Point/Counterpoint
Early vs Late Pharmacologic Therapy for RVO

Treatment of Macular Edema Due to RVO: Do Not Delay!

BY NANCY M. HOLEKAMP, MD

For the past 25 years, retina specialists have been taught to observe before treating patients with macular edema (ME) due to retinal vascular occlusive disease (RVO). With no blockbuster treatments available, it made sense: Why not observe, as the patient might get better with time?

A paradigm shift of tectonic proportions, however, occurred at the Retina Congress in the fall of 2009. The results of five randomized, prospective clinical trials of new interventions for the treatment of macular edema due to RVO were presented at that meeting. Four of the five trials had positive results, and we suddenly had the promise of beneficial interventions for macular edema in RVO.

The three industry-sponsored clinical trials led to US Food and Drug Administration (FDA) approval of the intravitreal dexamethasone implant (Ozurdex, Allergan, Inc.) and ranibizumab (Lucentis, Genentech) for treatment of macular edema in RVO (both branch retinal vein occlusion [BRVO] and central retinal vein occlusion [CRVO]) by meeting their respective primary endpoints in the first 6 months of the trials.[1-3] The 6-month data tell us we have effective treatments that appear safe. They do not, however, provide us with guidelines as to the timing of these treatments.

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DATA SHOW EARLY TREATMENT IS BETTER

Recently, 12-month data have become available for these two newly FDA-approved interventions. The 12-month data present a strong argument for early treatment. In the 12-month data for the intravitreal dexamethasone implant clinical trial, patients received either sham or dexamethasone at baseline.[4] At 6 months, all patients were treated with dexamethasone. The drug clearly works, but the sham group never catches up to the eyes that received treatment from the beginning. It appears that delaying dexamethasone implant injection by 6 months has been detrimental to the sham group.

Similarly, Figure 1 shows the 12-month data for the BRAVO clinical trial and Figure 2 shows the 12-month data for the CRUISE clinical trial.[5] At baseline, patients were dosed with either sham or ranibizumab. At 6 months, the sham groups in both trials were crossed over to active treatment with 0.5 mg ranibizumab, but they never caught up to the eyes that received treatment from the beginning. It appears that delaying ranibizumab injections by 6 months has been detrimental to the sham group.

RECOMMENDATIONS FOR TIMING TREATMENT

What do these data tell us? When treating patients

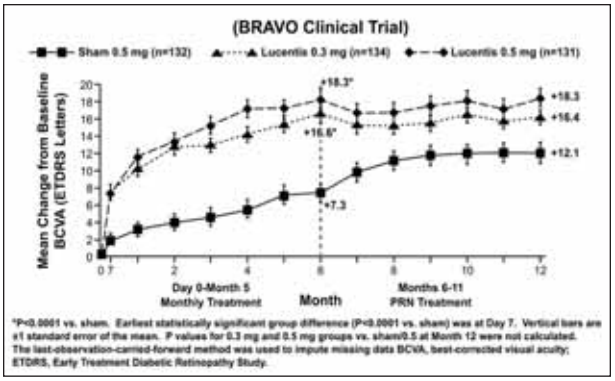

Figure 1. Mean change from baseline best corrected visual acuity (BCVA) over time to month 12.

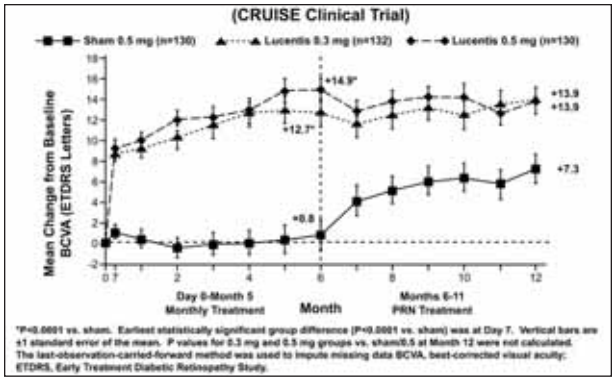

Figure 2. Mean change from baseline BCVA over time to month 12.

with macular edema due to RVO, do not delay! One caveat exists: In the BRVO trials there were a substantial proportion of patients who did well with observation (with or without grid laser). Perhaps an analysis of the intravitreal dexamethasone implant for BRVO and BRAVO clinical trials will identify these BRVO patients so that retina specialists will know whom not to treat. For the rest, however, there is good evidence that treatment should not be delayed.

