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Vein Occlusion

In this Issue...

Retinal vein occlusion (RVO) is a prevalent retinal vascular disease whose occurrence is second only to diabetic retinopathy. Because until recently no treatment was available for central retinal vein occlusion (CRVO), patients were simply observed for the development of severe complications and visual outcomes were generally poor. The only treatment for branch retinal vein occlusion (BRVO) was grid laser photocoagulation, which reduces edema very slowly and is beneficial in some, but not all, patients. However, recent clinical trials investigating 3 pharmacologic treatments—ranibizumab, triamcinolone acetonide, and dexamethasone implants—now present new options that alter the standard care for patients with RVO. Ophthalmologists should become familiar with the results of these trials and use them to guide treatment of patients with CRVO or BRVO. Although suggested treatment guidelines are presented for use as a template, modifications may be necessary, depending on individual patient characteristics.

In this issue, we review articles that have reported on these recent clinical trials and describe their clinical implications. The recommendations presented provide critical points that should be discussed with patients, so that patients and their physicians can select the treatment approach with which they are most comfortable.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Compare the outcomes of the BRAVO and CRUISE studies with those of the SCORE and GENEVA trials
- Describe the recommended treatment regimen for patients with macular edema caused by central retinal vein occlusion in the first year following diagnosis
- Discuss the recommended treatment regimen for patients with macular edema caused by branch retinal vein occlusion in the first year after diagnosis

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- **Susan Bressler, MD** has disclosed that she has received grants/research support from Bausch & Lomb, Genentech, Notal Vision and Novartis. She also has served as a consultant for GlaxoSmithKline.

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THIS ISSUE

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Peter A. Campochiaro, MD has disclosed that he has served on advisory boards for Genentech, Pfizer, and Regeneron. He has served as a consultant for Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Lpath Incorporated, Pfizer, and Regeneron. He has also has received grants/research support from Alcon, Alimera Sciences, Genentech, Genzyme, GlaxoSmithKline, and Molecular Partners.

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The author has indicated that he will refer to unlabeled/unapproved use of ranibizumab, dexamethasone intravitreal implant, and triamcinolone acetonide.

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COMMENTARY

Recent studies have provided new options for managing central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). In patients with CRVO, we have progressed from no treatments to at least 3 possible options. The treatments are not mutually exclusive but choices must be made, based on relative benefit/risk ratios, regarding which option becomes first-line treatment and which ones assume adjunctive roles. Using separate trials to assess relative benefit/risk ratios can be tricky, because differences in patient populations and procedures can confuse the issue. When one compares results from the Central Retinal Vein Occlusion Study: Efficacy and Safety (CRUISE; see Review 1) and the Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE; see Review 3) CRVO trials, it is clear that population differences existed between the 2 studies. Changes in mean best-corrected visual acuity (BCVA) letter score in the control groups differed (CRUISE: 6 months, +0.8 vs. SCORE: 8 months, -11.7; 12 months, -12.1), with 17% of the CRUISE control group gaining ≥15 letters, compared with 7% in the SCORE study. Differences in eligibility criteria may explain these variations. In CRUISE, patients were excluded for BCVA <20/320 (vs. BCVA<20/400 in SCORE), an afferent pupil defect, or CRVO for >1 year. The first 2 criteria may have limited the number of patients with poor visual prognosis, regardless of therapy, due to severe retinal ischemia. Duration of CRVO before initiating treatment can negatively affect patient outcomes,[1] although the mean duration of CRVO was 3.3 months in CRUISE vs. 4 months in SCORE.

In CRUISE (Review 1), the percentage of patients who gained ≥15 letters in BCVA was 46.2% with ranibizumab 0.3 mg, 47.7% with ranibizumab 0.5 mg, and 16.9% in the control group—a difference of 28% to 30%. In contrast in SCORE (Review 3), the percentage of patients who gained ≥15 letters in BCVA was 26.5% with triamcinolone acetonide (TA) 1 mg, 25.6% with TA 4 mg, and 6.8% in the control group—a difference of 19% to 20%. Thus, although the differences in study populations and trial designs render comparison difficult, the relative benefit seems to be greater with ranibizumab, and considering the risk for cataracts and increased intraocular pressure (IOP) associated with TA, ranibizumab has a superior benefit/risk ratio.

