

MEDICAL MANAGEMENT OF DIABETIC RETINOPATHY



Thanks to the development of pharmacotherapies for this disease state, patient outcomes are better than ever.

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Diabetes and diabetic retinopathy (DR) require prompt diagnosis, close monitoring, and proper evidence-based management, often involving multiple health care disciplines and professions. The DRCR Retina Network has conducted randomized clinical trials that provide level 1 evidence to establish guidelines for the treatment of patients with DR. This article offers an overview of the medical treatment and management of patients with this disease.

SYSTEMIC CONSIDERATIONS

Several factors (eg, excess weight and obesity, hypertension, dyslipidemia, and obstructive sleep apnea) drive micro- and macrovascular complications that arise in patients with diabetes. Proper treatment and management of patients who have diabetes and its comorbidities are integral to the prevention, treatment, and management of DR.

The most vital component of diabetes management is glycemic control. Glycosylated hemoglobin (HbA1c) measurement has emerged as the gold standard in the diagnosis and monitoring of patient status (Figure 1). HbA1c represents a mean glycemic measurement over an 8- to 12-week period.¹ Improved glycemic control has been shown to reduce complications of diabetes, including retinopathy.² Landmark clinical studies, such as the Diabetes Control and Complications Trial,³ have demonstrated the benefit of increased glycemic control with respect to DR, and follow-up studies have highlighted that continued glycemic control maintains this reduced risk.^{4,5}

THE SHIFTING PARADIGM OF DME TREATMENT

Diabetic macular edema (DME) may occur at any stage of retinopathy, ranging from minimal DR to severe proliferative disease. The treatment paradigm

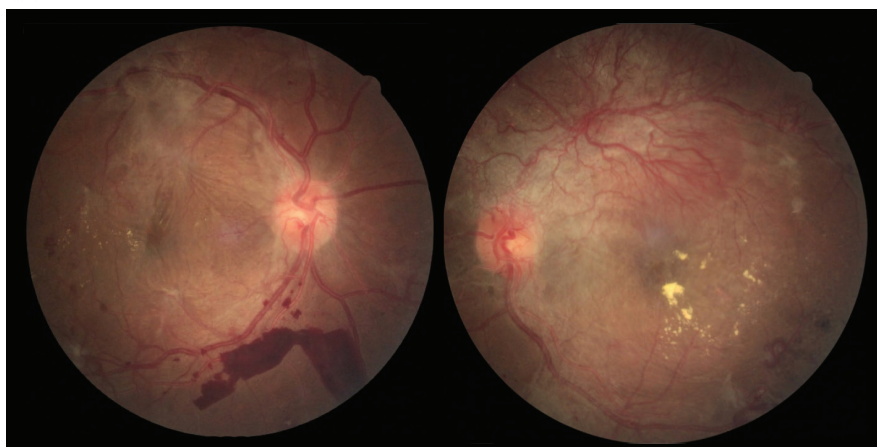


Figure 1. Bilateral proliferative diabetic retinopathy in a patient with poorly controlled type 2 diabetes (HbA1c = 13%). Note central macular exudate in the left eye with accompanying DME.

for patients with DME has shifted dramatically during the past 2 decades. For many years, the standard protocol was based on results from the Early Treatment Diabetic Retinopathy Study (ETDRS), which found that focal laser photocoagulation for clinically significant DME was superior to observation (although a large percentage of treated patients still lost vision over time).⁶

Today, in most cases of DME, first-line therapy consists of an intravitreal injection of one of several anti-VEGF agents. These medications can stabilize and even improve vision over time, and they have favorable safety

profiles.⁷ Whether or not DME is clinically significant as defined by the ETDRS is no longer an issue. Physicians now use OCT to determine whether edema is center-involving or non-center-involving and base treatment decisions on that finding as well as the patient's VA (Figure 2). OCT is clearly the standard of care for imaging, detection, classification, and management, particularly in patients whose BCVA is worse than 20/20 without another obvious cause of vision loss.^{6,7} (Of course we still look at the macula stereoscopically through the dilated pupil and perform OCT.)

