Retinal vein occlusion (RVO) is a significant cause of vision loss, second in prevalence only to diabetic retinopathy among vascular diseases of the retina. Most of the vision loss in RVO occurs as a result of macular edema. Vascular endothelial growth factor (VEGF) is known to play a role in macular edema secondary to RVO, and studies by our group at Wilmer Eye Institute and others have shown that intravitreal injection of the VEGF inhibitor ranibizumab (Lucentis, Genentech) can reduce macular edema and restore visual acuity in many patients with central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO).

Our investigation of anti-VEGF treatment for RVO began with a pilot trial in which 20 patients with CRVO and 20 with BRVO were treated with three monthly doses of either 0.3 or 0.5 mg intravitreal ranibizumab (Lucentis, Genentech). We found that the treatment was highly effective. At the 3-month primary endpoint, the median improvement in letters read at 4 m was 17 in the 0.3 mg group and 14 in the 0.5 mg group with CRVO, and 10 and 18 letters in those respective groups with BRVO.

That trial and a number of other pilot trials led to the design and initiation of the BRAVO and CRUISE studies, from which the primary 6-month endpoint results were published last year. Patients in our own pilot study have now reached 2-year follow-up, and we are able to draw some preliminary conclusions about long-term results of VEGF inhibition for treatment of BRVO and CRVO. This article reviews the results of these studies and offers some observations from our clinical experience regarding the management of patients with BRVO and CRVO.

BRVO

The BRAVO trial, a phase 3 multicenter clinical study, showed that patients receiving 6 monthly injections of 0.3 mg or 0.5 mg ranibizumab experienced a mean improvement of 16.6 and 18.3 letters, respectively, in visual acuity, compared with 7.3 letters improvement in those receiving sham injections. During the second 6 months of the study, all patients could receive 0.5 mg ranibizumab on an as-needed (PRN) basis if they met retreatment criteria; this included the patients who received sham injections in the first part of the study. At 1 year, visual acuity was well maintained in both ranibizumab treatment groups, and there was improvement of visual acuity in the sham group, although there was still statistically significantly less improvement in the sham group than the ranibizumab treatment groups.

The percentage of patients who gained three lines (15 letters) of visual acuity was 55.2% and 61.1% in the 0.3 mg and 0.5 mg ranibizumab groups, respectively, compared with 28.8% of patients receiving sham injection. That improvement was maintained during the PRN phase, and again the patients in the sham injection group also improved once they had access to ranibizumab treatment, although not to the same levels as the treatment groups.

There were rapid reductions in excess foveal thickness with ranibizumab treatment, and by 6 months there was a substantial mean difference from baseline. Interestingly, in the sham group, after one ranibizumab treatment in the second part of the study, excess foveal thickness was reduced almost to the same levels as the treatment groups, and it remained similar throughout the remainder of the PRN treatment period.

The results of the BRAVO study show, therefore, that ranibizumab is an effective treatment for macular edema secondary to RVO in the short term.

We recently compiled 2-year results from our original
Case 1: Patient with CRVO with severe edema at baseline (BL). Edema resolved after three injections of ranibizumab (R), and with only one additional injection of bevacizumab (B) the patient was free of edema with about five lines improvement in vision 2 years after starting treatment (Figures 1-3).

Case 2: Patient with CRVO who had severe persistent edema after three injections of ranibizumab (R) and has required frequent injections, including one bevacizumab (B) injection for more than 2 years to keep edema under control (Figures 4-6).

**Figure 1.** Color fundus photography and early, mid, and late fluorescein angiography at BL, month 3, and month 24.

**Figure 2.** OCT images at BL, day 7, and months 1 and 24.

**Figure 3.** Graph showing retinal thickness (left axis, yellow bars), visual acuity (right axis, triangles), and injections (R, B).

**Figure 4.** Color fundus photography and early, mid, and late fluorescein angiography at BL, month 3, and month 24.

**Figure 5.** OCT images at BL, day 7, and months 1 and 28.

**Figure 6.** Graph showing retinal thickness (left axis, yellow bars), visual acuity (right axis, triangles), and injections (R, B).
In 17 patients with BRVO who completed the study at 24 months, final visual acuity results (17.8 letters improvement from baseline) were similar to those at the primary endpoint of 3 months (16.1 letters improvement). During this follow-up phase, patients were seen every 2 months and treated only if they exhibited foveal thickness greater than 250 um. Even on this PRN regimen, with injections available only every other month, most patients maintained their improved visual acuity.

Foveal thickness measurements with optical coherence tomography (OCT) in our study reflected the visual acuity results. After 3 monthly injections, essentially all patients with BRVO had a rapid reduction in foveal thickness, and during the PRN phase most remained stable. Recurrence of macular edema was seen in a few patients.

During the second year, patients were eligible for a maximum of six injections of ranibizumab with recurrence of edema. The mean number of injections given was two. Patients seemed to fall into two categories: those whose edema resolved with a few injections and those who continued to need frequent injections.

CRVO
The CRUISE study mirrored the design of the BRAVO study. Patients with CRVO receiving six monthly injections of ranibizumab had substantial improvement in visual acuity: 12.7 letters with 0.3 mg and 14.9 letters with 0.5 mg ranibizumab injections, in comparison with 0.8 letters in sham-treated patients. Once those in the sham group were able to receive ranibizumab they also improved, but as in BRAVO they did not achieve the level of improvement seen in patients treated in the first 6 months of the study.

Similar results were seen regarding the percentage of patients who gained at least 3 lines of VA: 46.2% with 0.3 mg and 47.7% with 0.5 mg ranibizumab, compared with 16.9% of sham-treated patients.