Differences in study design are the main confounding factor when comparing ranibizumab with dexamethasone (DEX) intravitreal implants (see Review 4). Comparison of monthly injections of ranibizumab with a single injection of a DEX implant at 6 months is easy, because the mean change from baseline BCVA letter score was 0 with a 0.7-mg DEX implant and +2 with a 0.35-mg DEX implant, which did not differ significantly from that of -2 in the control group. It is anticipated that 2 DEX implant injections 3 months apart might provide improved efficacy but could also result in increased toxicity. Therefore, with our current state of knowledge, ranibizumab is favored over DEX implants as primary therapy in patients with CRVO.

My recommendation for the treatment of patients with CRVO is to administer 6 monthly injections of ranibizumab 0.5 mg. After 6 months, it is best to continue monthly follow-up visits, as ranibizumab injections for recurrent edema have been shown to maintain visual benefits for at least 1 year.[2] Some patients continue to experience recurrent edema after ≥1 year of treatment,[1] and to date, no information is available on how to manage such patients. An ongoing clinical trial (RELATE trial, clinicaltrials.gov identifier: NCT01003106) is investigating whether using laser photocoagulation in areas of capillary nonperfusion can reduce the number of ranibizumab injections required.

Although most patients respond quite well to ranibizumab injections, in rare instances in which patients exhibit substantial residual edema and reduced vision after 6 monthly injections, it might be reasonable to consider a DEX implant. Ranibizumab levels may decline more rapidly in vitrectomized eyes, so the threshold might be lower when considering a DEX implant in a vitrectomized eye that appears to be responding poorly to ranibizumab injections. Hopefully, future studies will provide guidance for combination therapy in patients who respond suboptimally to ranibizumab injections.

The comparative analysis is very similar for patients with BRVO and favors ranibizumab (see Reviews 2 and 3); however, integration of drug treatment with grid laser therapy is an additional consideration in these patients. Visual acuity improves rapidly after ranibizumab injections, whereas benefits occur slowly after grid laser therapy, and the presence of intraretinal hemorrhages in the macula often precludes the use of laser for several months.

My recommendation for patients with BRVO with macular edema is to administer 6 monthly injections of ranibizumab. This treatment has the advantage of inducing more rapid clearance of hemorrhages, in addition to improving vision and reducing macular edema.[3] Even the small percentage of patients who would have experienced spontaneous improvement obtain benefits from more rapid return of vision. If edema recurs after 6 ranibizumab injections, it is reasonable to consider grid laser therapy in combination with ranibizumab, as needed. If despite grid laser treatment, frequent injections of ranibizumab continue to be required to control edema after 1 year, it would be reasonable to discuss with the patient the pros and cons of a DEX implant.

The treatment of macular edema caused by retinal vein occlusion (RVO) is evolving. It is clear that vascular endothelial growth factor (VEGF) is a critical target in patients with RVO and that ranibizumab provides enormous benefits. We do not yet understand how other VEGF antagonists fit into the picture. We also do not know the efficacy and safety of DEX implants administered more frequently than every 6 months. New information regarding current treatments and novel therapies on the horizon will likely change the recommendations.

Commentary References

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2. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: 12-month outcomes of a phase III study. *Ophthalmology*. In press.
3. Brown DM, Campochiaro PA, Bhisitkul RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. *Ophthalmology*. In press.

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RANIBIZUMAB FOR CENTRAL RETINAL VEIN OCCLUSION

Brown DM, Campochiaro PA, Singh RP, et al; CRUISE Investigators. **Ranibizumab for macular edema following central retinal vein occlusion: 6-month primary end point results of a phase III study.** *Ophthalmology*. 2010;117(6):1124-1133.

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The CRUISE study was a phase 3, multicenter trial in which 392 patients who developed macular edema after CRVO were randomized to receive monthly intraocular injections of ranibizumab 0.3 mg (n=132) or ranibizumab 0.5 mg (n=130), or sham injections (n=130). Patients were eligible to participate if they had foveal-involved macular edema from a CRVO that occurred within 12 months of study entry, BCVA of 20/40 to 20/320, and center subfield thickness (CST) ≥250 µm (time domain OCT). Patients were excluded from the study if they had a brisk afferent pupil defect, had undergone scatter laser photocoagulation within 3 months, had received an intraocular injection of a steroid or a VEGF antagonist within 3 months, or had an improvement of ≥10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in BCVA between screening and baseline. Baseline characteristics were well balanced among the 3 groups; the mean patient age was 68 years, mean BCVA was 20/100, mean time from diagnosis of CRVO was 3.3 months, and mean center point thickness (CPT) was 685 mm.

