

Treatments for Retinal Vein Occlusion:

A Review of Recent Developments

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Retinal vein occlusions (RVOs), including both branch and central veins, are the second most common retinal vascular diseases after diabetic retinopathy.¹ The Beaver Dam Study reported a prevalence of 0.1% in patients older than 43 years.² The 15-year cumulative incidence of central retinal vein occlusion (CRVO) was 0.5% in the Beaver Dam Eye Study.³ A cross-sectional study from 6 communities across the United States reported that the prevalence of CRVO was 0.2%. This same study showed that the prevalence of CRVO was similar across different ethnic and racial groups.⁴ In a population-based study in Australia, the Blue Mountains Eye Study, the 10-year cumulative incidence of CRVO in a population older than 48 years was 0.4%.⁵ The Singapore Malay Eye Study reported a 0.2% prevalence of CRVO in the Malay population 40 to 80 years old living in Singapore.⁶ The Beijing Eye Study reported that the prevalence of CRVO in a Chinese population of people 40 years and older was 0.1%.⁷ No racial or gender predilection for the disease is apparent.

There are several systemic factors that have been identified as being associated with RVO, including diabetes, hypertension, and heart disease.² The standard of care for macular edema secondary to branch retinal vein occlusion (BRVO) has been guided since 1984 by the findings of the Branch Vein Occlusion Study, which showed that macular photocoagulation was superior in improving visual acuity compared with observation.⁸ The 1995 Central Vein Occlusion Study (CVOS) demonstrated that grid laser treatment of macular edema was of no visual benefit despite the elimination of macular edema in treated eyes.⁹ Thus, observation for macular edema secondary to CRVO was the standard of care set by this study. Since then, new pharmacologic agents have changed the treatment paradigm of macular edema secondary to RVO. Currently there are 3 treatment options recently approved by the US Food and Drug Administration (FDA) for treatment of macular edema

secondary to CRVO. These include a dexamethasone intravitreal implant (Ozurdex, Allergan), ranibizumab (Lucentis, Genentech), and aflibercept (Eylea, Regeneron). Two of these (dexamethasone intravitreal implant and ranibizumab) are also FDA approved for the treatment of macular edema secondary to BRVO. In addition, intravitreal injections of bevacizumab (Avastin, Genentech) have been extensively used off label for treating both CRVO and BRVO.

STERIODS FOR RETINAL VEIN OCCLUSION

The SCORE study^{10,11} compared the effects of 1-mg and 4-mg intravitreal triamcinolone acetonide (IVTA; Trivaris, Allergan) to standard of care, which was observation for CRVO and grid laser for BRVO.

In SCORE-CRVO, patients received an average of 2 injections of IVTA over the course of 1 year. At the end of year 1, 27% percent of patients who received 1-mg IVTA and 26% of patients who received 4-mg IVTA achieved a visual acuity gain of 3 or more lines compared with only 7% of patients in the observation group. The visual acuity was sustained throughout year 2. The side-effect profile for the lower dose was more favorable, however, indicating a higher level of safety for the 1-mg dose.

In SCORE-BRVO, patients who were randomized to grid laser underwent a mean 1.5 treatments in year 1, and those who received IVTA had an average of 2 injections. At 1 year, the percentage of patients in the laser group, 1-mg IVTA group, and 4-mg IVTA group who gained 3 or more lines of vision was 29%, 26%, and 27%, respectively. These visual acuity gains were sustained to year 3. The rates of cataract formation and intraocular pressure (IOP) elevation, however, were higher in the steroid groups, with a high number of patients requiring cataract surgery between the second and third year of the study. Based on these data, the recommendation from the study was that laser remain the standard of care for BRVO.

