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Individualized Stabilization Criteria–Driven Ranibizumab versus Laser in Branch Retinal Vein Occlusion

Six-Month Results of BRIGHTER

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Purpose: To compare the 6-month efficacy and safety profile of an individualized stabilization criteria–driven pro re nata (PRN) regimen of ranibizumab 0.5 mg with or without laser versus laser alone in patients with visual impairment due to macular edema secondary to branch retinal vein occlusion (BRVO).

Design: A 24-month, prospective, open-label, randomized, active-controlled, multicenter, phase IIIb study.

Participants: A total of 455 patients.

Methods: Eligible patients were randomized 2:2:1 to receive ranibizumab (n = 183), ranibizumab with laser (n = 180), or laser only (n = 92). Patients treated with ranibizumab with or without laser received a minimum of 3 initial monthly ranibizumab injections until visual acuity (VA) stabilization, and VA-based PRN dosing thereafter. In the ranibizumab with laser and laser-only groups, laser was given at the investigator's discretion at a minimum interval of 4 months and if VA was <79 letters.

Main Outcome Measures: Mean change from baseline at month 6 in best-corrected visual acuity (BCVA) (primary end point) and central subfield thickness, and safety over 6 months. Exploratory objectives were to evaluate the influence of baseline BCVA, disease duration, and ischemia on BCVA outcomes at month 6.

Results: Baseline mean BCVA was 57.7 letters, and mean BRVO duration was 9.9 months. Ranibizumab with or without laser was superior to laser only in improving mean BCVA from baseline at month 6 (14.8 and 14.8 vs. 6.0 letters; both $P < 0.0001$; primary end point met). Patients with a shorter BRVO duration at baseline had a higher mean BCVA gain than those with a longer BRVO duration. Patients with a poor baseline VA had a better BCVA gain than those with a higher baseline VA, although final BCVA was lower in those with poor baseline VA. In the ranibizumab with or without laser groups, the presence of some macular ischemia at baseline did not influence mean BCVA gains. There were no new ocular or nonocular safety events.

Conclusions: Ranibizumab with an individualized VA-based regimen, with or without laser, showed statistically significant superior improvement in BCVA compared with laser alone in patients with BRVO. Overall, there were no new safety events other than those reported in previous studies. *Ophthalmology 2016;123:1332-1344*

*Supplemental material is available at www.aaojournal.org.

Anti–vascular endothelial growth factor (VEGF) treatment is the current standard of care for macular edema secondary to branch retinal vein occlusion (BRVO).[1] Ranibizumab 0.5 mg was approved by the US Food and Drug Administration in June 2010 and by the European Union in 2011 for the treatment of visual impairment due to macular edema secondary to BRVO, based on the 6-month results of a phase III, randomized, double-masked, controlled study, the BRAnch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO) trial, using a fixed monthly injection regimen in the first 6 months.[2]

The BRIGHTER study (group members of this study are cited in Appendix 1, available at www.aaojournal.org) was a phase IIIb, multicenter study assessing the efficacy and safety profile of an individualized stabilization criteria–driven pro re nata (PRN) dosing regimen of ranibizumab 0.5 mg alone or in combination with laser versus laser photocoagulation in patients with visual impairment due to macular edema secondary to BRVO.

This study is being conducted to show that the stabilization criteria–driven PRN dosing regimen of ranibizumab 0.5 mg, as approved in the European Union,[3] with or without

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adjunctive laser has efficacy similar to the monthly dosing regimen that was assessed in the BRAVO study.[2]

The BRAVO study was the first prospective 12-month, randomized, sham-controlled, multicenter study that demonstrated the effectiveness of ranibizumab in managing patients with macular edema secondary to BRVO. The improvements in best-corrected visual acuity (BCVA) and central foveal thickness (CFT) observed with a monthly dosing of ranibizumab 0.5 mg in the first 6 months (baseline to month 5; at month 6, mean change in BCVA: +18.3 letters [primary end point] and mean change in CFT: −345.2 μm)[2] were largely maintained with a PRN dosing regimen and monthly monitoring until month 12 (mean change in BCVA: +18.3 letters and mean change in CFT: −347.4 μm).[4]

The HORIZON study (cohort 2; ClinicalTrials.gov identifier: NCT00379795) was a 1-year, open-label extension of the BRAVO and Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein OcclUslon Study: Evaluation of Efficacy and Safety (CRUISE) studies. In this study, it was observed that the gains in BCVA achieved at the end of 12 months in the BRAVO and CRUISE studies were maintained for an additional 12 months with a PRN dosing regimen and with less frequent monitoring. A total of 60.3% of patients gained ≥15 letters in the HORIZON study (similar to 60.3% at month 12 in the BRAVO study).[5,6]

