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Sustained Benefits of Ranibizumab with or without Laser in Branch Retinal Vein Occlusion

24-Month Results of the BRIGHTER Study

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Purpose: To evaluate the long-term (24-month) efficacy and safety of ranibizumab 0.5 mg administered pro re nata (PRN) with or without laser using an individualized visual acuity (VA) stabilization criteria in patients with visual impairment due to macular edema secondary to branch retinal vein occlusion (BRVO).

Design: Phase IIIb, open-label, randomized, active-controlled, 3-arm, multicenter study.

Participants: A total of 455 patients.

Methods: Patients were randomized (2:2:1) to ranibizumab 0.5 mg (n = 183), ranibizumab 0.5 mg with laser (n = 180), or laser (with optional ranibizumab 0.5 mg after month 6; n = 92). After initial 3 monthly injections, patients in the ranibizumab with or without laser arms received VA stabilization criteria-driven PRN treatment. Patients assigned to the laser arm received laser at the investigator's discretion.

Main Outcome Measures: Mean (and mean average) change in best-corrected visual acuity (BCVA) and central subfield thickness (CSFT) from baseline to month 24, and safety over 24 months.

Results: A total of 380 patients (83.5%) completed the study. Ranibizumab with or without laser led to superior BCVA outcomes versus laser (monotherapy and combined with ranibizumab from month 6; 17.3/15.5 vs. 11.6 letters; $P < 0.0001$). Ranibizumab with laser was noninferior to ranibizumab monotherapy (mean average BCVA change: 15.4 vs. 15.0 letters; $P < 0.0001$). However, addition of laser did not reduce the number of ranibizumab injections (mean injections: 11.4 vs. 11.3; $P = 0.4259$). A greater reduction in CSFT was seen with ranibizumab with or without laser versus laser monotherapy over 24 months from baseline (ranibizumab monotherapy −224.7 μm, ranibizumab with laser −248.9 μm, laser [monotherapy and combined with ranibizumab from month 6] −197.5 μm). Presence of macular ischemia did not affect BCVA outcome or treatment frequency. There were no reports of neovascular glaucoma or iris neovascularization. No new safety signals were identified.

Conclusions: The BRIGHTER study results confirmed the long-term efficacy and safety profile of PRN dosing driven by individualized VA stabilization criteria using ranibizumab 0.5 mg in patients with BRVO. Addition of laser did not lead to better functional outcomes or lower treatment need. The safety results were consistent with the well-established safety profile of ranibizumab. *Ophthalmology 2017;■:1−10 © 2017 American Academy of Ophthalmology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Branch retinal vein occlusion (BRVO) is one of the most common retinal vascular diseases and affects approximately 0.4% of the population worldwide.[1] Primary treatment options for BRVO include anti-vascular endothelial growth factor agents as monotherapy or in combination with laser.[2] Ranibizumab, an anti-vascular endothelial growth factor antibody fragment, has a well-established efficacy and safety profile, and is approved for several retinal conditions, including the treatment of visual impairment due to macular edema secondary to BRVO and central retinal vein occlusion.[3–5]

The BRIGHTER study (NCT01599650) evaluated the long-term efficacy and safety profile of ranibizumab 0.5 mg in a broad population of patients with BRVO, including those with retinal ischemia. The study was conducted (1) to provide data on long-term efficacy and safety of an individualized visual acuity (VA) stabilization criteria-driven pro re nata (PRN) dosing regimen of ranibizumab 0.5 mg with or without laser versus laser and (2) to evaluate the impact of adjunct laser treatment on VA outcome and the number of ranibizumab injections required.[6,7] Six-month results of the BRIGHTER study demonstrated superiority

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of ranibizumab 0.5 mg with or without laser compared with laser in improving best-corrected VA (BCVA), irrespective of the baseline macular ischemia status or disease duration.[7] We report the 24-month results of the BRIGHTER study.

Methods

Detailed materials and methods have been described by Tadayoni et al.[7] We report a brief summary.

Study Design

BRIGHTER was a 24-month, phase IIIb, randomized, open-label, active-controlled, 3-arm, multicenter study. It enrolled patients with BRVO from 17 countries worldwide. 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.

Patients

The detailed inclusion and exclusion criteria have been described by Tadayoni et al.[7] Briefly, the study included treatment-naïve patients aged ≥18 years with visual impairment due to macular edema secondary to BRVO and a BCVA letter score at screening and baseline between 73 and 19 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (approximate Snellen chart equivalent of 20/40 and 20/400).

Randomization and Treatment

All eligible patients were randomly assigned (2:2:1) to receive ranibizumab 0.5 mg (ranibizumab monotherapy), ranibizumab 0.5 mg with laser (ranibizumab + laser), or laser (laser monotherapy).

