By now the results of the BRAVO and CRUISE trials are well known to retina subspecialists. These two phase 3 randomized controlled trials, the top-line results of which were published in 2010, showed that patients with macular edema due to retinal vein occlusion (RVO) experienced clinically and statistically significant improvements in visual acuity after treatment with intravitreal ranibizumab (Lucentis, Genentech), compared with patients who received sham injections.

Many of us now have multiple patients with either branch or central RVO (BRVO or CRVO) who have benefited from treatment with this vascular endothelial growth factor (VEGF) inhibitor. But what can we tell these patients with RVO when they want to know how much better they can get or how much longer they will have to continue to receive injections? Which patients respond best to this therapy, and what are the predictors of their response?

Subgroup analyses of data from BRAVO and CRUISE suggest some answers to these questions. Patients’ characteristics and the dosing they received during the studies appear to influence their clinical outcomes. Subanalyses from BRAVO and CRUISE looked at patients’ baseline and 6-month characteristics, including age, baseline visual acuity, time from diagnosis to study entry, sex, baseline and month 6 central field thickness on optical coherence tomography (OCT), alcohol consumption, and the need for rescue laser during the treatment period. Also examined was the effect of treatment at month 6 of the studies, after the initial six mandated injections.5,6

This article reviews the results of the two studies and outlines the trends suggested by these post hoc subgroup analyses.

**BRAVO**

In the BRAVO study, patients with macular edema due to BRVO were randomized to receive injections of 0.3 mg or 0.5 mg ranibizumab or sham injection monthly for 6 months, followed by 6 months of as-needed (PRN) treatment with active ranibizumab in all groups. Rescue laser treatment was available to all patients who met prespecified criteria during the first 6 months. Therefore, the 0.3 and 0.5 ranibizumab patient groups received six active injections during the first half year of study, followed by PRN treatments. The sham group did not receive active drug but could receive rescue grid laser in the first 6 months, and these patients “crossed over” to active ranibizumab PRN in the second half year. The primary efficacy endpoint was mean change from baseline in best corrected visual acuity (BCVA) score at 6 months.1

At month 6 in BRAVO, patients who received 0.3 mg ranibizumab (n=134) experienced a mean gain of 16.6 letters (on the ETDRS chart) from baseline, and those who received 0.5 mg ranibizumab (n=131) experienced a mean gain of 18.3 letters. This compared with a gain of 7.3 letters in those receiving sham injection (n=132). Significant improvement in BCVA was seen as early as day 7. At 6 months, 55.2% of patients who received 0.3 mg and 61.1% of patients who received 0.5 mg ranibizumab experienced a mean gain of 18.3 letters. This compared with only a gain of 7.3 letters in those receiving sham injection (n=132). Significant improvement in BCVA was seen as early as day 7. At 6 months, 55.2% of patients who received 0.3 mg and 61.1% of patients who received 0.5 mg ranibizumab had an improvement of 15 letters (3 lines) or more from baseline, compared with 28.8% of patients receiving sham injection. OCT analyses of retinal thickness reflected the improvements seen in BCVA.1

Ho et al presented a subgroup analysis that suggests that certain patient characteristics influenced these results. First, while there was a greater mean gain in
visual acuity overall in the treatment groups than the sham injection group, those with worse vision at baseline gained the most letters on average. The same was true for those with greater OCT macular thickness at baseline.

Time since diagnosis and patient age also had an effect on outcomes. Patients who were treated within 3 months of diagnosis and those who were younger than 65 years had an average benefit of 5 letters (1 line) greater than those with longer time since diagnosis or older age.

Campochiaro et al also found that the dosing received after the first six monthly doses also showed some effect on BCVA and macular thickness in BRVO. Patients treated with a seventh injection at month 6, after the six mandated consecutive monthly injections, gained a mean 0.4 letters from month 6 to month 7, compared with a mean loss of 2.8 letters in those not treated. Those treated at month 6 also had a reduction in central field thickness on OCT at month 7 compared with those not treated, although this difference was not large.

Another subanalysis by Kitchens et al used logistic regression analysis of patient characteristics to predict the number of PRN injections during the second 6 months of the study. The analysis found that patients who required rescue laser during the first 6 months of treatment had nearly three times greater chance of needing PRN injections in the second 6 months than patients who did not need laser. Therapy for RVO before study entry also increased the odds for more PRN injections, but the confidence interval for this risk factor was wide.

