Treatment of Diabetic Retinopathy: A Review of Recent Research

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To understand the many treatments currently or soon-to-be available for diabetic retinopathy, clinicians must be familiar with the research.

Now is a very exciting time in the treatment of diabetic retinopathy. Not only is the number of diabetic patients growing steadily, but the management of diabetic retinopathy is changing in response to information gained from new diagnostic devices and clinical trials. As a result, all clinicians—retina specialists and generalists alike—would do well to keep abreast of the latest trends in the evaluation and treatment of this challenging condition.

Background

A landmark study, the Early Treatment Diabetic Retinopathy Study (ETDRS) gave us the definition of clinically significant macular edema and cemented focal and grid photocoagulation as the gold standard for the treatment of diabetic macular edema (DME) (Figure 1).[1] Similarly, the Diabetic Retinopathy Study showed that pan-retinal photocoagulation (PRP) for the treatment of proliferative diabetic retinopathy (PDR) should be initiated as soon as high risk characteristics become apparent.[2]

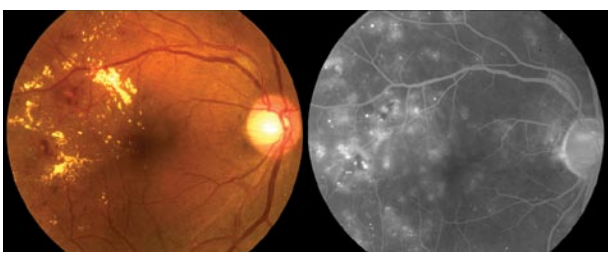

FIGURE 1 Color photo and fluorescein angiogram showing CSME and diffuse leakage in diabetic retinopathy.

While these early studies provided the foundation for today's research, much has changed since their results became available in 1985. It has, for example, become increasingly apparent that diabetic retinopathy results from a complex combination of factors, and treatment requires careful attention to disease progression and response to therapy.

Also, whereas laser was our primary mode of treatment for many years, we now have a growing body of knowledge that can help us decide how best to apply and combine new treatment options that have recently become available, such as intravitreal steroids and anti-VEGF medications.

Intravitreal Steroids

There has been a great deal of interest in the use of intravitreal steroids for the treatment of DME. As a result, numerous studies have compared intravitreal triamcinolone (Kenalog®; Bristol-Meyers Squibb) with macular laser.

One such study, conducted by the Diabetic Retinopathy Clinical Research Network, investigated the use of 1 mg and 4 mg intravitreal doses of triamcinolone in comparison with standard focal laser photocoagulation alone.[3] This large, multicenter effort showed that improvement of best corrected visual acuity (BCVA) was superior at 4 months in the 4 mg triamcinolone group, but that this difference disappeared and changed in favor of the laser group at 2 years.

On the safety side of the equation, studies have also shown that higher doses of intravitreal triamcinolone can be associated with glaucoma in nearly one-third of treated patients.[4] Laser is therefore preferred in part because it allows clinicians to avoid the adverse effects associated with intravitreal steroids.

As an alternative to steroid treatment, researchers are also investigating the use of anti-VEGF medications, including pegaptanib (Macugen®; Eyetech Inc.), ranibizumab (Lucentis®; Genentech), and bevacizumab (Avastin®; Genentech).

STUDIES EVALUATING DIABETIC RETINOPATHY TREATMENTS

- ☑ ETDRS
  - — Published 1985
  - — Defined clinically significant macular edema
  - — Focal and grid photocoagulation became gold standard treatment
- ☑ DRS
  - — PDR treated with PRP when high risk characteristics become apparent
- ☑ Diabetic Retinopathy Clinical Research Network Study
  - — Compared 1 mg triamcinolone, 4 mg triamcinolone, and laser
  - — At 2 years, BCVA was best in the laser-treated group
  - — Also found that IOP elevation occurred more often in steroid-treated groups
- ☑ Cunningham et al study
  - — Found that pegaptanib superior to sham injections for treatment of DME
  - — Efficacy of pegaptanib supported by additional studies
- ☑ RISE and RIDE trials
  - — Designed to compare ranibizumab with focal/grid laser therapy for treatment of DME
  - — Results not yet available