Visual acuity was the primary trigger of re-treatment; and a decrease of VA associated with disease activity (detected on optical coherence tomography [OCT] or by any other means) warranted re-treatment.

According to the treatment protocol, patients were to receive monthly ranibizumab treatment until the study eye's VA was stable for 3 consecutive monthly assessments (this implies a minimum of 3 injections given at monthly intervals from baseline). Once VA did not change after the last monthly treatment during the initial monthly treatment period or during any period of re-treatments (i.e., was stable), the next re-treatment was warranted only when VA decrease and the decrease was due to disease activity in the opinion of the investigator.

There were 2 treatment periods in the study: treatment period 1 (day 1 to month 6) and treatment period 2 (months 6–23).

In treatment period 1, patients from the ranibizumab monotherapy and ranibizumab + laser arms received individualized, stabilization criteria-driven, PRN ranibizumab 0.5 mg (as recommended in the European Summary of Product Characteristics 2012).[5] After injection on day 1, monthly treatment was continued until BCVA was stable (i.e., no change in BCVA for at least 3 consecutive months). If BCVA stability was achieved, ranibizumab treatment was temporarily discontinued and monthly monitoring was continued until BCVA loss due to disease activity warranted re-treatment with ranibizumab (PRN treatment). Patients in the ranibizumab + laser and laser monotherapy arms were treated with laser (at investigators' discretion) as soon as macular edema was observed. The minimum interval between laser applications was 4 months, and patients were not treated with laser if BCVA was ≥79 letters or dense macular hemorrhage was present.

In treatment period 2, PRN treatment was continued with a possibility to reduce the frequency of monitoring from month 12. Patients in the ranibizumab monotherapy and ranibizumab + laser arms continued to receive individualized, stabilization criteria-driven PRN ranibizumab 0.5 mg. Patients in the laser monotherapy arm continued to receive laser therapy PRN; however, from month 6, these patients were eligible to receive ranibizumab PRN in addition if visual impairment due to macular edema was present (laser + ranibizumab from month 6 arm).

Study Objectives

The study objectives included evaluating efficacy of the individualized, stabilization criteria-driven PRN ranibizumab 0.5 mg with or without laser assessed by the (a) mean change in BCVA from baseline to months 12 and 24; (b) proportion of patients with BCVA gain of ≥5, ≥10, ≥15, and ≥30 letters up to month 24; and proportion of patients with a BCVA value ≥73 letters (20/40 Snellen equivalent) from baseline to month 24; (c) mean change in Central Reading Center (CRC)–assessed central subfield thickness (CSFT) from baseline to month 24; and (d) evaluation of safety. The details of other secondary and exploratory study objectives reported in this article can be found on clinicaltrials.gov and are listed in Appendix 2 (available at www.aaojournal.org).[6] One of the key exploratory objectives was to evaluate the potential to skip visits from months 12 to 24 in patients with persistent VA stabilization in the absence of disease activity by assessing the proportion of patients who successfully skipped at least 1 visit and the number of successfully and unsuccessfully skipped visits.

Efficacy and Safety Assessments

Efficacy Assessments. Certified vision examiners assessed BCVA at every study visit by using ETDRS VA testing charts at an initial testing distance of 4 m. The vision examiner, who assessed parameters constituting the primary end point (BCVA), was masked to study treatment to avoid assessment bias. The OCT was performed by certified site personnel at the study sites at each visit using only spectral-domain OCT equipment, and images were forwarded to the CRC for independent analysis and storage. Throughout the study, patients were assessed using the same equipment. Retinal ischemia was assessed at baseline and months 3, 12, and 24 using fluorescein angiography in conjunction with 7-field color fundus photography, performed by certified operators at the site. We present the results of CRC-assessed macular ischemia, defined as present if the CRC scored retinal capillary loss or nonperfusion as mild, moderate, severe, or completely destroyed in ≥1 location of the center, inner, or outer subfields of the ETDRS grid as described in detail previously.[8]

Treatment Exposure. Data were collected for the number of ranibizumab 0.5 mg injections or laser administered in study eye over 24 months. After month 12, investigators were allowed to extend the interval between monitoring visits to 2 months (skipped visit). The number and outcomes of skipped visits was assessed.

Safety Assessments. At each visit over 24 months, data were collected for adverse events (AEs), serious AEs (SAEs), and their frequency, severity, and relationship to the study drug or ocular injection procedure.

Statistical Analysis

A sample size of 180 patients per arm,[7] while accounting for an approximately 10% dropout rate, had >92.1% power to establish (with a 1-sided α-level of 0.025) noninferiority of ranibizumab + laser compared with ranibizumab monotherapy for mean average