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Monthly Versus As-Needed Ranibizumab Injections in Patients with Retinal Vein Occlusion

The SHORE Study

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Objective: To compare pro re nata (PRN) and monthly injections of 0.5 mg ranibizumab in retinal vein occlusion (RVO) patients stabilized by monthly injections.

Design: Randomized, open-label, vision-examiner masked, 15-month study.

Participants: Subjects with macular edema secondary to branch or central RVO.

Methods: Subjects received monthly injections of 0.5 mg ranibizumab for 7 months and those meeting stability criteria between months 7 and 14 were randomized (1:1) to PRN injections versus continued monthly injections. Non-randomized (NR) subjects (never met stability criteria) received monthly injections.

Main Outcome Measures: The primary endpoint was the slope of change in best-corrected visual acuity (BCVA) between months 7 and 15.

Results: There was no significant difference in the slope of change in BCVA between months 7 and 15 in patients treated PRN versus those treated with monthly injections ($P = 0.509$). Mean (± standard deviation) change from baseline BCVA in Early Treatment Diabetic Retinopathy Study letter score at month 15 was 21.0±14.1 in the PRN group (n = 82) versus 18.7±14.1 in the monthly group (n = 80) and 14.5±14.7 in NR subjects (n = 13). The percentage of subjects who achieved BCVA ≥20/40 at month 15 was 76.8% in the PRN group, 71.3% in the monthly group, and 46.2% in NR subjects. The mean (± standard deviation) change from baseline central subfield thickness was −247.8±207.5 μm in the PRN group, −289.9±177.2 μm in the monthly group, and −93.2±225.2 μm in NR subjects. There were no significant differences in mean BCVA gains or central subfield thickness reductions at month 15 between the PRN and monthly injection groups (all > 0.05).

Conclusions: After edema resolution from 7 or more monthly ranibizumab injections in RVO subjects, visual outcomes at month 15 were excellent and not significantly different in subjects treated PRN versus those who continued monthly injections. *Ophthalmology 2014;■:1–11 © 2014 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

Retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy. Each year in the United States, there are approximately 30 000 new cases of central RVO (CRVO), in which the central retinal vein is occluded, and 150 000 new cases of branch RVO (BRVO), in which one of the major branches of the central retinal vein is occluded.[1] There is an increase in intraluminal pressure behind the obstruction that leads to variable amounts of reduced perfusion and retinal ischemia, which seems to be dependent on the amount of preexisting arterial disease. In ischemic retina, there is stabilization of hypoxia-inducible factor-1, leading to increased transcription of hypoxia-regulated genes including *vascular endothelial growth factor-A (VEGFA)*.[2]

The development of ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA), a monoclonal Fab fragment designed for ocular use that specifically binds all active isoforms of vascular endothelial growth factor (VEGF),[3] made it possible to test the effect of neutralizing VEGF in patients with RVO, and even in a small trial, it was clear that VEGF is a major contributor to macular edema.[4] This has been confirmed by 2 late-stage clinical trials: the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO)[5] study

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and the Treatment of Macular Edema following Central Retinal Vein Occlusion: Evaluation of Efficacy and Safety (CRUISE) study.[6]

In BRAVO, monthly injections of 0.3 or 0.5 mg ranibizumab for 6 months resulted in mean best-corrected visual acuity (BCVA) gains from baseline in Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 16.6 and 18.3, respectively, compared with a 7.3-letter gain in the sham injection group.[5] In CRUISE, at the month 6 primary end point, there was a mean improvement from baseline in BCVA ETDRS letter score of 12.7 (0.3 mg) and 14.9 (0.5 mg) versus 0.8 (sham).[6] After month 6, patients received injections of ranibizumab only if they had BCVA of 20/40 or worse or central foveal thickness of 250 μm or more on time-domain optical coherence tomography (OCT) while being administered a pro re nata (PRN) regimen. Change in BCVA between months 6 and 7 was −2.8 letters in BRVO patients who had not received an injection at month 6 versus +0.4 letter in those who had received an injection (Fig 1, available at www.aaojournal.org). In CRVO patients, the mean BCVA change was −7.2 letters in those who had not received an injection versus +1.7 in patients who had received an injection.

