Anti-VEGF Therapy for Diabetic Macular Edema: An Update

Ranibizumab as an adjunct to laser photocoagulation for DME will be evaluated in a phase 3 clinical trial.

BY PASCALE G. MASSIN, MD, PHD

In the past decade, the introduction of drugs that inhibit the action of vascular endothelial growth factor (VEGF) has had a significant impact on the field of ophthalmology. Groundbreaking research in the 1990s identified the key roles VEGF plays in pathologic angiogenesis as well as in normal vessel development.[1,2] Subsequently, it was recognized that levels of VEGF are elevated in many ocular neovascular diseases, including age-related macular degeneration (AMD), diabetic retinopathy (DR), diabetic macular edema (DME), central retinal vein occlusion, and iris neovascularization.[3-7]

Aiello and colleagues[3] found that levels of VEGF were elevated in a number of ocular neovascular diseases, including DR and retinal vein occlusion. In ocular fluid samples taken from patients undergoing surgery, they detected VEGF in 69 of 136 patients with DR, compared with two of 31 patients with no neovascular disorder. VEGF concentration was higher in patients with proliferative DR than in patients with nonproliferative DR or nondiabetic patients.

Diabetic retinopathy is the most common microvascular complication of diabetes, affecting approximately half of patients with diabetes.[8] DME, which is brought on by vascular permeability, is the principal cause of central vision loss in patients with DR. In patients who have been diagnosed with diabetes for 15 years, the prevalence of DME is 20% in those with type 1 diabetes, 25% in those with insulin-dependent type 2 diabetes, and 15% in those with type 2 diabetes not taking insulin.[9,10]

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Current treatment options for DME are suboptimal. Laser photocoagulation, the current reference standard treatment, reduces but does not eliminate the risk of vision loss from DR. In addition, laser does not reverse existing vision loss.

While laser photocoagulation is effective in halting the progression of focal DME, it is less effective in patients with diffuse DME, a generalized breakdown of the blood-retinal barrier. Randomized studies have shown that laser photocoagulation reduces visual loss due to DME, but despite laser treatment 15% of patients still lose vision.[11,12] For this reason, a number of alternative treatments for treatment of DME are under investigation, including the use of VEGF inhibitors.

RATIONALE FOR VEGF INHIBITION IN DME

The rationale for the use of a VEGF inhibitor in the treatment of DME is strong. Funatsu and colleagues[4] found elevated levels of VEGF in the aqueous humor in eyes of patients with DME. Qaum and colleagues[13] showed in mice that blood–retinal-barrier breakdown in experimental diabetes is VEGF dependent, creating an

imbalance in vascular permeability and a capillary permeability similar to that in AMD. They concluded that VEGF inhibition should be a useful approach to treatment of blood–retinal-barrier breakdown in diabetes.

A phase 1/2 study was conducted to investigate the efficacy of the VEGF-inhibiting drug ranibizumab (Lucentis, Genentech) in the treatment of DME. The RESOLVE (A Randomized, Double-Masked, Multicenter, Phase 2 Study Assessing the Safety and Efficacy of Two Concentrations of Ranibizumab [Intravitreal Injections] Compared With Non-Treatment Control for the Treatment of Diabetic Macular Edema With Center Involvement) study, was sponsored by Novartis and conducted at centers in Europe.

The study evaluated the effect of ranibizumab on retinal edema and visual acuity in 151 patients with DME with center involvement. Patients with central macular thickness of 300 µm or greater were randomly assigned to receive sham injection or one of two doses of ranibizumab — 0.3 mg or 0.5 mg — in three monthly intravitreal injections followed by treatment as required for 9 months. The primary endpoint in the 1-year study was visual function at 6 months. The study design allowed escape to photocoagulation if necessary, and also allowed the investigator to double the dose (from 0.3 mg to 0.6 mg or from 0.5 mg to 1.0 mg, depending on which arm the patient was in) after 1 month if resolution of edema was incomplete.

The RESOLVE trial is now concluded, and final data should be available soon. In an interim analysis of 6-month data in 42 patients,[14] an improvement in visual acuity and a decrease in central macular thickness was observed in patients treated with ranibizumab.