At 6 months, the primary endpoint of mean change from baseline BCVA letter score was 12.7 in the ranibizumab 0.3 mg group, 14.9 in the ranibizumab 0.5 mg group, and 0.8 in the sham group (P<.0001). The percentage of patients who gained ≥15 letters in BCVA was 46.2% with ranibizumab 0.3 mg, 47.7% with ranibizumab 0.5 mg, and 16.9% with sham injection (P<.0001).

The percentage of patients with a Snellen-equivalent BCVA of 20/40 or better was 43.9% in the ranibizumab 0.3-mg group, 46.9% in the ranibizumab 0.5-mg group, and 20.8% in the sham group (P<.0001). The percentage of patients with a Snellen-equivalent BCVA of 20/200 or worse was 15.2% with ranibizumab 0.3 mg, 11.5% with ranibizumab 0.5 mg, and 27.7% with sham injections (P<.005). Based on the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25), patients treated with ranibizumab felt they had experienced greater improvement (improvement from baseline in NEI VFQ score: 7.1, ranibizumab 0.3 mg; 6.2, ranibizumab 0.5 mg; 2.8, sham). Greater reduction in macular edema was observed in the ranibizumab groups, because CPT was reduced by 433.7mm with ranibizumab 0.3 mg and 452.3 mm with ranibizumab 0.5 mg, compared with 167.7mm with sham injections. The percentage of patients with CPT <250 µm at 6 months was 75.0% in the ranibizumab 0.3 mg group, 76.9% in the ranibizumab 0.5 mg group, and 23.1% in the sham group (P<.0001).

This study demonstrates that 6 monthly injections of ranibizumab 0.3 mg or ranibizumab 0.5 mg reduced macular edema and provided substantial benefits in BCVA in patients with CRVO.

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RANIBIZUMAB FOR BRANCH RETINAL VEIN OCCLUSION

Campochiaro PA, Heier JS, Feiner L, et al; BRAVO Investigators. **Ranibizumab for macular edema following branch retinal vein occlusion: 6-month primary end point results of a phase III study.** *Ophthalmology*. 2010;117(6):1102-1112

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The BRAVO study was a phase 3, multicenter trial in which 397 patients who developed macular edema after BRVO were randomized to receive monthly intraocular injections of ranibizumab 0.3 mg (n=134) or ranibizumab 0.5 mg (n=131), or sham injections (n=132). Patients were eligible to participate if they had foveal-involved macular edema from a BRVO that occurred within 12 months of study entry, BCVA of 20/40 to 20/400, and CST ≥250 mm (time domain OCT). Patients were excluded from the study if they had a brisk afferent pupil defect, had undergone grid laser photocoagulation within 4 months, had received an intraocular injection of steroid or a VEGF antagonist within 3 months, or had an improvement of ≥10 ETDRS letters in BCVA between screening and baseline. Baseline characteristic were well balanced among the 3 groups; mean BCVA was 20/80, mean time from diagnosis of BRVO was 3.5 months, and mean CPT was 520 mm. Beginning at month 3, patients were eligible to receive grid laser treatment if hemorrhages had cleared sufficiently to allow safe application of laser and the following criteria had been met: (1) Snellen-equivalent BCVA ≤20/40 or mean CST ≥250 mm, and (2) a gain of <5 letters in BCVA or a decrease of <50 mm in mean CST at the current visit compared with the visit 3 months ago. If rescue laser was not administered at month 3, the same criteria were applied at month 4, and if rescue laser was not administered at month 4, the criteria were applied at month 5.

