American Academy of Ophthalmology
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Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion

52-Week Results of the VIBRANT Study

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Purpose: To determine week 52 efficacy and safety outcomes in eyes with macular edema after branch retinal vein occlusion (BRVO) treated with 2 mg intravitreal aflibercept injection (IAI) compared with grid laser.

Design: VIBRANT was a double-masked, randomized, phase 3 trial.

Participants: Eyes randomized and treated in VIBRANT were followed to week 52.

Methods: In the IAI group, eyes received IAI every 4 weeks through week 24 and IAI every 8 weeks through week 48 with rescue grid laser if needed at week 36. In the grid laser group, all eyes received grid laser at baseline and, if prespecified rescue criteria were met, 1 additional laser from week 12 to 20 and IAI every 8 weeks after 3 monthly doses from week 24 onward (the laser/IAI group).

Main Outcome Measures: The primary outcome measure was percentage of eyes with improvement from baseline best-corrected visual acuity (BCVA) letter score $\geq$15 at week 24. All outcome measures at week 52 were exploratory, and *P* values are considered nominal.

Results: The percentage of eyes with improvement from baseline letter score $\geq$15 in the IAI and laser/IAI groups was 52.7% versus 26.7% ($P = 0.0003$) at week 24 and 57.1% versus 41.1% ($P = 0.0296$) at week 52. The corresponding mean change from baseline BCVA letter score was 17.0 versus 6.9 ($P < 0.0001$) at week 24 and 17.1 versus 12.2 ($P = 0.0035$) at week 52. The mean reduction from baseline central retinal thickness was 280.5 μm versus 128.0 μm ($P < 0.0001$) at week 24 and 283.9 μm versus 249.3 μm ($P = 0.0218$) at week 52. In the IAI group, 10.6% of eyes received rescue laser at week 36, and in the laser/IAI group, 80.7% received rescue IAI from week 24 to week 48. Traumatic cataract in 1 eye (1.1%) in the IAI group was the only ocular serious adverse event.

Conclusions: After 6 monthly IAI, injections every 8 weeks maintained control of macular edema and visual benefits through week 52. In the laser group, rescue IAI given from week 24 onward resulted in substantial visual improvements at week 52. *Ophthalmology 2015;■:1–7 © 2015 by the American Academy of Ophthalmology.*

Retinal vein occlusion is, after diabetic retinopathy, the most prevalent vision-threatening retinal vasculopathy.[1,2] Retinal vein occlusion can be categorized on the basis of the location of the luminal obstruction of the venous outflow system within the retinal vasculature.[3] In central retinal vein occlusion, blockage of the central retinal vein within the optic nerve causes involvement of the entire retina. Hemiretinal vein occlusion and branch retinal vein occlusion (BRVO) are alike in that obstruction occurs after the primary ramification of the central retinal vein at the optic nerve head, but differ in the relative involvement of downstream retina: the earlier in the venous vasculature obstruction occurs, the larger the retinal area affected by retinal vein occlusion.[3]

The pathophysiology of BRVO involves increased hydrostatic pressure within thin-walled veins proximal to a luminal obstruction.[2] This resistance to outflow causes hypoxia and consequently upregulation of vascular endothelial growth factor (VEGF), which promotes plasma exudation and formation of macular edema.[2] In addition, VEGF may participate in a feedback loop that, in some patients, causes progressive retinal ischemia.[4] In patients with BRVO, the vitreous level of VEGF significantly correlates with the severity of macular edema.[5] The most common cause of vision loss in patients with BRVO is macular edema.[6]

Several different strategies have been investigated for the treatment of macular edema after BRVO. Macular laser photocoagulation was the first treatment demonstrated to be effective in improving vision in the Branch Vein Occlusion Study.[7] Subsequent to the Branch Vein Occlusion Study, the Standard Care versus Corticosteroid for Retinal Vein Occlusion trial showed no treatment benefit for intravitreal triamcinolone versus laser in that protocol, with higher rates of ocular adverse events (AEs) in patients treated with triamcinolone.[8] Another corticosteroid, dexamethasone, formulated in an extended-delivery

http://dx.doi.org/10.1016/j.ophtha.2015.09.035
ISSN 0161-6420/15

system, was approved by the Food and Drug Administration in 2009 for macular edema due to retinal vein occlusion on the basis of trials demonstrating significantly greater improvement in vision and reduction in edema compared with sham when dosed at 6-month intervals, with an apparently more favorable safety profile than seen with triamcinolone, although not directly compared.[9,10] Finally, surgical arteriovenous sheathotomy has been reported anecdotally to benefit selected patients with macular edema after BRVO, but to date, no large randomized trials have been completed to support its widespread use.[11–13]

Both ranibizumab[14] (Lucentis; Genentech, South San Francisco, CA) and intravitreal aflibercept (Eylea; Regeneron Pharmaceuticals, Inc. Tarrytown, NY),[15] also known in the scientific literature as "VEGF Trap-Eye," have been demonstrated to be effective in treating vision loss associated with macular edema after BRVO. In the BRAVO trial,[14] monthly ranibizumab was compared with sham injection for macular edema after BRVO. Eyes treated with monthly 0.5 mg ranibizumab gained 18.3 letters, compared with 7.3 letters in the sham group.[14] These patients were then followed in the HORIZON study,[16] an open-label study to monitor safety and long-term treatment benefits. Overall, 76.6% of patients who participated in BRAVO were enrolled in the HORIZON study and were followed for another 12 months. Eyes received approximately 2 injections during HORIZON and demonstrated stabilization of visual gains seen in BRAVO.[16]