AT A GLANCE

- Improved glycemic control has been shown to reduce complications of diabetes, including retinopathy.
- In most cases of center-involved DME and reduced vision, first-line therapy consists of an intravitreal injection of one of several anti-VEGF agents.
- Panretinal photocoagulation remains the mainstay of treating proliferative disease, but a move toward pharmacotherapy has begun.
- Anti-VEGF therapy is gaining ground as an option for patients who are reliable in their follow-up and present with PDR, especially with concurrent DME.

The Lineup of Anti-VEGF Agents

In the RISE and RIDE trials of ranibizumab 0.3 mg (Lucentis, Genentech), patients gained 12 letters of VA over a 2-year period, an effect that was maintained with continued treatment.^{7,8} In addition to the drug's established clinical indication for DME, the FDA expanded the approved use of ranibizumab to treat DR in patients with DME.^{9,10} Similarly, in March 2015, the FDA expanded the approved use for aflibercept (Eylea, Regeneron) to treat DR in patients with DME.¹¹

Ranibizumab, aflibercept, and bevacizumab (Avastin, Genentech), which is used off-label in retinal care, differ in their molecular weight, structure and pharmacokinetics.¹² Ranibizumab is a monoclonal antibody fragment. Aflibercept is a fusion protein that combines the binding domains of VEGF receptors 1 and 2 with an antibody fragment. Bevacizumab, which was developed for use in oncology, is a full-length, bivalent monoclonal antibody against VEGF-A. When used off-label, bevacizumab must be prepared by a compounding pharmacy; small outbreaks of devastating ocular infections have been attributed to its use because multiple vials of the drug were contaminated.¹³ Providers must therefore select a compounding pharmacy carefully. Cost issues aside, most patients are more comfortable with an FDA-approved drug specifically packaged and manufactured for intraocular use.

The DRCR Retina Network's Protocol T study compared the safety and efficacy of aflibercept, ranibizumab, and bevacizumab and found that all three agents worked well. Patients with poor baseline vision achieved more substantial improvements in VA after 1 year of treatment with aflibercept. This drug also produced greater macular thinning on OCT than either ranibizumab or bevacizumab. At 2 years, aflibercept was no longer more effective than ranibizumab for the treatment of eyes with DME and more severe visual impairment.¹⁴

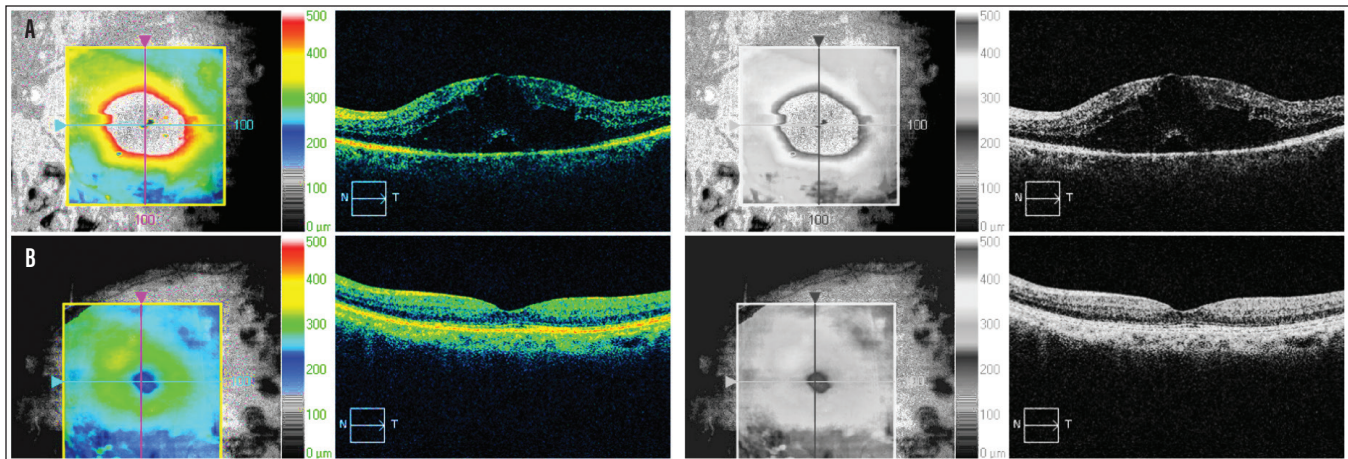
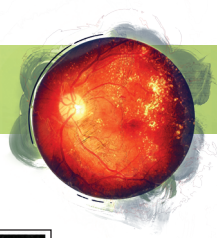


Figure 2. OCT shows center-involved DME with severe VA reduction at baseline (A) and after a series of anti-VEGF intravitreal injections (B).

