For this Practical Retina column, Michael A. Singer, MD, and Michael E. Jansen, MD, from San Antonio were asked to comment on the evolving treatments for treating diabetic macular edema (DME). The approval of ranibizumab (Lucentis; Genentech, South San Francisco, CA) for the treatment of DME in 2012 via the RISE/RIDE FDA registration trials was monumental given that it was the first U.S. Food and Drug Administration (FDA)-approved pharmacotherapy for the treatment of DME. The efficacy seen in treating DME with ranibizumab was without compare at the time. However, since then, the community has seen FDA approvals of aflibercept (Eylea; Regeneron, Tarrytown, NY), the intravitreal dexamethasone implant (Ozurdex; Allergan, Irvine, CA), and the fluocinolone implant (Iluvien; Alimera Sciences, Alpharetta, GA), which have all decreased treatment burden compared to ranibizumab. Only recently has our community begun figuring out the place for each of the four treatments in the DME treatment paradigm either as monotherapy or combination therapy. To make things more interesting, numerous clinical trials are underway to add therapies to our arsenal for managing patients with DME. These anticipated FDA approvals will only add to the questions regarding role of various therapies to manage patients with this condition.

Drs. Singer and Jansen will comment on past, present, and future treatments for DME, discussing unmet needs, treatment burdens of the various agents, and how innovation in this landscape will hopefully improve outcomes and patients’ perceptions of their disease.

Treatments for Diabetic Macular Edema: Past, Present, and Future

by Michael E. Jansen, MD, and Michael A. Singer, MD

Diabetic macular edema (DME) is the leading cause of vision loss in adults and a common complication of diabetes. It is due to the extravasation of blood and its solutes from the capillaries to the extracellular space under the macula, causing it to thicken and swell. It can be present in any stage of the disease, but it is usually seen in the later stages of the diabetic retinopathy severity scales. This article will provide an overview of currently available for the treatments, as well as the rationale for emerging agents, many of which are currently being evaluated in clinical trials.

TREATMENTS

Laser Photocoagulation

Laser photocoagulation has been the standard for the treatment of DME for the past two decades. Laser treatment for DME involves placing tiny laser burns within thickened areas of the retina in both direct (focal) treatment of microaneurysms and scattered spots in other areas of edema (grid). Laser photocoagulation efficacy was established by the Early Treatment Diabetic Retinopathy Study, which showed that focal laser decreased the incidence of 15-letter loss from 24% to 12%.

The advantage of this therapy is that, when effective, therapy is finite. The disadvantage is that focal laser burns have been observed to expand over time. At 2 years, laser scars increased 50% per year and 4.6% a year afterward, and 11 of 203 patients experienced foveal encroachment. Focal laser...
photocoagulation may be a highly effective treatment for macular edema in some patients and is a feasible adjunctive option for suboptimal responders to anti-VEGF or corticosteroid treatments.³

**Anti-VEGF**

The vascular endothelial growth factor (VEGF) family is the most critical with regard to the pathogenesis of diabetic retinopathy due to the fact that it increases vascular permeability and induces angiogenesis of new blood vessels. Due to its central role in the pathogenesis of DME, VEGF antagonists are a logical choice for therapy. The first anti-VEGF agent used for ophthalmology was pegaptanib (Macugen; OSI Pharmaceuticals, Farmingdale, NY), but was soon replaced by the availability of ranibizumab (Lucentis; Genentech, South San Francisco, CA). In the randomized clinical trial, Protocol I, researchers observed that ranibizumab tripled the mean change in visual acuity compared to the corticosteroid triamcinolone in 1 year.⁴ The RISE and RIDE studies were the pivotal studies that allowed U.S. Food and Drug Administration (FDA) approval of ranibizumab. These studies demonstrated that 39.2% of patients had 15-letter gains in visual acuity and a mean improvement of 12.4 letters versus sham during the course of 24 months. However, the treatment burden with ranibizumab is extraordinarily high, as the RISE and RIDE studies mandated 36 injections in the study eye during the course of 36 months.⁵