Pegaptanib

A pegylated aptamer with selective anti-VEGF inhibition, pegaptanib has been compared to sham injections for the treatment of DME in a phase II randomized double-blind trial.[5] Results of this study indicated that pegaptanib is superior to sham injections, with patients in the pegaptanib group needing fewer laser treatments and demonstrating improved vision and a decrease in retinal thickness. However, benefits seen at 36 weeks decreased once injections were withheld and disappeared by 54 weeks. Patients in the treatment group also did better if they received the lower drug dosage (0.3 mg), suggesting there may be a dose-dependent balance between VEGF suppression and progression of ischemia. A 3-year phase III clinical trial is currently underway in Europe to further evaluate the use of pegaptanib for DME, using doses that are 10 and 100 times less than the lowest dose used in the phase II trial.[6]

The effect of pegaptanib on DME with vascular ischemia was also examined in an FDA/IRB-approved prospective study that enrolled 30 patients with CSME and vascular ischemia, defined as capillary non-perfusion on fluorescein angiography (FA). Patients received four intravitreal injections of pegaptanib (0.3 mg)—once every 6 weeks—and were followed by optical coherence tomography (OCT), FA, and microperimetry (MP-1; Nidek). Results showed a normalization of OCT central thickness measurements compared with controls, as well as improvement in retinal sensitivity as demonstrated by MP-1 (Figures 2 and 3). Areas of improvement seen on MP-1 also seemed to correlate with re-perfusion in zones of previously nonviable ischemic retina.[7]

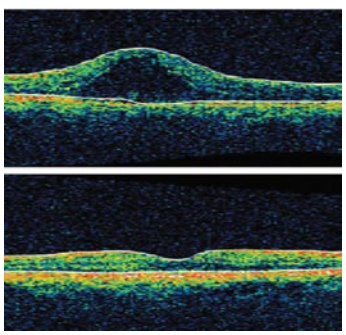

FIGURE 2 OCT showing resolution of CSME following pegaptanib injections.

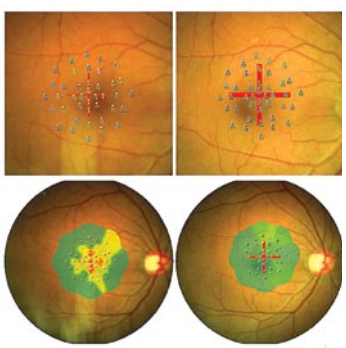

FIGURE 3 Microperimetry showing improved sensitivity following pegaptanib injections to treat CSME.

In addition, a separate FDA/IRB-approved prospective study was also performed to look at the use of sub-threshold selective PRP in combination with pegaptanib for the treatment of proliferative diabetic retinopathy. Twenty-eight patients with proliferative retinopathy were initially treated with intravitreal pegaptanib (0.3 mg), followed 1 week later by selective PRP using the PASCAL® laser (OptiMedica®). Laser treatments were titrated so that fluence (total energy) was reduced to a clinically sub-visible level, and laser treatments were applied selectively along the watershed area of peripheral ischemia. Patients were followed using the Optos® ultra wide-angle FA camera, which demonstrated regression of neovascularization and resolution of macular edema (Figure 4).[8]

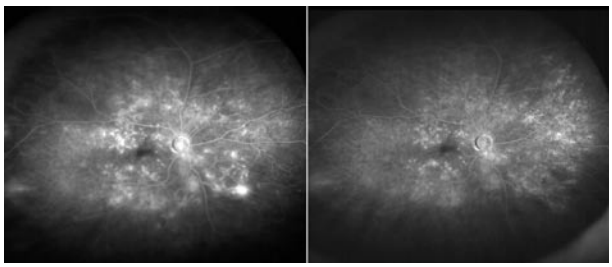

FIGURE 4 Fluorescein angiogram showing resolution of PDR and CSME following a single pegaptanib injection and selective pan-retinal photocoagulation.

Ranibizumab

Ranibizumab, one of two intraocular anti-VEGF medications with pan-VEGF antagonistic activity, is also being studied in a multicenter phase III double-masked, randomized, sham-injection controlled trial. This study, the RISE trial sponsored by Genentech, has been designed to assess the effect of ranibizumab on CSME with central macular involvement. Specifically, it is comparing changes in vision and OCT measurements over a 3-year period in patients given monthly intravitreal injections of ranibizumab versus patients treated with a standard focal laser.

