

# Macular Edema Associated With Retinal Vein Occlusion

Current treatments are associated with vision improvement in only a subset of patients.

BY INGRID U. SCOTT, MD, MPH

**C**entral retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) are common retinal vascular disorders. Branch retinal vein occlusion has been said to be second only to diabetic retinopathy in the frequency with which it produces retinal vascular disease.<sup>1</sup> Macular edema is a frequent cause of visual acuity loss in CRVO and BRVO.<sup>1-4</sup>

In the Central Vein Occlusion Study (CVOS), 728 eyes with CRVO were studied.<sup>2</sup> Of these 728 eyes, 155 (21%) had macular edema reducing visual acuity to 20/50 or worse (group M eyes, macular edema). In the largest group of eyes (group P, perfused) which included 547 eyes, 84% (460 eyes) had angiographic evidence of macular edema involving the fovea at baseline. The natural history of macular edema secondary to CRVO was first delineated in the CVOS.<sup>2-4</sup> The group M arm of the CVOS evaluated the treatment of macular edema in CRVO with grid laser photocoagulation in 155 eyes (77 treated eyes and 78 control eyes) over a 3-year follow-up period. All eyes had macular edema for a minimum of 3 months prior to enrollment.<sup>4</sup> For untreated eyes with an initial visual acuity between 20/50 and 5/200 at presentation (n=78 eyes), 53 eyes were available for follow up at the 2 year visit. Of these eyes, 10 (19%) gained two or more lines of visual acuity at the 2-year follow up. Thirty-one eyes (59%) remained within one line of baseline visual acuity and 12 eyes (22%) lost two or more lines of visual acuity at the 2-year follow-up. The final median visual acuity in untreated eyes was 20/160. The CVOS found no significant difference in visual outcome between the treatment and observation groups at any follow-up point. Although there was a definite

decrease in macular edema on fluorescein angiography in the treatment group when compared to the control group, this did not translate to a direct visual improvement.<sup>4</sup>

The Branch Vein Occlusion Study (BVOS) reported on the natural history of macular edema due to BRVO.<sup>1</sup> All eyes had macular edema for 3 to 18 months prior to study entry; eyes with obvious areas of capillary nonperfusion in the macula were excluded from the study. After 3 years, of 35 untreated eyes available for follow-up, only 12 eyes (34%) with a presenting visual acuity of 20/40 or worse achieved a visual acuity of 20/40 or better. Furthermore, eight eyes (23%) had 20/200 or worse visual acuity at their final 3-year follow-up visit.

The group III arm of the Branch Vein Occlusion Study (BVOS) was designed to evaluate grid photocoagulation treatment of macular edema secondary to BRVO that had persisted for at least 3 months (and less than 18 months), in eyes with visual acuity of 20/40 or worse. One-hundred thirty-nine eyes (71 treated eyes and 68 control eyes) were studied. This arm of the study demonstrated a benefit for eyes treated with macular grid photocoagulation.<sup>1</sup> Of 43 treated eyes available for follow up at the 3-year visit, 28 eyes (65%) had gained two or more lines of visual acuity from baseline and maintained this gain for at least 8 months, as compared with the same gain in 13 of 35 (37%) untreated eyes. At the 3-year visit, nearly twice as large a percentage of treated vs control eyes had visual acuity of 20/40 or better.

Although the BVOS demonstrated a visual acuity benefit for eyes treated with grid photocoagulation, the BVOS also identified a subset of patients who derive lim-

It is important to explore other avenues for managing this common cause of vision loss, and to compare the effectiveness and safety of various treatment options.

ited benefit from macular grid photocoagulation. In the BVOS 40% of treated eyes (n=43) had worse than 20/40 vision at 3 years and 12% of treated eyes had 20/200 or worse visual acuity at 3 years.<sup>1</sup>

The lack of a proven and effective therapy for macular edema secondary to CRVO, the suboptimal outcomes of grid photocoagulation treatment for macular edema secondary to BRVO, and community enthusiasm for intravitreal triamcinolone provided strong rationale for initiating the Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) Study.

