

Intravitreal Ranibizumab for Treatment of Macular Edema Secondary to Retinal Vein Occlusion

The BRAVO and CRUISE trials are designed to evaluate the efficacy of the drug in branch and central retinal vein occlusions, respectively.

BY DANTE J. PIERAMICI, MD

Retinal vein occlusion (RVO) is a common retinal vascular disease that can lead to significant visual loss and blindness. The 15-year cumulative incidences of branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) are 1.8% and 0.5%, respectively, thus representing a serious public health problem. The main risk factors for RVO include age, hypertension, arteriosclerosis, diabetes, and hypercholesterolemia. Visual loss associated with RVO can be a result of macular edema, macular ischemia, and other complications associated with anterior and posterior segment neovascularization. The main strategy to reduce visual loss in these patients has been the treatment of macular edema.¹

The pathophysiology of some RVOs appears to begin with the compression of the vein by the adjacent retinal artery. Systemic disease processes, such as hypertension and atherosclerosis, create hypertrophy of the arterial muscular wall, producing additional compression. This compression further narrows the retinal veins, leading to blood-flow turbulence and thrombus formation. With the thrombus formation, there is an increase in retinal venous pressure and stagnation of blood flow through the proximal capillary bed. The tissue in the distribution of these capillaries becomes ischemic, with resulting upregulation of vascular endothelial growth factor (VEGF). The release of VEGF in turn leads to increased capillary permeability, with vascular

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leakage and retinal edema, and in some cases eventual retinal and anterior segment neovascularization.²⁻⁴

Current treatment options for the complications associated with RVO are numerous, although the efficacy and long-term safety of most have not been demonstrated in randomized clinical trials. Macular edema has traditionally been managed with laser photocoagulation. However, laser photocoagulation results in little or no improvement in visual acuity in patients with CRVO and modest improvement relative to observation in BRVO.^{5,6} Other modalities currently under investigation for treatment include vitrectomy with or without sheathotomy, optic nerve decompression, creation of laser or surgical anastomoses, antiaggregative and thrombolytic therapies, isovolemic hemodilution, intravitreal and periocular steroid injection, and, recently, treatment with anti-vascular endothelial growth factor (VEGF) agents.⁷

There is a rationale for the use of VEGF inhibitors in RVO to reduce macular edema, an important cause of visual loss in patients with vein occlusions. Ranibizumab (Lucentis, Genentech), a humanized antibody fragment that inhibits

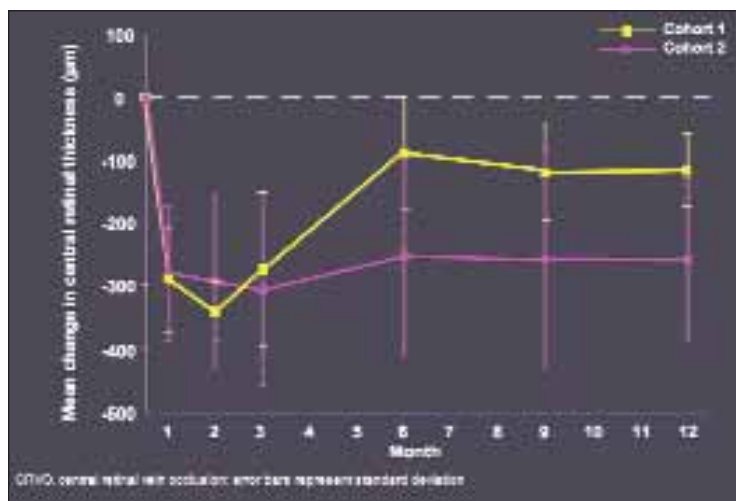


Figure 1. A rapid reduction in macular edema was seen during the induction phase in all patients, followed by some regression of the reduction during the quarterly as-needed injection period in cohort 1, but relative stabilization in cohort 2.