Mean central macular thickness increased in 17 patients receiving sham injection and decreased in 25 patients receiving either dose of ranibizumab. In accord with the study design and treatment criteria, the dose was doubled in 12 of the 14 patients receiving 0.3 mg and in four of the 11 patients receiving 0.5 mg.

Visual acuity decreased at 6 months in the patients receiving sham injections and increased in both treatment groups.

While these preliminary results were promising, few patients in this interim analysis experienced complete resolution of DME. With this in mind, a phase 3 trial of ranibizumab for DME, which recently began enrolling patients, has been designed to include a laser photocoagulation group and further explore the effect of ranibizumab on visual function and macular thickness.

PHASE 3 TRIAL DESIGN

The phase 3 trial, called RESTORE (A Randomized, Double-Masked, Multicenter, Laser-Controlled Phase 3 Study Assessing the Efficacy and Safety of Ranibizumab [Intravitreal Injections] as Adjunctive and Mono-Therapy in Patients With Visual Impairment Due to Diabetic Macular Edema),[15] will enroll 315 patients with either type 1 or type 2 diabetes.

This multicenter international trial, sponsored by Novartis, is designed to confirm the efficacy and safety of ranibizumab 0.5 mg as adjunctive therapy added to laser photocoagulation and/or as monotherapy in patients with visual impairment due to DME.

Patients in the RESTORE trial will be randomly assigned to one of three arms: laser photocoagulation plus ranibizumab 0.5 mg, laser plus sham injection, and sham laser plus ranibizumab injection. They will receive monthly treatments for 12 months.

Notably, the primary endpoint of the RESTORE trial is symptomatic or functional rather than anatomic change. The primary endpoint will be mean change in best corrected visual acuity from baseline over 12 months. Secondary endpoints will include central retinal thickness, patient-reported outcomes and other measures.

Treatment begins with a loading phase, with three consecutive monthly injections of ranibizumab or sham. This is followed by a maintenance phase, in which monthly injections continue unless stable vision is reached. Stable vision is defined as either (1) no further improvement in BCVA is attributed to treatment with intravitreal injection at the last two consecutive visits in the opinion of the investigator, or (2) BCVA of greater than 84 letters (the approximate equivalent of Snellen 20/20) is observed at the two last consecutive visits. If BCVA decreases due to DME progression in the investigator's opinion, treatment is reinitiated with more than two monthly injections until stable vision is reached again.

CONCLUSIONS

A strong rationale exists for the further study of ranibizumab as a treatment for DME. The aim of treatment of ocular neovascular diseases with ranibizumab is to reduce hyperpermeability of retinal vessels and inhibit neovascularization. Preliminary results from early exploratory clinical trials are encouraging and will clarify the future role of ranibizumab therapy across the spectrum of retinal vascular diseases.[16,17]

Treatment of DME with ranibizumab has shown promising results in investigator-initiated phase 1 and 2 clinical trials in the United States.[18] In the READ (Ranibizumab for Edema of the Macula in Diabetes) phase 2 study, the vision of ranibizumab-treated patients improved to a mean 20/63 at 6 months, while acuity remained essentially unchanged at 20/80 in both laser and combination treatment groups.

The study design for the RESTORE trial, using

ranibizumab as an adjunct to laser photocoagulation in the treatment of DME, is a rational concept worthy of evaluation. Laser photocoagulation remains the gold standard of treatment for DME. In our participation in phase 2 RESOLVE study, many patients treated with ranibizumab experienced improvement in edema, but few experienced complete resolution. With ranibizumab as an adjuvant to laser photocoagulation, the chance of resolving edema and improving visual acuity promises to be much greater. ■

Pascale G. Massin, MD, PhD, is in the Department of Ophthalmology of the Hôpital Lariboisière, Paris, France. Dr. Massin states that she is a paid consultant for Novartis and principal investigator in the RESOLVE and RESTORE studies. She may be reached at +33 1 49 95 64 88; fax: +33 1 49 95 64 83; or e-mail: p.massin@lrb.aphp.fr.

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