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1. Haller JA, Blumenkranz MS, Bandello F, et al. Six-month randomized controlled clinical trial of an intravitreal dexamethasone implant in macular edema associated with retinal vein occlusion. Paper presented at: Retina Congress 2009; October 4, 2009; New York, NY.
2. Campochiaro P, Heier J, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology.* 2010;117(6):1102-1112.
3. Brown D, Campochiaro P, Singh R, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology.* 2010;117(6):1124-1133.
4. 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.
5. Ho A, Gray S, Rundle A, et al. Ranibizumab in patients with macular edema following retinal vein occlusion: 12-month outcomes of BRAVO and CRUISE. Poster presented at: the Association for Research in Vision and Ophthalmology; May 2-6, 2010; Fort Lauderdale, FL.

Natural History of RVO Should Guide Treatment

BY MICHAEL S. IP, MD

The timing of initiation of pharmacotherapy for retinal venous occlusive disease should be guided, in part, by the natural course of the disease. In a disease such as branch retinal vein occlusion (BRVO), the natural course is often one of improvement, whether the patient is observed initially, or if laser photocoagulation is delayed by several months.

DATA FOR BRVO SUPPORTS DELAY

This has been demonstrated by data from the BRAVO study in which there was a mean gain in visual acuity letter score of 7.3 from baseline to 6 months in the sham group.[1] Thus, in eyes with a BRVO, immediate reduction in macular edema with a pharmacotherapy such as an anti-vascular endothelial growth factor (anti-VEGF) agent does not need to be performed immediately. There is no evidence that a delay of a few months is ultimately detrimental to visual acuity.

Furthermore, grid photocoagulation is an effective and safe therapy proven to work over the natural history in the BVOS (Branch Vein Occlusion Study)[2] and appearing to be better than the natural history in the SCORE Study.[3] Thus, the combination of a natural course that is often characterized by gradual improvement and the availability of an effective treatment that is safer than repeated intravitreal injections suggests that grid photocoagulation should be considered as a first-line therapy in many patients who present with a BRVO. If a patient has

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an inadequate response to laser then, intravitreal pharmacotherapy can be considered.

CRVO CAN BENEFIT FROM EARLY THERAPY

A central retinal vein occlusion (CRVO) is a different ocular condition than a BRVO. The natural course of this disease is often poor. After 6 months of sham therapy in the CRUISE study most patients did not gain any visual acuity.[4] In the SCORE study there was a mean loss of 12 letters from baseline to month 12.[5] Thus, the poor natural course of CRVO, in distinction to the natural course of BRVO, supports early intervention with a pharmacotherapy at presentation. As there is no laser option, the first-line therapy for vision loss associated with macular edema from a CRVO should be consideration of immediate pharmacotherapy with either ranibizumab (Lucentis, Genentech) or a corticosteroid (intravitreal dexamethasone implant; Ozurdex, Allergan, Inc.). Both treatment modalities have level 1 evidence to support their use (CRUISE, SCORE, intravitreal dexamethasone implant study).[6] ■

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1. Campochiaro P, Heier J, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology.* 2010;117(6):1102-1112.
2. The Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. *Am J Ophthalmol.* 1984;98:271-282.
3. 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.
4. Brown D, Campochiaro P, Singh R, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology.* 2010;117(6):1124-1133.
5. 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.
6. Haller JA, Blumenkranz MS, Bandello F, et al. Six-month randomized controlled clinical trial of an intravitreal dexamethasone implant in macular edema associated with retinal vein occlusion. Paper presented at: Retina Congress 2009; October 4, 2009; New York, NY.