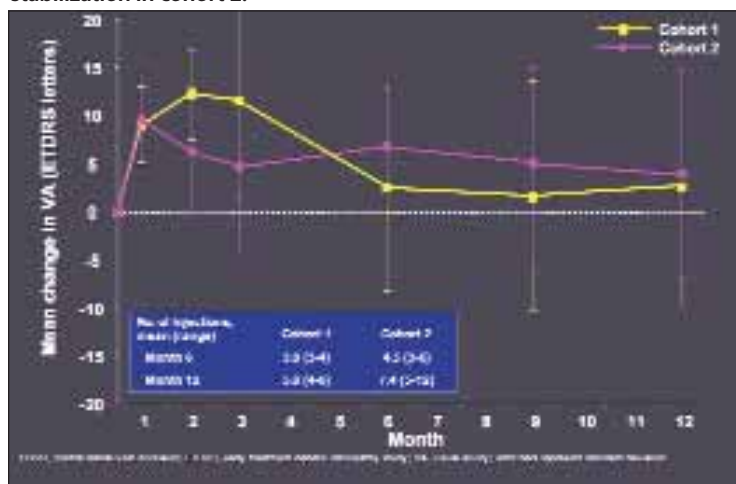


Figure 2. Visual acuity results show rapid improvement during induction, but return toward baseline during the as-needed dosing intervals in most patients.

VEGF, has been shown in randomized prospective clinical trials to be an effective treatment for choroidal neovascularization secondary to age-related macular degeneration.^{8,9} In the treatment of these patients, the main pathophysiologic benefit appears to be the reduction of vascular leakage and the elimination of retinal and subretinal fluid. Ranibizumab has also been investigated in other eye diseases in which macular edema plays a role, including diabetic macular edema.^{10,11} The off-label use of anti-VEGF agents in patients with RVO has been impressive in some cases, although it is well recognized that the natural history is variable in patients with RVO. Controlled clinical trials are needed to determine and quantify the safety and benefit of treating macular edema with anti-VEGF therapy vs current standard

therapies or observation.

A number of pilot trials and two larger multicenter trials are currently evaluating whether inhibition of VEGF by ranibizumab may be an effective treatment for macular edema associated with RVO.

PRELIMINARY EVIDENCE

A phase 1, prospective, open-label study at our center is evaluating the safety, biological effect, and changes in best corrected visual acuity (BCVA) associated with intravitreal ranibizumab in patients with significant macular edema associated with perfused CRVO. We recently reported interim results of this 2-year study.^{12,13}

The study included 20 patients randomly assigned to one of two treatment strategies. In cohort 1 (n=10), patients received three monthly injections of either 0.3 or 0.5 mg ranibizumab in an induction phase, followed by pro re nata (PRN) injections of the same doses on a quarterly basis. In cohort 2 (n=10), patients again received three monthly doses of either 0.3 or 0.5 mg ranibizumab in an induction phase; they then received a monthly PRN dosing.

There were no severe ocular or nonocular adverse events in the study. There was evidence of biologic activity at the 0.3- and 0.5-mg doses, although there were no differences in efficacy between the two doses. Macular edema was responsive to the injections, with a mean decrease in central retinal thickness shown on optical coherence tomography (OCT). Mean visual acuity also improved, although this was more variable.

Figure 1 shows anatomic results from the study, with a rapid reduction in macular edema during the induction phase in all patients, fol-

lowed by some loss of the reduction during the quarterly PRN injection period in cohort 1, but relative stabilization in cohort 2. Figure 2 shows visual acuity results, with rapid improvement during the induction phase but a return toward baseline during the PRN dosing intervals in most patients.

Results of this small, uncontrolled trial suggest that ranibizumab injection in patients with macular edema associated with perfused CRVO is generally well tolerated and may improve BCVA and central retinal thickness. Follow-up in this 2-year pilot study is ongoing.