Aflibercept is a 115 kDA soluble receptor fusion protein that was shown in preclinical studies to have a higher affinity than bevacizumab or ranibizumab for VEGF.[17] Pharmacokinetic modeling suggests that intravitreal aflibercept may have a longer biologic effect than other agents that target VEGF.[18] Intravitreal aflibercept has been shown to be effective in the treatment of vision loss related to age-related macular degeneration,[19] macular edema after central retinal vein occlusion,[20] diabetic macular edema,[21] and myopic choroidal neovascularization.[22] The VIBRANT study compared intravitreal aflibercept with macular laser photocoagulation.[15] It enrolled 183 eyes that were followed monthly after random assignment to initial monthly intravitreal aflibercept or laser. The study met its primary outcome measure at week 24, with improvement from baseline best-corrected visual acuity (BCVA) letter score $\geq$15 in 52.7% of eyes in the intravitreal aflibercept injection (IAI) group compared with 26.7% in the laser group. At week 24, all eyes in the IAI group were switched to IAI every 8 weeks, and patient eyes in the laser group received IAI (3 monthly injections followed by IAI every 8 weeks) as rescue treatment if prespecified criteria were met. Eyes in the IAI group that met rescue criteria at week 36 received grid laser photocoagulation. We report week 52 outcomes in the VIBRANT study.

Methods

Study Design

VIBRANT was a phase 3, multicenter, randomized, double-masked, active-controlled, 52-week clinical trial. The study was conducted at 58 sites in North America and Japan. Each respective institutional review board/ethics committee approved the study protocol. The study was carried out in adherence with guidelines established by the Declaration of Helsinki, the International Conference on Harmonization guidelines for Good Clinical Practice, and, for US patients, the Health Insurance Portability and Accountability Act of 1996. All patients provided written informed consent to participate in this trial. The study was registered with ClinicalTrials.gov (identifier no. NCT01521559). Data described were collected between April 2012 and March 2014.

The design and patient eligibility for the VIBRANT study have been described.[15] In brief, eyes with BRVO or hemi-retinal vein occlusion with foveal center–involved macular edema were randomized 1:1 into the IAI and laser groups. Only 1 eye from each patient was included in the study. Eyes in the IAI group received 2 mg IAI every 4 weeks from baseline to week 20 and continued to receive 2 mg IAI every 8 weeks from week 24 to week 48 with sham injections in between. A sham laser treatment was also performed at baseline. Eyes in the laser group received macular laser photocoagulation at baseline and sham injections every 4 weeks from baseline to week 48.

Rescue treatment could be given from week 12 onward on the basis of the following prespecified criteria: >50 μm increase in central retinal thickness (CRT) compared with the lowest previous measurement; presence of new or persistent cystic retinal changes, subretinal fluid, or persistent diffuse edema in the central optical coherence tomography (OCT) subfield; or loss of $\geq$5 letters compared with the best previous measurement because of BRVO in conjunction with any increase in CRT. When at least 1 rescue treatment criterion was met, eyes in the IAI group received sham laser at week 12, 16, or 20; no treatment at weeks 24, 28, 32, 40, 44, and 48; or active laser at week 36. Eyes in the laser group eligible for rescue treatment before week 24 received 1 additional laser from week 12 to week 20. From week 24 to week 48, eyes in the laser group that were eligible for rescue treatment received 2 mg IAI every 8 weeks after 3 initial monthly doses. At week 36, eyes in the laser group eligible for rescue treatment received sham laser in addition to IAI. Only eyes that developed clinically significant ocular neovascularization after BRVO could receive scatter laser photocoagulation at any time during the study.

Outcome Measures

The primary efficacy outcome measure was the percentage of eyes that gained $\geq$15 letters in BCVA by Early Treatment Diabetic Retinopathy Study visual acuity at week 24.[15] We report the 52-week results of the VIBRANT study. Prespecified efficacy outcome measures at week 52 were all exploratory and included the percentage of eyes that gained $\geq$15 in letter score in BCVA; mean change from baseline in BCVA, CRT, National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) total scores; and percentage of eyes with a decrease in retinal ischemia. A prespecified subgroup analysis was the mean change from baseline BCVA at weeks 24 and 52 by baseline perfusion status. Ad hoc analyses included the percentage of eyes that gained $\geq$0, $\geq$5, $\geq$10, and $\geq$30 in letter score in BCVA at week 52; percentage of eyes that lost >0, $\geq$5, $\geq$10, and $\geq$15 in letter score in BCVA at week 52; percentage of eyes with BCVA of $\geq$20/40 at weeks 24 and 52; percentage of eyes with a change in retinal perfusion at weeks 24 and 52; percentage of eyes with dry retina under fovea at weeks 24 and 52; and change from baseline in NEI VFQ-25 subscales (near activities, distance activities, and visual dependency) at week 52. Safety assessments included collection of ocular and nonocular AEs and serious adverse events (SAEs).

The BCVA and CRT were evaluated every 4 weeks from baseline to week 52. The BCVA was assessed using the Early