At 6 months, the primary endpoint of mean change from baseline BCVA letter score was 16.6 in the ranibizumab 0.3-mg group, 18.3 in the ranibizumab 0.5-mg group, and 7.3 in the sham group (P<.0001). The percentage of patients who gained ≥15 letters in BCVA was 55.2% with ranibizumab 0.3 mg, 61.1% with ranibizumab 0.5 mg, and 28.8% with sham injections (P<.0001). The percentage of patients with a Snellen-equivalent BCVA of 20/40 or better was 67.9% in the ranibizumab 0.3-mg group, 64.9% in the ranibizumab 0.5-mg group, and 41.7% in the sham group (P<.0001). The percentage of patients with a Snellen-equivalent BCVA of 20/200 or worse was 1.5% with ranibizumab 0.3 mg, 0.8% with ranibizumab 0.5 mg, and 9.1% with sham injections (P<.01). Based on the NEI VFQ-25 survey, patients treated with ranibizumab felt they had experienced greater improvement (improvement from baseline in NEI VFQ score: 9.3 with 0.3 mg; 10.4 with 0.5 mg: 5.4 with sham). Greater reduction in macular edema was observed in the ranibizumab groups, because CPT was reduced by 337.3 µm with ranibizumab 0.3 mg, 345.2 µm with ranibizumab 0.5 mg, and 157.7mm with sham injections. The percentage of patients with CPT ≤250 µm at month 6 was 91% in the ranibizumab 0.3 mg group, 84.7% in the ranibizumab 0.5 mg group, and 45.5% in the sham group (P<.0001). More patients in the sham group (54.5%) than in the ranibizumab 0.3 mg group (18.7%) or the ranibizumab 0.5 mg group (19.8%) received rescue grid laser therapy. No safety signals were identified.

This study demonstrates that 6 monthly injections of ranibizumab 0.3 mg or ranibizumab 0.5 mg reduced macular edema and provided substantial benefits in BCVA in patients with BRVO.

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TRIAMCINOLONE ACETONIDE VS STANDARD CARE IN PATIENTS WITH BRVO OR CRVO

Ip MS, Scott IU, VanVeldhuisen PC, et al; **SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion. The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5.** *Arch Ophthalmol*. 2009;127(9):1101-1114.

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Scott IU, Ip MS, VanVeldhuisen PC, et al; **SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6.** *Arch Ophthalmol*. 2009;127(9):1115-1128.

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The SCORE studies compared intravitreal injections of preservative-free TA with standard care in patients with macular edema caused by CRVO or BRVO. In the CRVO study, 271 patients were randomized to receive TA 1 mg (n=92), TA 4 mg (n=91), or observation (n=88). In the BRVO study, 411 patients were randomized to receive TA 1 mg (n=136), TA 4 mg (n=138), or grid laser photocoagulation (n=137). In both studies, patients were eligible to participate if they had foveal-involved macular edema from a CRVO occurring within 12 months of study entry, BCVA of 20/40 to 20/400, and CST ≥250 µm (time domain OCT). Patients were excluded from the studies if they had received a prior intraocular steroid injection or vitrectomy, had undergone laser photocoagulation within 3.5 months, or had a history of glaucoma or IOP ≥25.

In the CRVO study, baseline characteristics were well balanced among the 3 groups; the mean patient age was 68 years, mean BCVA was 20/100, mean time from diagnosis of CRVO was 4 months, and mean CPT was 659 mm. At month 12, the primary endpoint of mean change from baseline BCVA letter score was -1.2 in the 2 TA groups and -12.1 in the observation group. The percentage of patients who gained ≥15 letters in BCVA was 26.5% with TA 1 mg, 25.6% with TA 4 mg, and 6.8% with observation. Reduction in CPT at month 12 was 196 mm in the TA 1-mg group and 261mm in the TA 4-mg group, compared with 277 mm in the observation group. The percentage of patients with CPT £250 mm at month 12 was 32% with TA 1 mg, 45% with TA 4 mg, and 28% with observation. More patients in the TA groups (4 mg, 35%;1 mg, 26%) required initiation of IOP-lowering drops compared with the observation group (8%). Moreover, significantly more patients in the TA 4 mg group (n=21) than in the observation group (n=3) required cataract surgery in the study eye between 1 and 2 years. The investigators recommended injection of TA 1 mg for patients with macular edema caused by CRVO, with injections repeated every 4 months for persistent/recurrent edema.

In the BRVO study, baseline characteristics were well balanced among the 3 groups; the mean patient age was 67 years, mean BCVA was 20/80, mean time from diagnosis of BRVO was 4 months, and CPT was 525 mm. At month 12, the primary endpoint of mean change from baseline BCVA letter score was 5.7 with TA 1 mg, 4.0 with TA 4 mg, and 4.2 with grid laser photocoagulation. The percentage of patients who gained ≥15 letters in BCVA was 26% in the TA 1-mg group, 27% in the TA 4-mg group, and 29% in the laser group. Thus, TA injections were not superior to the use of grid laser in these patients.

The authors of these studies concluded that injections of TA appear to provide modest benefits in patients with CRVO but not in those with BRVO.