MULTICENTER STUDIES

Two phase 3 multicenter, prospective clinical trials are currently underway, assessing the safety, tolerability, and efficacy

of intravitreal ranibizumab injections in the treatment of macular edema secondary to BRVO and CRVO. Called, respectively, BRAVO (A phase 3, multicenter, randomized, sham injection-controlled study of the efficacy and safety of ranibizumab injection compared with sham in patients with macular edema secondary to BRVO) and CRUISE (A phase 3, multicenter, randomized, sham injection-controlled study of the efficacy and safety of ranibizumab injection compared with sham in patients with macular edema secondary to CRVO), these Genentech-sponsored trials were designed in conjunction with the US Food and Drug Administration (FDA), potentially to allow approval of the drug for treatment of RVO.

Enrollment in the two trials is complete, and follow-up is ongoing. The BRAVO trial includes patients with BRVO or hemiretinal vein occlusion, the CRUISE trial patients with CRVO. The primary objectives of each trial are to evaluate the efficacy of intravitreal ranibizumab in improving BCVA in macular edema secondary to the respective RVO, as well as the safety and tolerability of the ranibizumab injections. Secondary endpoints include evaluating the efficacy of the treatment in improving other visual acuity measures, anatomic outcomes, and patient-reported measures of visual function.

The study includes patients at least 18 years of age with macular edema secondary to RVO. After screening by a reading center to determine eligibility, patients are randomized 1:1:1 to either sham injection, ranibizumab 0.3 mg, or ranibizumab 0.5 mg. They receive monthly injections for 6 months. In BRAVO, patients are eligible for rescue laser therapy if criteria are met at months 3, 4, and 5. During the second 6-month period, patients are evaluated monthly and treated on a PRN basis. Patients in the sham injection group receive 0.5 mg ranibizumab for the second 6 months. Again, rescue laser therapy is available in BRAVO at months 9, 10, and 11 if criteria are met.

To be included in the study, patients must have evidence of center-involved macular edema secondary to RVO, defined as central subfield thickness of 250 μ m or greater on OCT. Visual acuity must be between 20/40 and 20/400 for BRAVO and between 20/40 and 20/320 for CRUISE. Sufficient media clarity, pupillary dilation, and patient cooperation to obtain adequate fundus photographs are also required, as well as the patient's signed informed consent.

Patients are excluded from these trials if they have evidence of a prior RVO in the study eye, a history of previous laser photocoagulation for macular edema in the study eye within 4 months prior to enrollment, or a brisk afferent pupillary defect. They may have received previous intravitreal injection of corticosteroids or anti-VEGF agents, but not within the 3 months prior to study enrollment.

The primary endpoint of the study is mean change in BCVA score from baseline at 6 months. Secondary endpoints include visual and anatomic (OCT) outcomes at 6

and 12 months. Mean changes over time in visual acuity, central foveal thickness, and scores for near and distance activities on the NEI-VFQ25 will also be assessed.

Safety endpoints will include incidence and severity of ocular and nonocular adverse events, incidence of serum antibodies to ranibizumab, changes in laboratory parameters over time, and changes in vital signs. Serum ranibizumab concentrations at 6 and 12 months will be a pharmacokinetic endpoint.

CONCLUSIONS

There is an unmet need in the treatment of macular edema in patients with venous occlusive disease. VEGF has been implicated as a critical component in the pathophysiology of RVO, and it is reasonable to assume that blocking VEGF may be helpful in these patients. The VEGF inhibitor ranibizumab has been shown to be effective in reducing macular edema in other types of retinal diseases, and its ability to alter vascular permeability may reduce macular edema in RVO.

The ongoing BRAVO and CRUISE phase 3 trials are currently evaluating the safety and efficacy of ranibizumab in patients with macular edema secondary to BRVO and CRVO, respectively. Enrollment is complete, and data from the 6-month primary endpoint should be available in the second half of this year. ■

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