Bevacizumab (Avastin; Genentech, South San Francisco, CA) is another VEGF antagonist that has come into widespread clinical use for the treatment of various retinal diseases. The BOLT study compared bevacizumab versus macular laser in patients with DME. The bevacizumab arm gained a median of 9 ETDRS letters versus 2.5 letters with laser treatment \( (P = .005) \), with a mean gain of 8.6 letters for bevacizumab versus a mean loss of 0.5 letters for laser. Forty-nine percent of patients gained 10 or more letters \( (P = .001) \) and 32% gained at least 15 letters \( (P = .004) \) for bevacizumab versus 7% and 4%, respectively, for macular laser. The percentage who lost fewer than 15 letters in the laser arm was 86% versus 100% for bevacizumab \( (P = .03) \).⁶

Afibercept (Eylea; Regeneron, Tarrytown, NY) is the most recent anti-VEGF medication approved to treat DME. It is unique as it not only is an anti-VEGF molecule but also an anti-placental growth factor molecule. In the randomized clinical studies VIVID and VISTA, researchers compared intravitreal afibercept injections to laser monotherapy for the treatment of DME. The results of the trials demonstrated that afibercept given either every 4 weeks or every 8 weeks (after five initial monthly doses) is superior to laser and results in 10.7 letters to 12.4 letters gained at 1 year. In addition, 32% to 41% of patients gained 15 letters at 1 year, as well.⁷ These visual acuity results indicate that a large portion of patients with DME may be effectively treated with an every-8-week dosing regimen in year one, compared to the higher injection burden required when using older-generation anti-VEGF agents.

**EARLY Analysis**

About 50% of patients with DME experience only a moderate reduction of edema and improvement in vision from VEGF antagonists alone. However, for most clinicians, it takes many months or years to determine the need for a switch in therapy. The EARLY analysis was a post hoc analysis of Protocol I of the diabetic retinopathy clinical research group.⁸,⁹ This analysis included the two arms of patients who received ranibizumab and compared baseline to 3-month vision to vision at 12 months and 3 years. The study showed that patients could be divided into three groups: those who were good responders (10 letters or greater improvement), those who were fair responders (five to nine letters of improvement), and those who were suboptimal responders (five or fewer letters of improvement). The study showed that the best-corrected visual acuity (BCVA) response after three anti-VEGF injections (12 weeks) is a strong predictor of long-term BCVA response at 12 months and 3 years. This study demonstrated that physicians can recognize suboptimal DME responders much earlier in the treatment cycle and should consider different therapies in patients who are subresponders.

**Corticosteroids**

Inflammation is a significant factor in the pathogenesis of DME. Cytokines and chemokines released by leukocytes in the blood significantly increase vascular permeability leading to more fluid buildup under the retina. These cytokines also carry VEGFs, which can aggravate and worsen macular edema by promoting angiogenesis.¹⁰

Corticosteroids have shown the ability to lower inflammatory mediators as well as VEGF, whereas anti-VEGF treatment only treats the VEGF portion of macular edema. Anti-VEGF treatment does not work for all patients; in a Diabetic Retinopathy Clinical Research Network subanalysis of Protocol I, 50% of patients respond significantly and quickly, 25% of patients had an intermediate response, and 25% of patients did not respond to anti-VEGF treatment. Steroids have been shown to lower the central subfield thickness (CST) and improve visual acuity for
suboptimal responders to anti-VEGF and pseudophakics. Corticosteroids also appear to be effective for both naïve and chronic macular edema, whereas anti-VEGF treatment is thought to be a less-effective treatment for chronic DME.

There are currently two approved corticosteroid therapies for DME: the dexamethasone intravitreal implant (Ozurdex; Allergan, Irvine, CA) and fluocinolone (Iluvien; Alimera Sciences, Alpharetta, GA). The MEAD study showed that the dexamethasone intravitreal implant was able to improve patients’ vision during a 3-year period. Vision improved by six letters in pseudophakic patients and by four letters overall during the 3-year duration of the study. In the MEAD study, there was steroid-related intraocular pressure (IOP) elevation, and 40% of patients taking steroids were later prescribed medication for IOP. However, patients’ increase in IOP usually peaked at 6 weeks to 8 weeks and then returned to baseline by the end of 4 months. One patient required IOP-lowering surgery, but the remaining patients who had a steroid-induced IOP increase were treated with topical therapy. In addition, nearly 60% of phakic patients required cataract surgery.

