

The Role of VEGF in Macular Edema for Patients With RVO

Ranibizumab provides substantial short-term benefit.

BY PETER A. CAMPOCHIARO, MD

The compromise in venous outflow in patients with central retinal vein occlusion (CRVO) results in massive transudation of blood into the retina and a marked increase in interstitial pressure, which compromises perfusion and leads to retinal ischemia. The same phenomenon occurs in patients with branch vein occlusion (BRVO), but to a lesser extent, because generally only 25 to 50% of the retina is affected. Thus, in both CRVO and BRVO retinal ischemia occurs and serves as an exacerbating factor to changes that occur because of altered hemodynamics. The major source of visual loss in patients with CRVO and BRVO is macular edema, and it is not clear how much of the edema is due to hemodynamic changes from the obstruction and how much is due to chemical mediators. Ischemic retina releases vascular endothelial growth factor (VEGF), which underlies neovascular complications, but also causes excessive vascular permeability.^{1,2} The development of ranibizumab (Lucentis, Genentech), a Fab fragment that binds and neutralizes all isoforms of VEGF-A,³ has provided a means to explore the contribution of VEGF to macular edema in patients with retinal vein occlusion (RVO).

VEGF FOR BRVO, CRVO

My colleagues and I recently published the results of a study in which patients with macular edema due to CRVO (n=20) or BRVO (n=20) were randomized to receive 3 monthly injections of 0.3 or 0.5 mg of ranibizumab.⁴ At the primary endpoint, month 3, the median improvement in letters read at 4 meters was 17 in the 0.3 mg group and 14 in the 0.5 mg group for CRVO, and 10 and 18, respectively, for the BRVO group.

Compared to injections of 0.3 mg, injections of 0.5 mg of ranibizumab tended to cause more rapid reductions of central retinal thickening as measured by optical coherence tomography (OCT), which lasted longer in between injections. But by 3 months, excess central retinal thickening which is a quantitative assessment of the macular edema, was reduced by roughly 90% in all four treatment groups. There were no drug-related adverse effects, including no elevation of blood pressure, thromboembolic events, or other systemic problems.

SMALL STUDY, CONSISTENT RESULTS

Although this is an uncontrolled, open-label trial involving a relatively small number of patients, the results were consistent among patients and suggest that intraocular injections of ranibizumab have a substantial effect on macular edema due to CRVO or BRVO. In both patient populations, the results were good with either 0.3 or 0.5 mg of ranibizumab, and no clear differences could be discerned between the doses except that more patients seemed to have rapid improvements in center subfield thickness and more had improvements that lasted for a month after the initial injection in the 0.5 mg groups compared to the 0.3 mg groups. Improvements from baseline in visual acuity were large in both dose groups for patients with macular edema due to CRVO or BRVO. These data indicate that VEGF is a major contributor to macular edema in patients with retinal vein occlusions.

The Central Retinal Vein Occlusion Study was a large multicenter trial that investigated the effect of grid laser photocoagulation in patients with macular edema due to CRVO.⁵ Although 69% of patients in the treated group

compared to 0% in the untreated group showed reduction of fluorescein leakage in the macula at 1 year, there was no difference in final visual acuity (20/200 in treated patients vs 20/160 in untreated patients). It has been proposed that a possible explanation is that chronic edema due to CRVO leads to permanent visual loss. We found that with injections of ranibizumab, visual improvement is possible in some patients who have had edema for more than 1 year and in some cases several years. In fact, there was no inverse correlation between duration of edema at baseline and improvement in VA after 3 injections of ranibizumab, suggesting that patients with chronic edema should not be excluded from treatment based solely upon duration of edema. Thus, chronicity of edema and the relatively slow resolution of edema after grid laser therapy are not likely to explain the poor visual results after grid laser therapy.

Measurement of VEGF levels in aqueous samples collected at baseline demonstrated that patients with CRVO have significantly higher levels of VEGF in the eye than patients with BRVO. For the entire 40 patients and for the CRVO subgroup, there was a negative correlation between aqueous VEGF level at baseline and amount of improvement in visual acuity 3 months after initiation of ranibizumab therapy. Further work is needed to determine the predictive value of baseline aqueous levels of VEGF and to determine the range of VEGF levels that occur in other disease processes such as neovascular age-related macular degeneration and diabetic macular edema.

SUMMARY

The results of our study are encouraging with regard to the potential usefulness of ranibizumab in patients with RVO because of the magnitude and consistency of response among patients and the rarity of spontaneous improvements in patients with macular edema due to CRVO;⁵ however, they are not definitive because of the relatively small number of patients studied, the lack of a control group, and the short follow-up. A major unanswered question is the duration of treatment that will be needed. Three injections was not sufficient in most patients to achieve long-term benefit, and it is important to determine if and when injections can be terminated without recurrent edema. The CRUISE and BRAVO phase 3 trials investigating the effects of ranibizumab in patients with macular edema due to CRVO or BRVO are under way and should provide a definitive answer as to the usefulness of intraocular ranibizumab in these conditions. ■

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1 Ozak H, Hayashi H, Vinorez SA, Moromizato Y, Campochiaro PA, Oshima K. Intravitreal sustained release of VEGF causes retinal neovascularization in rabbits and breakdown of the blood-retinal barrier in rabbits and primates. *Exp Eye Res.* 1997;64(4):505–517.

2 Derevjaniuk NL, Vinorez SA, Xiao, et al. Quantitative assessment of the integrity of the blood-retinal barrier in mice. *Invest Ophthalmol Vis Sci.* 2002;43:2462–2467.

3 Ferrara N, Damico L, Shams N, Lowman H and Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. *Retina.* 2006;26:859–870.

4 Campochiaro PA, Hafiz G, Shah SM, et al. Ranibizumab for macular edema due to retinal vein occlusions; implication of VEGF as a critical stimulator. *Molec Ther.* 2008;16:791–799.

5 The Central Retinal Vein Occlusion Study Group. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. The central vein occlusion study group M report. *Ophthalmology.* 1995;102:1425–1433.

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