The safety profile in BRAVO was consistent with those of previous trials involving intravitreal injection of ranibizumab in patients with age-related macular degeneration (AMD). Ocular adverse events were generally uncommon, and systemic serious adverse events were low across all groups.

CRUISE
The CRUISE study design was similar to that of BRAVO. Patients with macular edema due to CRVO were randomized to receive injections of 0.3 mg or 0.5 mg ranibizumab or sham injection monthly for 6 months, followed by 6 months of PRN treatment with active ranibizumab. No rescue laser was available in this CRVO study. The primary efficacy endpoint was mean change from baseline in BCVA score at 6 months.

At month 6 in CRUISE, patients who received 0.3 mg ranibizumab (n=131) had a mean gain from baseline BCVA of 12.7 letters, and those who received 0.5 mg ranibizumab (n=130) had a mean gain of 14.9 letters,
compared with a gain of 0.8 letters in those receiving sham injection (n=129). Also at month 6, 46.2% of patients receiving 0.3 mg and 47.7% of those receiving 0.5 mg ranibizumab gained 15 or more letters of BCVA, compared with 16.9% of those receiving sham injections. As in BRAVO, improvement in BCVA was seen as early as day 7, and reduction of retinal thickness on OCT reflected the improvements seen in BCVA.

Marcus et al. in a subanalysis of CRUISE found, as in BRAVO, that certain patient characteristics influenced results. Patients who started with worse vision (those with lower BCVA and greater thickness on OCT at baseline) had greater mean gains in BCVA and reductions in retinal thickness.

In contrast with BRAVO, the time from diagnosis to treatment had a less significant effect on outcome in CRUISE. However, age younger than 65 here again provided an advantage of at least 1 line of BCVA over older age at baseline.

Regarding the PRN dosing period of the CRVO study, Singh et al. found a trend for patients treated at month 6 to gain and for those for whom treatment was withheld at month 6 to lose BCVA. Those who received treatment at 6 months gained a mean 1.7 letters at month 7, whereas those not treated lost a mean 7.2 letters. Many patients for whom treatment was withheld at month 6, therefore, lost some of the visual gains they achieved in the first 6 months of the study.

The change in central field OCT when treatment was withheld at month 6 was more significant in CRUISE than was seen in BRAVO; most patients who did not receive ranibizumab at month 6 lost the improvement they had gained over the previous 6 months, with a mean increase of 200 µm by month 7; those who received treatment had a mean decrease of 19 µm.

The logistic regression subanalysis in CRUISE by Wieland et al. did not identify any factors that were strong predictors of an increased number of PRN injections. There was a higher odds ratio for more injections with increased alcohol consumption, but alcohol use was not well balanced across the groups, so the analysis did not likely have sufficient power to demonstrate a clinically meaningful effect.

The safety profile in CRUISE, as in BRAVO, was consistent with that of previous trials involving intravitreal injection of ranibizumab in patients with AMD. Ocular adverse events were generally uncommon, and systemic serious adverse events were low across all groups.

IMPLICATIONS

Based on these subanalyses, what can we tell our patients with RVO? First, RVO patients on average experienced rapid and sustained improvements in vision and retinal thickness when treated with ranibizumab according to the study protocols.

In addition, the subanalyses generally confirmed our existing impressions and instincts about our patients’ responses. Patients with BRVO or CRVO who were younger or who had worse vision and greater retinal thickness at baseline fared better. Patients with BRVO fared better if time from diagnosis to treatment was less than 3 months. Patients with CRVO had similar results regardless of time to treatment.

Withholding the dose at month 6 was on average associated with further vision loss and increased retinal thickness. This effect was more pronounced in patients with CRVO than those with BRVO.

Predictors of the number of PRN injections in patients with BRVO included the need for rescue laser during the treatment period and the need for prior therapy before the start of the trial. In patients with CRVO, no clinically relevant predictive factors were identified.

In general, then, in BRVO, patients who needed fewer therapies, such as laser or other previous treatments, probably had milder RVO requiring less treatment. Patients who were younger did better than those who were older. And patients with CRVO had a more unpredictable course than those with BRVO, and therefore warrant even closer observation than those with BRVO.

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