For patients in the sham treatment group there was a contrast between visual acuity and foveal thickness results in the PRN portion of the study. After the first injection of ranibizumab at 6 months, foveal thickness measurements for patients in the sham group decreased to the level of the two treatment groups, and the curves are essentially superimposable over the entire PRN period. However, even though the macular edema resolved quickly after treatment was offered at 6 months, there seemed to be a visual penalty for delaying treatment. During the PRN phase, the visual acuity of patients in the sham treatment group did not reach the levels of patients in the ranibizumab treatment groups.
Currently, in my own practice, my bias is to start treatment early, as soon as an RVO is recognized, especially if the patient is symptomatic.

As in BRAVO, there were rapid reductions in excess foveal thickness in the ranibizumab groups with statistical significance by month 6 (P<.0001). After one injection of ranibizumab in the PRN phase of the study, the foveal thickness in the group who had been assigned to sham for the first 6 months was reduced to similar levels as the treatment groups and remained stable to month 12.

In the 2-year follow-up of patients with CRVO in our pilot trial, results for the 14 patients who completed the study were quite different from those of patients with BRVO. After the initial three monthly injections, these patients experienced a mean gain of 12 letters at 3 months, but by month 24 the mean gain had decreased to 8.5 letters. This compares with the 17.8 letter gain seen at month 24 in patients with BRVO.

OCT measurements again reflected the visual acuity results, with a mean increase in foveal thickness at month 24 compared with month 3.

As with the BRVO patients, the patients with CRVO were seen every 2 months and received an injection only if their foveal thickness exceeded 250 µm on OCT. These results indicate that this regimen did not maintain visual acuity as effectively in patients with CRVO as it did in those with BRVO.

The maximum possible number of injections in year 2 was six, and the mean number given was three.

Again, as with BRVO, there seemed to be two populations of CRVO patients: those who experienced early resolution of their edema and did not require any more injections and those who continued to require frequent injections.

PREDICTORS

The 2-year results of this pilot trial indicate that some patients with RVOs can achieve excellent visual acuity with the proper treatment, time, and effort. We looked for factors that could help predict which patients are likely to experience good outcomes after treatment for RVO.

The BRVO population in our pilot trial included eight patients with macular edema of more than 1 year duration at study entry and nine with macular edema for less than 1 year. Both these groups had substantial improvement in visual acuity, a mean of more than 3 lines of improvement. However, the final visual acuity at month 24 was significantly lower in patients with chronic edema. They showed improvement but did not achieve the same level of final visual acuity as patients with edema of shorter duration.

Chronic edema before the start of treatment, therefore, is a possible predictor of a suboptimal visual outcome.

Another factor that was predictive of worse final visual acuity in the patients with BRVO was closure of perifoveal capillaries. Patients who had 180° or 360° disruption of perifoveal capillaries, while they achieved substantial improvement in vision, had worse final visual acuity than those whose perifoveal capillaries were preserved.

The effect of these predictive factors was even more striking in CRVO. Patients with CRVO who had chronic edema showed little improvement in visual acuity during the course of the trial, and those who had complete disruption of perifoveal capillaries had worse final vision.

These preliminary observations about potential predictive factors were derived from a small number of patients and must be evaluated in larger studies.

PRACTICAL CONSIDERATIONS

Many questions remain about treatment of patients with RVO. How long do we need to treat? Can higher doses of ranibizumab provide greater benefit? What do we do with nonresponders? What is the benefit of steroids?

We are investigating some of these questions currently in a trial called RELATE. In this trial, patients with BRVO or CRVO are randomly assigned to receive six monthly injections of either 0.5 or 2.0 mg ranibizumab. At the end of that time period the patients are re-randomized to receive either PRN ranibizumab (the same dose as originally assigned) alone or PRN ranibizumab plus scatter photocoagulation to the periphery in areas of nonperfusion. The trial is designed to address two questions. First, will the higher dose of ranibizumab be more effective in patients who do not respond as well as we would wish to 0.5 mg, and will it allow a greater percentage of patients to avoid additional treatment after 6 months? And, second, in patients who continue to require injections after 6 months, will laser photocoagulation to peripheral areas of nonperfusion reduce the need for continued injections?

Regarding the value of intravitreal steroids for RVO, it will be worthwhile to determine whether steroid injections or implants can reduce the burden of treatment for patients with RVO who continue to require anti-VEGF injections for a long period of time.

Currently, in my own practice, my bias is to start treatment early, as soon as an RVO is recognized, especially if the patient is symptomatic. I generally give six monthly injections of ranibizumab and then follow patients monthly and give injections PRN. As noted above, some patients can become independent of injections after a short period of treatment, but many continue to require frequent injections for a long period of time. In general,
patients who are younger at onset tend to be in the group that resolves in a shorter period of time.

**FINAL THOUGHTS**

My general recommendation at the current time would be to initially treat a patient with BRVO with 6 monthly injections. If frequent injections are still needed to control edema, I would consider grid laser therapy. If frequent injections are still needed after laser, I would consider injection of triamcinolone or implantation of the dexamethasone intravitreal implant (Ozurdex, Allergan). For a patient with CRVO the regimen would be similar, except that instead of grid laser I would proceed immediately to triamcinolone injection or the dexamethasone intravitreal implant. If frequent injections were still needed, I would consider laser to areas of capillary nonperfusion, although the efficacy of this intervention has not been determined yet.

It appears that VEGF production can be a long-term problem in many patients with RVOs. A period of aggressive pharmacologic blockade of VEGF may be one key to reducing the need for repeated injections. It is to be hoped that, as we gain more long-term experience with the use of anti-VEGF agents and other interventions for the treatment of BRVO and CRVO, we can identify regimens that will reduce edema and restore good vision to our patients relatively quickly.

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