The advantage of corticosteroid sustained-delivery systems, such as the dexamethasone intravitreal implants, is that they require far fewer treatments compared to the anti-VEGF agents. The fluocinolone implant was investigated in the FAME study and showed an improvement of 15 or more letters in 28.7% of patients in the study group versus 18.9% in sham eyes and a 6-letter improvement in vision at 24 months. IOP medications were required in 42% of patients, with seven patients requiring IOP-lowering surgery. Cataract surgery occurred in 75% of patients. The current FDA label for the fluocinolone implant mandates that a patient has received previous corticosteroid treatment without a steroid-induced IOP elevation before receiving this 2-year to 3-year implant to reduce the risk of IOP elevation.

Combination Therapy

Although anti-VEGF medication is usually first-line therapy for DME, there are many cases for which anti-VEGF therapy alone is not adequate. This should not be unexpected, as the clinical trials were only able to significantly improve vision in fewer than 50% of patients. VEGF inhibitors are logical drugs that treat DME well, but to maintain efficacy, patients require frequent retreatment, and VEGF inhibitors do not address additional inflammatory cytokines upregulated in DME. Patients who are suboptimal responders may benefit from receiving therapies that utilize different mechanisms of action. Diabetic maculopathy is a combination of both inflammatory mediators as well as VEGF-mediated factors. Corticosteroids decrease inflammatory cytokines and have a modest anti-VEGF effect, whereas anti-VEGF agents have a modest anti-inflammatory effect. Using a combination of anti-VEGF with a corticosteroid is a reasonable approach where one can expect a superior synergistic effect to either monotherapy alone.

A 12-month randomized study of eyes with persistent DME assessed the efficacy of a corticosteroid (dexamethasone) delivery system as an adjunct to the VEGF antagonist, bevacizumab, compared with continued bevacizumab monotherapy. Although there were no differences in vision after 12 months, there were differences in vision at different monthly time points, and the CST was significantly better in the combination group. Subgroup analysis suggests the greatest benefit of dexamethasone implant is in the group with the most bevacizumab injections prior to enrollment in the study. Although visual acuity changes are not superior to continued bevacizumab monotherapy, combination therapy significantly improved visual acuity and macular morphology in eyes with refractory DME.

In another study examining the role of corticosteroids in treating macular edema, researchers explored the effect and safety of fluocinolone acetone in patients with chronic DME considered insufficiently responsive to available therapies with or without intravitreal corticosteroid therapy. The study covered 12 patients who received a single injection of fluocinolone acetone and were followed for 6 months. Of the 11 patients who completed the study, nine maintained or improved their BCVA from baseline, and the 11 patients experienced an average decrease in CST of 300.6 µm from baseline.

Combination therapy is a rational approach to treat patients who are suboptimal responders to monotherapy. It may be an alternative for patients who have a suboptimal response or are unresponsive to VEGF antagonists. This therapy may provide a sustained duration of action, as well as increasing efficacy and convenience. However, there are potential adverse effects, such as cataracts and elevated IOP, that need to be considered.

EMERGING THERAPIES IN CLINICAL TRIALS

As previously mentioned, patients with DME have increased inflammatory cytokines and new therapies are being developed to block different factors along the inflammatory cascade. The molecules discussed below are just a partial list of medications that are currently in clinical trials.
Aerpio

Aerpio is developing AKB-9778, a first-in-class Tie2 activator that works by inhibiting the enzyme vascular endothelial protein, tyrosine phosphatase (VE-PTP). The Tie2 tyrosine kinase receptor, so named because it mediates cell signals by inducing the phosphorylation of key tyrosines, is located almost exclusively on endothelial cells. The phosphorylation of these tyrosines promotes vascular stability by reducing responsiveness to VEGF and other angiogenic factors. The VE-PTP enzyme, which is the target of AKB-9778, acts as a negative regulator, or brake, at the Tie2 receptor. AKB-9778 works by inhibiting VE-PTP and effectively removes this negative regulation on the Tie2 receptor by inhibiting the dephosphorylation of Tie2, maintaining Tie2 signaling and vascular integrity.

The TIME-2 study, a randomized, 3-month, phase 2a proof-of-concept clinical trial was initiated to explore the efficacy and safety of AKB-9778 in patients with DME. In this study, the combination of subcutaneous AKB-9778 twice-per-day dosing at 15 mg and 0.3 mg ranibizumab injection provided a clinically significant reduction in CST compared to ranibizumab alone ($P = .008$) (Figure 1). As a measure of activity in diabetic retinopathy, the rate of two-step or greater improvement in diabetic retinopathy severity score (DRSS) was equivalent across arms in study eyes. In fellow eyes, the proportion of patients with a greater than two-step improvement in DRSS was more than double in the arms receiving systemic AKB-9778 compared to the arm that received no systemic therapy. Confirmatory studies with a once-a-day formulation of AKB-9778 are currently being planned. To date, AKB-9778 is the only Tie2 targeted agent to demonstrate clinical efficacy in a phase 2, randomized, placebo-controlled setting. The ability to positively remodel retinal blood vessels, as demonstrated by proportion of patient with a greater than two-step improvement in DRSS,
in both eyes without the need for an intravitreal injection could change the treatment paradigm for diabetic eye disease as well as other retinopathies such as DME and wet age-related macular degeneration.