In both BRAVO and CRUISE, the 0.3-mg and 0.5-mg treatment groups each showed a substantial decrease in mean BCVA between months 6 and 7. This occurred to a greater extent in CRVO patients of CRUISE, and there was gradual improvement thereafter using the PRN regimen. There was no significant difference in mean BCVA between months 6 and 12 in any of the treatment groups.[7,8] However, the initial decline in BCVA after instituting PRN therapy raised questions as to whether visual outcomes at 1 year could have been even better if patients had continued to receive monthly injections during the second 6 months, and whether providing additional monthly injections before a PRN regimen could eliminate this initial loss in visual acuity (VA). To address these questions, the Food and Drug Administration requested a phase 4 study to compare continued monthly injections of ranibizumab versus PRN injections for macular edema in patients with RVO who achieve edema resolution and stable vision at some visit between months 7 and 14, with the primary end point at month 15. Herein we report the results of that study.

Methods

Study Design

The Study Evaluating Dosing Regimens for Treatment with Intravitreal Ranibizumab Injections in Subjects with Macular Edema following Retinal Vein Occlusion (SHORE) was a 15-month, phase 4, multicenter, randomized trial in which 202 patients with BRVO (including hemicentral RVO) or CRVO were enrolled. The primary objective was to compare the efficacy and safety of monthly versus PRN injections of 0.5 mg ranibizumab in patients who had received at least 7 injections 1 month apart and met VA and spectral-domain (SD) OCT stability criteria at some visit between months 7 and 14. The primary end point was at month 15 and the primary efficacy outcome measure was the slope of change from baseline in BCVA in ETDRS letter score from month 7 through month 15 (during the alternate-dose period of monthly vs. PRN treatment). Secondary outcome measures included the proportion of subjects who gained 15 letters or more from baseline, the proportion of subjects with BCVA of 20/40 or better, the mean change from baseline in BCVA letter score, the proportion of subjects who lost fewer than 15 letters from baseline, VA change from the previous month in patients who met the VA and SD OCT stability criteria, and the proportion of subjects with intraretinal edema. Ocular and systemic adverse events (AEs) were coded by Medical Dictionary for Regulatory Activities (MedDRA) version 15.1. The study design consisted of a fixed-dose period (ranibizumab 0.5 mg/month) between baseline and month 6 (Fig 2, available at www.aaojournal.org), followed by an alternate-dose period (monthly vs. PRN dosing) between months 7 and 15. The study was open label, with masking of VA examiners, and was registered at www.clinicaltrials.gov (identifier NCT01277302; accessed October 21, 2013). The protocol was approved by the institutional review board at each study site, and the study was conducted according to the International Conference on Harmonisation E6 Guideline for Good Clinical Practice and any national requirements. All patients provided informed consent before participation in the study.

Patients

Eligible patients were 18 years of age or older with macular edema involving the foveal center after BRVO or CRVO diagnosed within 12 months of screening, study eye Snellen-equivalent BCVA of 20/40 to 20/320, and mean central subfield thickness (CST) of more than 300 μm on 2 SD OCT measurements obtained on different days. Patients were not eligible if they had previously received any anti-VEGF treatment in the study eye or had a brisk afferent pupil defect, age-related macular degeneration of more than stage 1 on the Age-Related Eye Disease Study severity score, a history of focal laser within 4 months, or a history of a cerebral vascular accident or myocardial infarction within 3 months. Patients were seen every month for measurement of BCVA, a complete eye examination, SD OCT, measurement of vital signs, safety assessments, and review of medical history (including concomitant medications and concurrent ocular procedures).

Randomization

At each visit between months 7 and 14, patients were assessed for VA and SD OCT stability. The criteria for VA stability were met when BCVA showed no improvement or worsening by an amount determined by the previous month's BCVA. Because of increased variability in measuring BCVA with worsening vision, the specified range for stabilization widened with poorer vision. When letter score in the previous month was more than 50 (approximately 20/100), more than 35 (approximately 20/200) to 50 or less (approximately 20/100), or 35 or less (approximately 20/200), meeting stability criteria required a change, either positive or negative, in BCVA letter score from the prior month of less than 5 letters, less than 10 letters, or less than 15 letters, respectively. The stability criteria for SD OCT were met if there was no disease activity, defined by absence of edema, thickening, intraretinal fluid, intraretinal cysts, or subretinal fluid as determined by the clinical investigator. Patients who met VA and OCT stability criteria at month 7 were randomized to monthly or PRN dosing (did not receive an injection at month 7) and were reassessed for VA and OCT stability at each subsequent visit. At subsequent visits, patients in the monthly arm received an injection regardless of whether they met stability criteria, whereas patients in the PRN arm received an injection of ranibizumab only if VA and OCT stability criteria were not met. Patients who were not randomized at month 7 were randomized at the first subsequent visit at which they met VA and OCT stability criteria. Randomization was stratified by the