Clinical Implications of the BRAVO and CRUISE Trials

How should physicians apply this new information in their treatment of CRVO and BRVO?

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Retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy, affecting as many as 180,000 people in the United States.[1] Macular edema leads to vision loss in many patients with either central or branch retinal vein occlusions (CRVO or BRVO). BRVO is the more common of the two presentations, accounting for approximately 80% of RVO.

There has been no proven treatment for CRVO; the Central Vein Occlusion Study (CVOS) found no visual acuity benefit of grid laser photocoagulation over observation in patients with CRVO.[2] Argon laser treatment of BRVO resulted in improvement in vision in patients who met the criteria of the Branch Vein Occlusion Study (BVOS).[3] However, the disease is self-limiting in about one-third of BRVO cases, so historically patients were usually observed for several months after initial presentation.

Recently, there has been interest in the use of vascular endothelial growth factor (VEGF) inhibition in the treatment of RVO because of the observation of increased VEGF in the vitreous and aqueous of patients with these conditions.[4] Two randomized controlled trials assessed the efficacy and safety of intravitreal ranibizumab (Lucentis, Genentech) in BRVO and CRVO. The results, presented at the Retina Congress last year,[5,6] showed that with intensive, monthly treatment, patients achieve very good results, superior to anything we have seen previously with other treatment modalities.

In these two phase 3 clinical trials, patients with macular edema due to RVO given either of two doses of ranibizumab had, on average, clinically and statistically significant improvements in best corrected visual acuity (BCVA) compared with patients receiving sham injections.

What are the implications of these trials for clinicians and their patients with RVO? Naturally, as with the use of anti-VEGF agents for treatment of choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD), physicians may be reluctant to undertake the treatment burden of monthly injections in their patients with RVO, despite the evidence of significant visual improvement in these recent trials. This article reviews the results of the trials of anti-VEGF treatment for RVO and offers some insights into how these results can be implemented in retina practices.

BRAVO AND CRUISE RESULTS

The BRAVO trial (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) assessed the safety and efficacy of ranibizumab in patients with BRVO.[5] Patients included in the study had macular edema involving the foveal center secondary to BRVO, central subfield macular thickness of 250 µm or greater on optical coherence tomography, and BCVA of 20/40 to 20/400. Patients were randomly assigned to six monthly injections of ranibizumab, either 0.3 mg or 0.5 mg, or to sham injections. The primary efficacy outcome was mean change from baseline BCVA at 6 months. Secondary outcomes included the percentage of patients who gained 3 lines (15 letters) of BCVA at 6 months. Patients were eligible for laser rescue treatment at 3 months if macular edema showed little or no improvement, visual acuity was 20/40 or worse, and central subfield thickness was 250 µm or greater.

In 397 patients randomized, the mean gain from baseline at month 6 was 16.6 letters in patients receiving

0.3 mg of ranibizumab, 18.3 letters in those receiving 0.5 mg, and 7.3 in those receiving sham injection. Improvement in BCVA was evident as early as 1 week, with patients achieving a mean gain of 7.6, 7.4, and 1.9 letters in the 0.3 mg and 0.5 mg ranibizumab and sham groups at 1 week, respectively. By month 6, most patients in the two ranibizumab groups gained at least 3 lines of BCVA (55.2% in the 0.3 mg group and 61.1% in the 0.5 mg group), while most of those in the sham group did not (28.8%).

The CRUISE trial (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) assessed the safety and efficacy of ranibizumab in patients with CRVO.[6] Inclusion criteria were similar to those in the BRAVO study: macular edema involving the foveal center secondary to CRVO, central subfield macular thickness of 250 µm or greater on optical coherence tomography, and BCVA of 20/40 to 20/320. Patients were randomly assigned to six monthly intravitreal injections of 0.3 or 0.5 mg ranibizumab or sham injection. The primary efficacy outcome was mean change from baseline BCVA at 6 months. Secondary outcomes included the percentage of patients who gained 3 lines (15 letters) of BCVA at 6 months.

The results of CRUISE mirror those of BRAVO. In 392 patients randomized, the mean gain from baseline BCVA at month 6 was 12.7 letters in patients who received 0.3 mg ranibizumab, 14.9 letters in patients who received 0.5 mg ranibizumab, and 0.8 letters in those who received sham injections. Again, gain in BCVA was seen as early as 1 week, with patients achieving mean gains of 8.8, 9.3, and 1.1 letters in the 0.3 mg and 0.5 mg ranibizumab and sham groups at 1 week, respectively. At month 6, gains of three lines or more in BCVA were seen in 46.2% of patients receiving 0.3 mg ranibizumab, 47.7 of those receiving 0.5 mg ranibizumab, and 16.9% of those receiving sham injections.

The safety profiles of both trials were similar to those of previous phase 3 trials of ranibizumab intravitreal injection in patients with AMD. Safety events in both trials were uncommon. Serious adverse events included, in BRAVO, one retinal detachment and one case of endophthalmitis, and in CRUISE, one case of vitreous hemorrhage in the sham group. No endophthalmitis occurred in any group in CRUISE.

