diabetic macular edema

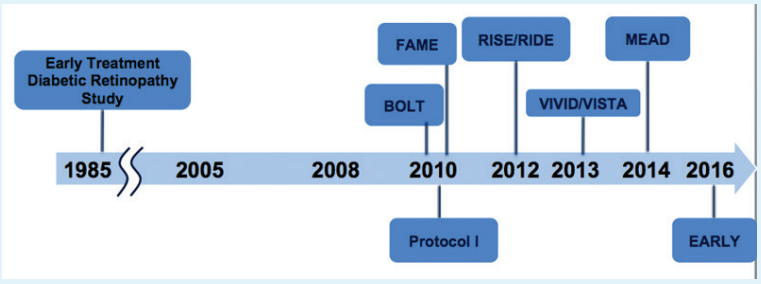

Figure. Changes in the treatment landscape for DME from 1985 to 2016.[10]

The primary method of treatment for diabetes-related ophthalmic complications is the management of underlying systemic risk factors, which include intensive glycemic control, blood pressure management, and regulation of lipid levels. However, these methods are often insufficient in controlling DME, in which case more invasive pharmacologic and non-pharmacologic therapy is frequently needed. The EDTRS in 1985 showed the benefit of focal laser for DME (Figure). Focal laser photocoagulation has been considered the standard of care for DME for more than 3 decades. Although laser therapy slows the progression of vision loss in patients with DME, it rarely results in improvement of vision.[10] With the advent of intravitreal pharmacologic agents, the prognosis of DME has changed from stabilization to improvement of vision.[11]

Use of VEGF Inhibitors

Elevated blood glucose leads to a reduction in pericyte function and damage to capillaries, causing retinal hypoxia and ischemia and the activation of inflammatory pathways. The pathogenesis of DME involves upregulated expression of multiple inflammatory cytokines, including VEGF, intercellular adhesion molecule 1 (ICAM-1), interleukin 6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and pigment epithelium–derived factor (PEDF), which promotes vascular permeability and leakage through the blood-retina barrier.[12] Anti-VEGF agents directly inhibit the cascade of vascular dysfunction and decrease the risk of worsening DR.[13]

Several VEGF inhibitors have shown clinical efficacy in the treatment of DME, including ranibizumab (Lucentis, Genentech), bevacizumab (Avastin, Genentech), and aflibercept (Eylea, Regeneron). Two phase 3 prospective randomized controlled trials, RISE and RIDE, demonstrated improvements in visual acuity of 11.7 letters after 2 years in patients with DME who received ranibizumab.[14] The BOLT study determined that bevacizumab led to an improvement of 8.6 letters of visual acuity in patients with DME.[15] The VIVID and VISTA studies showed improvement in visual acuity of 11.5 letters after 2 years of therapy with aflibercept in patients with DME (Table 1).[16]

The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I study compared four treatment strategies: (1) focal laser, (2) focal laser plus intravitreal triamcinolone, (3) intravitreal ranibizumab plus prompt focal laser, and (4) intravitreal ranibizumab plus deferred focal laser. The two cohorts of patients treated with ranibizumab in that study experienced greater mean gains in visual acuity and OCT outcomes compared with those receiving laser treatment without ranibizumab.[21]

Use of Steroids

Intravitreal sustained delivery of steroids, such as with the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) or the fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera Sciences), affects not only VEGF but also other mediators of inflammation.[8] In the MEAD study, mean change in best corrected visual acuity (BCVA) from baseline was 3.6 letters with the dexamethasone implant 0.35 mg and 2 letters with sham treatment. The mean number of injections was 4.1 over 3 years.[16] The FAME study found improvement of 4.4 letters in patients with low-dose fluocinolone acetonide intravitreal implants and 5.4 letters in those receiving high-dose implants, compared with 1.7 letters in those receiving sham treatment (Table 2).[18]

EARLY INTERVENTION IN DME

The RISE, RIDE, VIVID, and VISTA studies further support the notion that early intervention in DME is crucial to achieving optimal improvement in visual acuity. In these studies, treatment with ranibizumab or aflibercept led to rapid vision improvements, with statistically significant changes observed as early as 7 days after the first injection. Sham- or laser-treated patients who were crossed over to ranibizumab or aflibercept treatment after 24 months achieved smaller visual acuity gains than those who started treatment at the onset of their respective study.[16,20]

TABLE 2. IMPROVEMENT IN BCVA WITH INTRAVITREAL STEROID IMPLANTS[17,18]

Study	Year	Intravitreal Steroid	Number of Injections Over 3 Years	BCVA Letter Improvement
MEAD	2014	dexamethasone implant	4.1	3.6
FAME	2010	fluocinolone acetonide implant (low dose)	1	4.4

THE OTHER SIDE OF THE STORY

Despite the impressive results achieved in clinical trials of anti-VEGF agents, there is a subset of patients who do not achieve these excellent outcomes. In the RISE, RIDE, VIVID, and VISTA studies, 60% of patients did not achieve a 15-letter improvement in visual acuity. In the DRCR.net Protocol I, 50% of patients did not achieve a 10-letter gain in visual acuity and 26% of patients were nonresponders, defined by a reduction of central subfield thickness on OCT of less than 20%.[22]

The Early Treatment Diabetic Retinopathy (EARLY) study was performed to determine whether early visual acuity response to anti-VEGF therapy could help to predict who would be a longer-term responder to therapy. This study was a post hoc subset analysis of data from the DRCR.net Protocol I study that examined patterns of improvement in visual acuity in patients who were treated promptly with ranibizumab. The EARLY study found that patients' responses to therapy could be predicted by as early as 3 months. Mean improvement in BCVA was followed for 3 years, and patients were stratified based on having an excellent response (≥10 letters), an average response (5-9 letters), or a poor response (<5 letters) to treatment with ranibizumab.[23] In each group, mean improvements in BCVA through year 3 were within 5 letters of the response seen at week 12 (Table 3).[24]

TREATMENT BURDEN

Although treatments for DME have shown great promise in clinical trials, the translation of these results into clinical practice remains challenging. Diabetic patients with DME often have higher rates of vascular comorbidities, which result in a significantly higher rate of health care utilization than is seen in those without DME. Patients with DME have an average of 12 additional health care appointments per year compared with diabetic patients with no DME.[25] A recent study of compliance trends in patients with DME in the United States demonstrated higher rates of appointment cancellations (10.01%) and no-shows (14.32%) compared with patients with wet age-related macular degeneration.[26]

A combination of early detection and effective treatment algorithms for DME is needed to reduce the health care burden and improve clinical outcomes for this potentially devastating complication of diabetes. ■

TABLE 3. CHANGE IN MEAN BCVA IN THE EARLY STUDY[24]

Cohort	Mean Letters Gained at 12 Weeks	Mean Letters Gained at 3 Years
<5 Letters	-0.3	3.0
+5 to +9 Letters	6.9	8.2
≥10 Letters	15.2	13.8

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