The GENEVA trial,¹² published in 2010, examined the effects of the dexamethasone intravitreal implant (Ozurdex, Allergan) in patients with macular edema secondary to either BRVO or CRVO. The trial enrolled 1267 patients and evenly divided them into 3 groups. The first group received a 0.7-mg dexamethasone implant, the second group received a 0.35-mg dexamethasone implant, and the third group received a sham implant. The results of the study showed that the dexamethasone implant was effective. After a single implant, both treatment groups had best corrected visual acuity (BCVA) improvements of 15 or more letters in less time than the sham group ($P < .001$). At days 30 and 90, the percentage of eyes with 15 or more letters lost was higher for the sham group than either treatment group ($P < .001$). Although the study design was based on the implant delivering therapeutic levels of drug for 6 months, in reality, visual acuity peaked between 3 and 4 months. Patients with BRVO and a 0.7-mg implant had a 10.3-letter improvement at 60 days that fell to 7.4 letters at 180 days; for patients with CRVO and a 0.7-mg implant, the 8.7-letter improvement at 60 days dropped to 0 letters at 180 days.

The percentage of eyes with IOP of at least 25 mm Hg that were treated with dexamethasone was 16% at day 60 for both treatment arms, and this was equal to the percentage of sham eyes with IOP increases of at least 25 mm Hg at day 180. There was no significant difference in occurrence of cataract or cataract surgery between the treatment groups and the sham group.

Subsequently, a 6-month open-label extension study was performed.¹³ At the start of this extension study, 997 patients were given a 0.7-mg dexamethasone implant if their BCVA was less than 84 letters and their retinal thickness was greater than 250 μ m. Those in the sham group during the first 6 months were given their first 0.7-mg dexamethasone implant at day 180 and had a 30% improvement in BCVA from baseline. The group that received a dexamethasone implant during the first 6 months received a second implant and had a 32% improvement in BCVA from baseline.

Over 12 months, cataract progression was found in 90 of 302 phakic eyes (29.8%) that received 2 implants of 0.7 mg vs 5 of 88 sham-treated phakic eyes (5.7%); cataract surgery was performed in 4 of 302 phakic eyes (1.3%) that received 2 implants of 0.7 mg and in 1 of 88 sham-treated phakic eyes (1.1%). In eyes that received 2 of the 0.7-mg implants, an increase in IOP of at least 10 mm Hg was seen in 12.6% of eyes after the first treatment and 15.4% of eyes after the second treatment.

Recently, the SHASTA study¹⁴ retrospectively studied the effects of multiple dexamethasone implants.

The study population consisted of 289 patients with macular edema secondary to CRVO or BRVO. Patients received a mean 3.2 dexamethasone implants as monotherapy (29.1% of patients) or as combination therapy. The mean injection interval between implants was 5.6 months. After the first 6 dexamethasone implants, 59.7% of BRVO patients and 66.7% of CRVO patients achieved a gain of 2 or more lines of BCVA. Additionally, patients experienced a significant reduction in central retinal thickness. Intraocular pressure increases of 10 mm Hg or higher occurred in 32.6% of patients; 33.7% had an IOP of 25 mm Hg or more at any single visit, and 9.4% had an IOP of 35 mm Hg or more at any single visit. This led to 29.1% of patients requiring medication to lower increased IOP. In addition, 1.4% and 1.7% of patients underwent glaucoma laser surgery and glaucoma incisional surgery, respectively. Almost 16% of patients underwent cataract extraction during the study period. Most of these patients had some degree of lens opacity at baseline.

INTRAVITREAL ANTI-VEGF AGENTS FOR RETINAL VEIN OCCLUSION

The BRAVO¹⁵ and CRUISE¹⁶ studies, published in 2010, evaluated the effects of ranibizumab (Lucentis, Genentech) in patients with macular edema secondary to BRVO and CRVO, respectively. In both studies patients were randomly assigned to receive monthly injections of 0.3 mg or 0.5 mg ranibizumab or sham injections for 6 consecutive months. At the sixth month, patients were followed monthly and reinjected as needed. Also at the sixth month, the patients that were in the sham group were allowed to cross over to the 0.5 mg ranibizumab group. After month 12, patients were monitored on a quarterly basis until month 24 and reinjected accordingly. Reinjection criteria were based on time-domain optical coherence tomography (TD-OCT) findings of a central subfield thickness of at least 250 μ m or signs of intraretinal fluid. In the BRAVO study, macular grid laser rescue treatment was allowed after month 3 and could be repeated every 3 months.