IMPLICATIONS FOR PRACTICE

BRVO and CRVO are off-label indications for the use of both ranibizumab and bevacizumab (Avastin, Genentech), but last year's Patterns and Trends Survey by the American Society of Retina Specialists showed that approximately 50% of respondents are nevertheless using off-label intravitreal bevacizumab as first-line therapy for CRVO and BRVO.[7]

The results of these two studies in patients with BRVO and CRVO, while impressive, leave us with questions about how to conduct our daily retina practice. What can we tell our patients who present with RVO about potential outcomes of treatment with anti-VEGF agents? As in the trials of ranibizumab in patients with CNV secondary to AMD, patients in BRAVO and CRUISE received monthly injections. Can the alternative anti-VEGF dosing strategies now widely used in patients with AMD be applied to patients with RVO?

WHEN TO TREAT

The trials give us several points to consider. First, both trials enrolled all comers, no matter the duration of their disease. If patients met the screening criteria, they could be enrolled in the trial. Some physicians feel that, if the disease will resolve spontaneously in a third of patients, maybe some period of time should elapse before we initiate treatment. However, initial subgroup analysis from BRAVO and CRUISE that has not yet been presented (Genentech statistics personnel, personal communication) suggests that there was a definite benefit for patients who presented with a short duration of disease as well as those who presented with long duration, compared with patients with comparable duration of disease in the control arm. In other words, no matter the duration of the disease, treated patients did better than sham-treated patients.

Because patients with RVO are in general younger than our patients with AMD and more likely to be involved in the working world, it is often important that they recover their vision quickly so that they can drive to work and function in the workplace. The month or two of improved visual acuity that an early injection of a VEGF inhibitor can potentially deliver might help these patients keep their jobs. We must not forget we are living through a time when it will be difficult for patients to come by another job if they lose one due to poor or monocular vision affecting job performance.

As with any treatment, the risk-benefit ratio must be considered. In these studies the rates of adverse events—endophthalmitis, retinal tear, vitreous hemorrhage—were very low, but the benefit rate—the chance of improving BCVA—was high. So from the point of risk-benefit ratio there is not a great rationale for delaying treatment, unless the patient's other eye is healthy and the RVO is not affecting his or her lifestyle.

On the other hand, unlike with AMD, patients with RVO can potentially tolerate more time with edema

before permanent vision loss occurs. RVO is an inner retinal disease, and edema in the inner retina does not result in photoreceptor damage as rapidly as in AMD, in which photoreceptors and retinal pigment epithelium damage leads quickly to permanent vision loss. Therefore, treatment for RVO can often be delayed 3 months without great risk if the patient and physician choose to do so.

These factors should all be considered in the decision-making process regarding when to treat RVO.

DOSING SCHEDULE

Once the decision is made to treat with an anti-VEGF agent, a dosing strategy must be devised. The BRAVO and CRUISE trials used monthly dosing schedules, but because RVO is an inner retinal disease it may be more forgiving and less demanding of frequent injections. In practice, most physicians will probably give their RVO patients several monthly injections as a loading dose and then either treat on an as-needed basis (PRN) or with a treat-and-extend strategy.

For patients being treated on a PRN basis, examination will determine when treatment can stop. If patients being treated on a treat-and-extend basis can be extended past 3 months without recurrence of edema, the physician will know the treatment can be stopped because there is no active drug in the eye after 3 months.

In patients with persistent edema, however, treatment must continue or the benefit will be lost. In patients with BRVO who require continued treatment, the physician may decide to add grid laser photocoagulation. In the BRVO portion of the SCORE study[8] comparing laser and steroid, visual acuity kept improving in the second and third years in the laser arm. This may suggest that treatment with ranibizumab plus laser may allow earlier resolution of edema and discontinuation of therapy than ranibizumab alone. The same may be true in CRVO, but there is currently no evidence to support this.

When laser is added to anti-VEGF therapy in BRVO patients, it is recommended to perform laser a week or so after the anti-VEGF injection. The rationale for this is that laser can be applied more precisely and at lower power in retinal tissue that is not edematous. When edematous retina is treated with laser, the spot size is increased at the level of the RPE compared with laser spots in nonedematous retina. The thickened retina acts like a prism and spreads out the light, resulting in a larger, more diffuse burn that requires greater laser power. It makes sense to use the least amount of laser energy possible, and that can be achieved by applying the laser after anti-VEGF injection rather that in the reverse order.

The SCORE study found laser alone superior to steroids in patients with BRVO, but that study did not compare laser with anti-VEGF regimen. It is unlikely that laser would provide a benefit in BRVO that would be as robust in the short term as the response to anti-VEGF treatment in BRAVO. In the long term, for instance at 2 years, laser might yield a similar response to anti-VEGF therapy, but as noted earlier, working-age patients—and indeed, patients of any age—may benefit from earlier visual recovery.

Regarding the choice of anti-VEGF agent, the Comparison of AMD Treatment Trials (CATT) is testing the efficacy of ranibizumab versus bevacizumab in AMD. The results of these trials, expected by next year, may shed some light on the relative efficacy of these two agents in other diseases such as RVO. From case series, we know that there is a definite response to bevacizumab in RVO, but we do not know if it is inferior, superior, or equal to ranibizumab. Until further trials are conducted, we have only the evidence from the BRAVO and CRUISE studies with ranibizumab to guide our clinical decisions.

CONCLUSION

The availability of antiangiogenic therapy has made a tremendous difference in the lives of patients with AMD in the past 5 years. As evidence mounts regarding the efficacy of anti-VEGF agents in RVO, we may hope that a similar change is in the wings for patients with these sight-threatening conditions. ■

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