The SCORE Study, sponsored by the National Eye Institute (NEI), includes two prospective, randomized controlled clinical trials: one among patients with CRVO (the SCORE-CRVO trial) and one among patients with BRVO (the SCORE-BRVO trial). The trials were designed (1) to determine whether intravitreal triamcinolone acetate at 1-mg and 4-mg doses produces greater visual benefit, with an acceptable safety profile, than standard care for the treatment of vision loss associated with macular edema secondary to retinal vein occlusion, and (2) to compare the efficacy and safety of 1-mg and 4-mg triamcinolone doses. In the SCORE-CRVO trial, standard care consisted of observation; in the SCORE-BRVO trial, standard care consisted of grid photocoagulation in eyes without dense macular hemorrhage and deferral of photocoagulation until hemorrhage clears in eyes with dense macular hemorrhage.

The SCORE-CRVO trial evaluated a CRVO cohort similar to that of the CVOS, except that the SCORE-CRVO cohort had a shorter mean disease duration and larger areas of retinal thickening on color fundus photography.<sup>5</sup> The SCORE-CRVO trial demonstrated that intravitreal injections of triamcinolone acetate were superior to observation for vision loss associated with macular edema secondary to CRVO, and the 1 mg dose of intravitreal triamcinolone had a safety profile superior to that of the 4 mg dose of intravitreal triamcinolone and similar to the observation group.<sup>6</sup> In the SCORE-CRVO trial, the percentages of participants who achieved a gain in visual acuity letter score of 15 or more from baseline to month 12 were 27%, 26%, and 7% in the 1 mg, 4 mg, and observation groups, respectively.<sup>6</sup> Although the SCORE-CRVO trial demonstrated a visual acuity benefit for eyes treated

with intravitreal triamcinolone, among the eyes treated with 1 mg intravitreal triamcinolone, 75% of eyes did not achieve a gain in visual acuity letter score of 15 or more, the mean change in visual acuity from baseline to 12 months was a decrease of one letter, 28 eyes (34%) had 20/200 or worse visual acuity at 12 months, and only 25 (30%) eyes achieved a visual acuity at 12 months of 20/40 or better. Additionally, 50% of eyes still had an optical coherence tomography-measured center point thickness of more than 250  $\mu$ m at 12 months.

In SCORE-BRVO, which included a BRVO study cohort similar to that of the BVOS, intravitreal injections of triamcinolone acetate was not found to be associated with improved visual acuity outcomes compared with grid photocoagulation. The rates of adverse events were highest in the 4 mg triamcinolone group.<sup>7</sup> The rates of adverse events in the 1 mg triamcinolone group were similar, with respect to surgical intervention for cataract and glaucoma, to the laser group, but laser treatment excluded any possibility of injection-related adverse events. The SCORE Study Investigative Group concluded that grid photocoagulation should remain the benchmark against which other treatments are compared in clinical trials for eyes with vision loss associated with macular edema secondary to BRVO.

Currently available treatments for vision loss associated with macular edema secondary to CRVO and BRVO are associated with visual improvement in only a subset of patients. As a result, it is important to explore other avenues for managing this common cause of vision loss, and to compare the effectiveness and safety of various treatment options. ■

*Ingrid U. Scott, MD, MPH, is a Professor of Ophthalmology and Public Health Sciences, Penn State College of Medicine, and is a member of the Retina Today Editorial Board. She may be reached by phone: +1 717 531 4662; fax: +1 717 531 5475; or via e-mail at [iscott@psu.edu](mailto:iscott@psu.edu).*



1. The Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. *Am J Ophthalmol*. 1984;98:271-282.
2. Central Vein Occlusion Study Group. Baseline and early natural history report. The Central Vein Occlusion Study. *Arch Ophthalmol*. 1993;111:1087-1095.
3. The Central Vein Occlusion Study Group. Natural history and clinical management of central retinal vein occlusion. *Arch Ophthalmol*. 1997;115:486-491.
4. The Central Vein Occlusion Study Group. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. The Central Vein Occlusion Study Group M Report. *Ophthalmology*. 1995;102(10):1425-1433.
5. Ip MS, Oden NL, Scott IU, et al. SCORE Study Report 3. Study design and baseline characteristics. *Ophthalmology*. 2009;116:1770-1777.
6. The SCORE Study Research Group. SCORE Study Report 5. 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. *Arch Ophthalmol*. 2009;127:1101-1114.
7. The SCORE Study Research Group. SCORE Study Report 6. 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. *Arch Ophthalmol*. 2009;127:1115-1128.