While results of this study are still pending, experience to date seems to indicate that monthly injections of ranibizumab are very effective at reducing macular edema and improving vision. However, as is similarly the case with macular degeneration, monthly treatments seem to be required in order to maintain improvement.

Bevacizumab

Finally, many clinicians are curious about the potential benefit of bevacizumab for the treatment of diabetic retinopathy. Currently, there is no FDA-approved Phase I, II, or III data available regarding the intravitreal use of bevacizumab, but this drug has been used extensively off-label for the treatment of wet age-related macular degeneration and diabetic retinopathy. Numerous studies have also looked at the use of bevacizumab for the treatment of DME and PDR. One such study found that bevacizumab is able to cause regression of neovascularization, but that this effect was short-lived and did not prevent recurrence.[9]

Another study recently compared three different treatments: intravitreal bevacizumab alone, bevacizumab plus low dose intravitreal triamcinolone, and standard

macular laser alone. While this study demonstrated that a single intravitreal injection of bevacizumab can improve vision for up to 24 weeks, the resulting decrease in macular edema was transient and depended on the degree of edema present at baseline.[10]

Improvements in Monitoring

While preventing moderate vision loss may have been a reasonable treatment goal at the time of the ETDRS, clinicians now hope to do better. In part, this desire to improve treatment stems from the availability of new diagnostic imaging devices that allow us to better assess disease severity. For example, widefield fluorescein angiogram images—such as those obtained using the Optos device—allow us to visualize areas of peripheral ischemia that were beyond our reach in the past. By showing us how a patient's disease is progressing, this technology allows us to treat areas of ischemia more selectively during periods of uncontrolled hyperglycemia.

For those utilizing the Heidelberg FA Spectralis® HRA, the Staurenghi contact lens allows for the capture of 150-degree images during FA. Similarly, the MP-1 allows clinicians to assess macular function in a way that can be correlated directly with changes in macular thickness and visual acuity.

Treatment Advances

There has been considerable interest in the use of intravitreal steroids for DME because of their cost and often dramatic effect. While these drugs can yield short-term benefit, the duration of effect and improvement in vision do not seem to surpass results obtained with standard focal laser. In addition, repeated use of intravitreal steroids may put patients at considerable risk for developing intractable glaucoma. Ongoing studies looking at the use of lower doses of intravitreal steroids in DME will hopefully offer additional insight into their potential role in combination therapy.

Intravitreal anti-VEGF medications also offer an additional treatment option for diabetic retinopathy. Studies have demonstrated the efficacy of these drugs for treating DME and PDR, but these benefits need to be weighed against their possible short duration of effect, potential systemic effects, and possible exacerbation of intraocular ischemia. Currently, many clinicians are using bevacizumab to treat diabetic retinopathy because of the cost difference compared with ranibizumab. Since anti-VEGF medications are not yet universally covered by insurance for this indication, affordability is still a concern. Results from ongoing studies and health care reform will likely affect the use and availabilty of these medications in the future.

Finally, new diagnostic modalities are enormously helpful for detecting early proliferative disease and tracking response to therapy, and an array of new treatments is allowing for a more customized and flexible approach to treating this disease. Clinicians can therefore improve patient outcomes by tailoring treatment options based on the severity of disease, keeping in mind that hemoglobin Alc measurements do not always correlate with aggressiveness of disease and that the degree of capillary nonperfusion is a powerful indicator of future progression. Also, it is important to remember that macular laser remains a proven method for treating CSME, with studies showing that sub-threshold laser application can be just as effective as, but less damaging than, the energy levels used in the ETDRS.

THE BOTTOM LINE

To appropriately treat diabetic retinopathy, clinicians need to be aware of the various options available and how they compare with each other. Several studies have been conducted to compare laser treatments, steroids, and anti-VEGF medications, and additional trials are ongoing. By combining knowledge of this research with the new diagnostic tools now available, clinicians can create a custom treatment plan that has a much better chance of halting disease progression and improving vision.

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