The BRIGHTER study is designed to address the following questions to aid physicians in optimizing treatment for patients with BRVO: (1) provide long-term data on the efficacy and safety of the individualized visual acuity (VA) stabilization criteria−driven PRN dosing regimen of ranibizumab 0.5 mg in a broad patient population with BRVO, including those with macular ischemia; and (2) the impact of adjunct laser treatment on BCVA outcome and the number of ranibizumab injections required. Here, we report the 6-month primary and main secondary outcomes from the 24-month BRIGHTER study (Group members of this study are cited in Appendix 1, available at www.aaojournal.org).

Methods

Study Design

The BRIGHTER study was a 24-month, phase IIIb, randomized, open-label, active-controlled, 3-arm, multicenter study assessing the efficacy and safety profile of an individualized stabilization criteria−driven PRN dosing regimen of ranibizumab 0.5 mg with or without laser versus laser alone in patients with visual impairment due to macular edema secondary to BRVO. The study is being conducted across 17 countries worldwide (Appendix 2, available at www.aaojournal.org). The study started in May 2012 and was completed in 2015. The first 6 months of the BRIGHTER study were conducted from May 2012 and November 2015 and included recruitment and all the other steps.

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was reviewed and approved by an independent ethics committee or institutional review board at each contributing center. Patients provided written informed consent before entering the study. The study is registered with Clinicaltrials.gov as NCT01599650.

Patients

The study population consisted of patients aged ≥18 years with visual impairment due to macular edema secondary to BRVO. The key inclusion criteria included a BCVA letter score at screening and baseline between 73 and 19 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, inclusive (approximate Snellen equivalent of 20/40 and 20/400).

The key exclusion criteria included stroke or myocardial infarction <3 months before screening; uncontrolled blood pressure (>160/>100 mmHg) at screening or baseline; periocular or ocular infection or inflammation at screening or baseline; intravitreal anti-VEGF injections ≤3 months before baseline and systemic anti-VEGF injections ≤6 months before baseline; uncontrolled glaucoma (intraocular pressure ≥30 mmHg on medication or according to the investigator's judgment) at the time of screening or baseline or diagnosed within 6 months before baseline; laser photocoagulation for macular edema ≤4 months before baseline; intraocular or periocular corticosteroid use ≤3 months before baseline; and known hypersensitivity to ranibizumab or any component of the ranibizumab formulation or fluorescein. In addition, pregnant or nursing women were excluded from the study (inclusion and exclusion criteria are listed in Appendix 3, available at www.aaojournal.org).

Randomization and Treatment

At enrollment, eligible patients were randomized in a 2:2:1 ratio to receive ranibizumab 0.5 mg, ranibizumab 0.5 mg with laser, or laser alone. The randomization list was generated using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization was balanced across the sites. Although this was an open-label study, the vision examiner who assessed the BCVA outcomes was masked and not allowed to perform any additional study tasks that would have unmasked him or her to study treatment.

In the ranibizumab with or without laser groups, ranibizumab 0.5 mg was administered as recommended in the European Union Summary of Product Characteristics (2012).[7] Patients received ranibizumab 0.5 mg injections on day 1, followed by initial monthly injections until the study eye's VA was stable (based on the judgment of the investigator) for at least 3 consecutive months; by design, at least 3 initial injections were required[8] (Fig 1, available at www.aaojournal.org). Once VA was stable, ranibizumab treatment was temporarily discontinued at the investigator's discretion. In the ranibizumab with laser and laser-only groups, patients were treated with laser as soon as indicated by the investigator. When ranibizumab and laser were to be administered on the same day to the study eye, the laser treatment was applied ≥30 minutes before the ranibizumab injection.

Maintenance and Re-treatment

All patients were monitored monthly for VA and disease activity. If there was a loss of VA due to disease activity as judged by the investigator, monthly ranibizumab injections were again administered to the patients in the ranibizumab with or without laser groups until stability was achieved for 3 consecutive months; this required at least 2 consecutive injections.[8] In the ranibizumab with laser and laser-only groups, patients were re-treated with laser at the investigator's discretion at minimum intervals of 4 months in the presence of macular edema secondary to BRVO, as long as the BCVA was <79 letters.

In all 3 groups, the last possible treatment was administered at month 5, and the last assessment was performed at month 6 for