# Ozurdex Shows Promise for Macular Edema Due to RVO

The intravitreal 700 µg dexamethasone implant (Ozurdex, Allergan, Inc.) was well tolerated and produced substantial improvements in best corrected visual acuity (BCVA) in patients with macular edema due to central or branch retinal vein occlusions, researchers announced. When a second treatment was given by the 6-month visit, visual acuity again improved and edema decreased in some cases in a manner similar to the response to the first treatment, although there was no continuation of sham treatment for comparison, said Anat Loewenstein, MD, who presented 12-month results with the implant at the Macula Society meeting in Tucson, Arizona. Dr. Lowenstein is Chairman of the Department of Ophthalmology, Tel Aviv Sourasky Medical Center, Israel.

Ozurdex received US Food and Drug Administration (FDA) approval in June 2009 for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Ozurdex is a biodegradable implant administered by intravitreal injection that delivers dexamethasone to the vitreous cavity via Allergan's proprietary Novadur solid polymer delivery system, which enables extended release and sustained effects of dexamethasone.

In two identical double-masked studies, patients with macular edema due to CRVO or BRVO (duration 1.5 to 9 months for CRVO, 1.5 to 12 months for BRVO) were randomized to receive Ozurdex 700 µg, Ozurdex 350 µg, or sham treatment. Patients could also receive open-label treatment with Ozurdex 700 µg at 6 months if BCVA was less than 84 letters or retinal thickness as measured by OCT was greater than 250 µm. Patients entering the open-label phase (regardless of whether they were treated at 6 months) were followed for an additional 6 months. At baseline, 427 patients received Ozurdex 700 µg and 426 received sham. At 6 months, 341 patients in the 700-µg group and 327 in the sham

group entered the open-label phase and were treated with Ozurdex 700 µg.

Of patients who received two treatments of Ozurdex 700 µg (n=341), 30% achieved 15 or more letters of improvement 60 days after the first injection and 32% achieved 15 or more letters of improvement 60 days after the second injection (peak response). Among patients who received only a single treatment with Ozurdex 700 µg at the beginning of the study and entered the open-label phase (n=80), 28% gained 15 or more letters at 2 months, 45% at 6 months, and 39% at 1 year. Among patients who received their first treatment at 6 months, 26% achieved 15 or more letters of improvement 2 months after treatment.

"Not all patients had a significant increase in visual acuity, but a large percentage of patients gained more than 15 letters, especially patients who had relatively short duration of macular edema," Dr. Lowenstein said in an interview with *Retina Today*. "Of patients who had macular edema for less than 90 days, especially those with low visual acuity, 50% gained at least 3 lines, or 15 letters at 12 months, which is clinically relevant."

When the 6-month results are compared with the 12-month results after a second injection, the clinical effect at 12 months was less pronounced, Dr. Lowenstein said. However, for patients who have relatively short duration of macular edema secondary to vein occlusion, Ozurdex should be considered a viable treatment option, she said.

Increases in intraocular pressure were generally transient and similar following each treatment. Cataract adverse events occurred in 26% of patients treated with two injections and in 5% of patients who received no treatment over the 12-month study.

Loewenstein A, Haller J, Bandello F, et al. 12-month evaluation of an applicator-delivered dexamethasone intravitreal implant in patients with macular edema due to branch or central retinal vein occlusion. Paper presented at: the 33rd Annual Macula Society Meeting; February 26, 2010; Tucson, AZ.