**Ampio**

Danazol, a synthetic steroid derived from ethisterone, has been shown to increase intercellular adhesion and decrease vascular permeability in ultra-low doses (Figure 2). The Optimeyes study was a phase 2 study to determine the proper dosing of oral danazol in different diabetic patient populations as well as the effect of danazol in combination with other systemic medications. The study showed the best effect in patients with a BMI of 27 kg/m² to 31 kg/m² who were taking renin angiotensin blockers. In these patients, visual acuity improved six letters and optical coherence tomography (OCT) thickness decreased 49 µm during a 12-week period. A phase 3 study is being planned.

**Aestellis**

Aestellis is conducting a phase 2, double-masked, randomized, active-controlled study that evaluates the efficacy and safety of ASP8232 in reducing central retinal thickness in subjects with diabetic macular edema. The primary objective is to evaluate the percent change from baseline from excess CST in the study eye by assessed by spectral-domain OCT for ASP8232 monotherapy at month 3.

**Allegro**

Luminate (Alegro Ophthalmics, San Juan Capistrano, CA) is a synthetic integrin antagonist that treats vitreoretinal diseases by targeting integrins, cell receptors that serve as the bridges between cells, regulating their interactions with each other and with the extracellular matrix. An arginine-glycine-aspartic acid class oligopeptide, Luminate binds to multiple integrin receptor sites affecting multiple pathways. This and its dual mechanisms of action — anti-angiogenesis and vitreolysis — make it effective across a number of different vitreoretinal conditions.

Luminate is currently in phase 2b clinical trials for patients with centrally involved DME for posterior vitreous induction in patients with nonproliferative diabetic retinopathy, and for symptomatic vitreomacular adhesion and vitreomacular traction (Figure 3).

**ASP-8232**

VAP-1 is expressed in retinal capillaries and acts as an amine oxidase and as an endothelial adhesion molecule for leukocytes. In discussing the scientific rationale for VAP-1 inhibition as a treatment for DME, VAP-1 activity in plasma, as well as oxidative stress, have been associated with the presence of macular edema in patients with diabetic retinopathy.

In a preclinical study performed in the streptozocin-induced diabetic rat model, treatment with ASP-8232 improved retinal hyperpermeability and inhibit-
ed plasma VAP-1 activity; combination treatment with an anti-VEGF antibody was associated with greater benefit than that achieved with either agent alone.

An ongoing phase 2 study, VAP-1 Inhibition in Diabetes, is a controlled study being conducted at 15 centers across the United States. Patients are randomized to either ASP-8232 as standalone treatment or in combination with ranibizumab 0.3 mg. The primary endpoint is reduction of central retinal thickness.

The Ruby Study
This is a randomized, double-masked, active-controlled, phase 2 study investigating the efficacy, safety, and tolerability of repeated doses of intravitreal REGN910-3 in patients with DME. The primary objective of the study is to compare the efficacy of intravitreal REGN910-3 to intravitreal aflibercept injection to improve BCVA in patients with DME. Two different doses of REGN910-3 are being compared to aflibercept in a phase 2 trial.

CONCLUSION
The treatment of DME is currently focused on using anti-VEGF medications to combat macular edema and only using corticosteroids to control inflammatory processes when anti-VEGF medications do not provide an adequate response. Given the accepted rationale that DME is a multifactorial disease, the EARLY study encourages us to evaluate earlier whether patients are responsive to anti-VEGF medications and if not consider, therapy supplementation with the corticosteroids.

We are encouraged by the robust pipeline of medications in clinical trials being developed to combat DME. Clinicians, patients, and caregivers are becoming overwhelmed by the treatment burden of our current medications. Hopefully, innovation in this landscape will decrease treatment burden, improve outcomes, and most importantly improve patients’ perceptions of their condition.

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