In the first 6 months a rapid improvement in BCVA (+18.3 letters for the 0.5 mg group, +16.6 letters for the 0.3 mg group, and +7.3 letters for the sham group; $P < .05$) that was statistically significantly different from the sham group was observed in both ranibizumab groups. There was no difference between the ranibizumab groups. It was noted that, at month 12, both ranibizumab groups maintained the visual acuity gains of the first 6 months. Patients who crossed over from sham to the 0.5 mg ranibizumab group also experi-

enced an improvement in BCVA. However, their gains (12.1 letters) never matched those of the eyes that were injected with ranibizumab from the beginning of the trial.

In the HORIZON extension trial,¹⁷ patients who were initially enrolled in the BRAVO and CRUISE trials and completed the 12 month follow-up were followed on a mandatory quarterly basis for the next year. However, patients could be followed monthly if the treating physician deemed it necessary. Reinjections were performed if intraretinal fluid was identified. Macular grid laser was permitted as well in the HORIZON-BRAVO study. Almost half of all eyes enrolled in the HORIZON-BRAVO study had macular laser photocoagulation during the BRAVO portion of the study. Another 8% had macular laser photocoagulation during the HORIZON extension trial. Despite less frequent follow-up and fewer injections, eyes in the HORIZON-BRAVO study maintained the gains from the BRAVO trial. The use of macular grid laser may have contributed to the stability of these eyes.

The RETAIN study¹⁸ was an extension study for patients who completed the HORIZON study. Only 34 patients from the BRAVO study were enrolled in the RETAIN study. Patients were followed monthly during the first year of the study and at least every 3 months during the second year of the study. Reinjections were performed if intraretinal fluid was identified. On average, patients had a follow-up of 4 years. The results from this study demonstrate the excellent long-term outcomes of eyes with macular edema secondary to BRVO. Fifty percent of eyes had resolution of macular edema. Resolution of macular edema was defined as the absence of intraretinal fluid for at least 6 months from the last injection. At the last visit, 62% of eyes had an improvement of 3 lines or more from the BRAVO trial baseline and 80% of eyes had a BCVA of 20/40 or better.

The CRUISE trial had a design similar to the BRAVO trial. The only difference was that no macular laser treatment was allowed. Reinjection criteria were identical to those of the BRAVO study. In the first 6 months a rapid improvement in BCVA (+14.9 letters for the 0.5 mg group, +12.7 letters for the 0.3 mg group, and +0.8 letters for the sham group; $P < .05$) that was statistically significantly different from the sham group was observed in both ranibizumab groups. There was no difference between the ranibizumab groups. At month 12, both ranibizumab groups maintained the visual acuity gains of the first 6 months. Patients who crossed over from sham to the 0.5 mg ranibizumab group experienced an improvement in BCVA of 7.3 letters from baseline. However, their gains never caught up with the

gains seen in the eyes that were initially treated with ranibizumab.

In the HORIZON extension trial, patients who were initially enrolled in the CRUISE trial were followed on a mandatory quarterly basis. Similar to the HORIZON extension of the BRAVO study, patients could be followed monthly if deemed appropriate by their treating physician. Reinjection criteria remained the same as in the CRUISE trial. At the end of the HORIZON-CRUISE trial, the BCVA gains were not sustained in and patients lost an average of 4 letters. These results indicate that as-needed (prn) quarterly dosing is not sufficient to treat macular edema due to CRVO. It appears that some eyes stabilize after a few consecutive monthly injections and require a few injections thereafter, but the vast majority require frequent follow-up and multiple injections to control macular edema. Findings from TD-OCT may be used to predict visual outcomes. Persistent macular edema at month 3 as measured by TD-OCT indicates a worse prognosis and probable need for more injections and continuous monitoring.