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DEXAMETHASONE IMPLANTS FOR RETINAL VEIN OCCLUSIONS

Haller JA, Bandello F, Belfort R Jr, et al; for the OZURDEX GENEVA Study Group. **Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion.** *Ophthalmology*. 2010; 117(6):1134–1146.

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The 2 phase 3 GENEVA trials compared the effects of intraocular injections of DEX 0.7 mg or DEX 0.35 mg implants with those of sham injections in patients with macular edema caused by CRVO or BRVO. Since the trials were identical, the pooled results were reported: DEX 0.7 mg group (n=427), DEX 0.35 mg group (n=414), sham group (n=426). Patients were eligible to participate if they had foveal-involved macular edema from a CRVO (1.5 to 9 months) or BRVO (1.5 to 12 months), BCVA of 20/50 to 20/200, and CST ≥300 µm (time domain OCT). Patients were excluded from the studies if they had glaucoma or ocular hypertension that required ≥1 medication. Twice as many BRVO (n=830 with 66%) as CRVO (n=437 with 34%) patients were enrolled.

The design of this study is unusual. In particular, data from the entire population, which combine outcomes for CRVO and BRVO, are difficult to interpret because of differences in the patients' natural histories. Patients with BRVO experience a higher rate of spontaneous improvement in macular edema, lower rates of vitreous hemorrhage and neovascular glaucoma (which can adversely affect visual outcomes), and potential confounding effects from treatment with grid laser. Therefore, the subgroup analyses from these 2 studies provide the information most relevant to patient care.

In the BRVO subgroup at the 6-month primary endpoint, the mean change from baseline BCVA letter score was 7.5 in the 2 DEX implant groups vs. 5.0 in the sham group (P=.008). The percentage of patients who gained ≥15 letters in BCVA was 23% with a 0.7 mg DEX implant, 21% with a 0.35 mg DEX implant, and 20% with sham injections. In the CRVO subgroup, the mean change from baseline BCVA letter score was 0 with a 0.7 mg DEX implant and 2 with a 0.35-mg DEX implant, which did not differ significantly from that of -2 in the sham group. The percentage of patients who gained ≥15 letters in BCVA was 18% with a 0.7 mg DEX implant, 17% with a 0.35 mg DEX implant, and 12% with sham injections—a difference that was not statistically significant. Thus, 6 months after receiving DEX implant injections, patients with BRVO demonstrated little evidence of any benefit, and those with CRVO showed no evidence of any benefit.

Both patient populations did demonstrate some evidence of a benefit at earlier time points, however. Peak effects were observed at 60 days. In the CRVO subgroup, the mean change from baseline BCVA letter score was 9 in the DEX implant 0.7 mg group and 10 in the DEX implant 0.35 mg group, which was significantly better than that of 0 in the sham group. Also at 60 days, 29% and 33% of patients receiving a 0.7 mg DEX implant and a 0.35 mg DEX implant, respectively, gained ≥15 letters in BCVA, compared with 9% with sham injections. At 3 months, the mean change from baseline BCVA letter score was 4 in the DEX implant 0.7 mg group and 6 in the DEX implant 0.35 mg group, which was significantly better than that of 0 in the sham group. Moreover, at 6 months, 18% and 24% of patients treated with a 0.7 mg DEX implant and a 0.35 mg DEX implant, respectively, gained ≥15 letters in BCVA, compared with 10% with sham injections.

At 2 months in the BRVO subgroup, the mean change from baseline BCVA letter score was 10 with DEX implant 0.7 mg and 9 with DEX implant 0.35 mg, which was significantly better than that of 5 in the sham group, Also at 6 months, 30% and 26% of patients in the DEX implant 0.7 mg group and the DEX implant 0.35 mg group, respectively, gained ≥15 letters in BCVA, compared with 13% with sham injections. At 3 months, the mean change from baseline BCVA letter score was 9 in the DEX implant 0.7 mg group and 8 in the DEX

implant 0.35 mg group, which was significantly better than that of 5 in the sham group. Moreover, at 3 months, 24% and 23% of patients treated with DEX implant 0.7 mg and DEX implant 0.35 mg, respectively, gained ≥15 letters in BCVA, compared with 15% with sham injections.

This study showed that 6 months after injection of a DEX implant of 0.35 mg or 0.7 mg, modest benefits were observed in patients with BRVO and no significant benefits were seen in those with CRVO. Because of the shorter-than-anticipated duration of action of DEX implants, it would be useful to know the effect of repeated injections at 3-month intervals. Hopefully, such a trial will be conducted in the future.

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