Center-Involved DME

In a recent issue of *JAMA*, DRCR Retina Network investigators reported on another randomized clinical trial designed to evaluate three treatments for patients with DME that involved the center of the macula but who had a VA of 20/25 or better.¹⁵ Participants were randomly and equally assigned to three forms of treatment: intravitreal injection of aflibercept 2 mg ($n = 226$), laser photocoagulation ($n = 240$), or observation ($n = 236$). Patients were followed for up to 2 years. Those who were randomly assigned to aflibercept received injections every 4 weeks as needed, depending on VA and OCT-measured retinal thickness. Participants in the laser group received treatment every 13 weeks, and patients in the observation group initially received no therapy. If VA decreased by 1 eye chart line at two consecutive visits or by 2 lines at one visit, aflibercept injections were initiated in the laser and observation groups.

The study thus evaluated a strategy of immediate anti-VEGF therapy versus waiting for a threshold of decreased VA before starting anti-VEGF therapy. No statistically significant differences were seen among the three treatment groups in the primary outcome (the proportion of subjects who experienced a decrease in VA of ≥ 5 letters from baseline).

The latest data from this study demonstrate no difference in the risk of vision loss at 24 months with the three treatment strategies and showed no harm to patients' visual function from waiting to initiate anti-VEGF therapy until clinically meaningful changes in VA were noted on follow-up.¹⁵

Proliferative Disease

Although panretinal photocoagulation (PRP) remains the mainstay of treatment for proliferative disease, a move toward pharmacotherapy with anti-VEGF injections for proliferative diabetic retinopathy (PDR) has begun. PRP comes at a price: Side effects can include a loss of peripheral vision, difficulty with night vision, and the development of DME.

The DRCR Retina Network performed a multicenter, randomized clinical trial comparing PRP with intravitreal ranibizumab 0.5 mg in patients who had high-risk PDR.¹⁶ The investigators concluded that ranibizumab may be a reasonable alternative to PRP through 2 years. A decreasing number of injections in year 2 suggested that some disease modulation occurs after 1 year of therapy with ranibizumab. Anti-VEGF therapy is gaining ground as an option for patients who are reliable in their follow-up and present with PDR, especially with concurrent DME.

STERIOD THERAPY FOR DME

Anti-VEGF therapy may be the most common first-line treatment for DME, but steroids appear to be making a comeback. In addition to inhibiting the activity of VEGF, corticosteroids suppress other inflammatory cytokines that are involved in the pathophysiology of DME.^{17,18} Corticosteroids restore patency to retinal vessels and decrease vascular leakage. They may also benefit patients who do not respond to or who only partially respond to anti-VEGF treatment. The downsides to steroid therapy are that it can cause cataracts to develop and can raise IOP.

Sustained-release formulations are the newest take on steroid therapy. The dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) is FDA approved for the treatment of DME, based on the efficacy and safety results reported in the MEAD trial.¹⁹ This biodegradable device releases medication for 4 to 6 months, reducing the injection burden typically associated with steroid therapy. Another available option is the fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera Sciences), which is also approved for the treatment of DME, based on the efficacy and safety results reported in the FAME trial.²⁰ There are some notable differences between the two

implants. For one, the fluocinolone implant, which is not biodegradable, is injected through a smaller needle than that used to implant the dexamethasone device. Additionally, a single injection of fluocinolone has a 3-year duration of effect, compared with the dexamethasone implant's 4-to-6-month effect. It is important to note that the fluocinolone implant may be used only in patients previously treated with a corticosteroid who did not experience elevated IOP.

A CHANGE FOR THE GOOD

Not long ago, the only treatment option and management tool physicians could offer to patients with DME and PDR was laser therapy and low vision rehabilitation. The emergence of safe and effective pharmacologic treatments that improve both visual outcomes and quality of life means the future is brighter than ever before for patients with diabetic eye disease. ■

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