In the RETAIN-CRVO extension study, 32 patients were enrolled and had an average follow-up of 4 years. Unlike in BRVO, the long-term outcomes in CRVO were more guarded. Results from this study showed that 44% of eyes had resolution of macular edema, 53% had an improvement of 3 lines or more from the CRUISE trial baseline, and 44% of eyes had a BCVA of 20/40 or better. Eyes that had resolution of macular edema had a statistically significantly greater improvement in BCVA (25.2 letters vs 4.3 letters), and a statistically significantly greater proportion achieved BCVA of 20/40 or better (64.3% vs 27.8%) compared with those eyes without resolution. Results from another small study indicate that progression of retinal nonperfusion continues, particularly in eyes in which macular edema has not resolved and anti-VEGF injections are given sporadically. The authors of this study state that, in eyes with macular edema secondary to RVO, the resolution of macular edema should not be the sole treatment objective. The prevention of worsening retinal nonperfusion should be a treatment objective as well. Periodic fluorescein angiograms, preferably wide-angle, should be performed to monitor perfusion status.

The COPERNICUS^{19,20} and GALILEO²¹ trials evaluated the use of aflibercept (Eylea, Regeneron) in eyes with macular edema secondary to CRVO. All eyes received mandatory monthly injections of aflibercept during the first 6 months. From week 24 to week 52, the treatment protocol differed in both studies. Patients in COPERNICUS received 2.0 mg of intravitreal aflibercept prn according to prespecified retreatment criteria.

Sham-treated eyes were allowed to receive aflibercept after week 24. In contrast, patients in GALILEO maintained their original randomization through week 52. If retreatment criteria were met, patients would receive the treatment of their original allocation. Eyes that were originally randomized to sham injections continued to receive sham injections if retreatment criteria were met. Eyes originally randomized to intravitreal aflibercept continued to receive intravitreal aflibercept if retreatment criteria were met. In COPERNICUS at week 52, patients were followed every 12 weeks, whereas patients in GALILEO were seen every 8 weeks. The results of both studies showed that patients in the treatment arms gained 17.3 to 18 letters at week 24. At week 52 those gains were sustained. However, the COPERNICUS 2-year study²⁰ results showed that the improvements in the treatment group diminished with prn treatment and less frequent follow-up. After the conclusion of the second year, the treatment group gained 13.0 letters from baseline ($P < .001$). Patients who initially received sham followed by crossover to prn treatment also showed improvement, but the visual acuity improvements never caught up to the visual acuity gains in the treatment arm.

The phase 3 VIBRANT trial²² was a double-masked, randomized, active-controlled study of 183 patients with macular edema following BRVO. Patients received either 2 mg intravitreal aflibercept every 4 weeks or laser treatment, up to week 24. At week 24, 53% of aflibercept-treated eyes gained at least 15 letters of BCVA from baseline compared with 27% of laser-treated eyes. Aflibercept-treated eyes also had a mean gain of 17 letters at 24 weeks compared with 6.9 letters in the laser-treated group.

There are many retrospective case series, very few prospective comparative studies, and even fewer clinical trials examining the effects of bevacizumab in patients with RVO. A Swedish study randomized 60 eyes with macular edema secondary to CRVO to receive an intravitreal injection of 1.25 mg bevacizumab or sham injection every 6 weeks for 6 consecutive months.²³ After the sixth month, all eyes received intravitreal bevacizumab every 6 weeks until month 12. The mean gain at 12 months was 16 letters in the bevacizumab group compared with 4.6 letters in the sham group. The available evidence suggests that intravitreal bevacizumab is effective in reducing macular edema and improving visual acuity in eyes with macular edema secondary to RVO.

There has been a concern that anti-VEGF agents may potentially induce systemic thromboembolic events, but none of the trials with ranibizumab or aflibercept have shown that either drug increases the rate of thromboembolic events in this population of patients.

WHERE ARE WE GOING?

Despite the advances in pharmacologic therapy, many eyes with RVO continue to lose vision. The common final pathway appears to be photoreceptor cell death. Future research for RVO treatments may focus on neuroprotective and photoreceptor regeneration therapies to improve sight in patients who have limited vision due to RVO. ■

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