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Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion

52-Week Results of the VIBRANT Study

W. Lloyd Clark, MD,[1] David S. Boyer, MD,[2] Jeffrey S. Heier, MD,[3] David M. Brown, MD,[4] Julia A. Haller, MD,[5] Robert Vitti, MD,[6] Husain Kazmi, MD,[6] Alyson J. Berliner, MD, PhD,[6] Kristine Erickson, OD, PhD,[6] Karen W. Chu, MS,[6] Yuhwen Soo, PhD,[6] Yenchieh Cheng, PhD,[6] Peter A. Campochiaro, MD[7]

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

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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

Treatment Diabetic Retinopathy Study protocol.[23] The CRT was evaluated with spectral-domain OCT. The OCT images were evaluated by an independent central reading center (Duke Reading Center, Durham, NC). Fundus photography and fluorescein angiography were performed at baseline and weeks 12, 24, 36, and 52 and were evaluated by an independent central reading center (Digital Angiography Reading Center, New York, NY). Perfused and nonperfused retinas were defined as retinas with $<$10 disc areas and $\geq$10 disc areas of retinal capillary nonperfusion, respectively. The reduction in retinal ischemia was measured as an absolute reduction in the number of quadrants containing any amount of retinal capillary nonperfusion from baseline to weeks 24 and 52. Vision-related quality of life was assessed at baseline and weeks 12, 24, and 52 using the NEI VFQ-25, which was administered by masked, certified site personnel.

Statistical Analyses

Efficacy outcome measures were analyzed in the full analysis set, which comprised all randomized eyes that received the study drug and had a baseline and at least 1 post-baseline BCVA assessment. Between-group differences in categoric variables were evaluated by the Cochran−Mantel−Haenszel test with adjustment for geographic region (North America and Japan) and baseline BCVA ($>$20/200 and $\leq$20/200) at a 2-sided significance level of 5%. Between-group differences in continuous variables were analyzed by 2-way analysis of covariance with baseline measurement as covariate and treatment group, region, and baseline BCVA category ($>$20/200 and $\leq$20/200) as fixed factors. Missing data were imputed using the last observation carried forward method. All outcome measures at week 52 and ad hoc analyses were evaluated in an exploratory manner, and *P* values reported are considered nominal. The safety analysis set included all randomized patients who received any study treatment.

Results

Patient Disposition, Demographics, and Baseline Characteristics

A total of 91 eyes were randomized to IAI, and 92 eyes were randomized to grid laser. All randomized eyes in both treatment groups were included in the full analysis set, except for 2 eyes in the laser group that did not have a post-baseline BCVA assessment. The safety analysis set included all randomized patients. Overall, 80.2% of patients in the IAI group and 83.7% of patients in the laser group completed the study at week 52. Major reasons for discontinuation before week 52 in the IAI and laser groups were patient withdrawal (12.1% and 9.8%, respectively), lost to follow-up (1.1% and 3.3%, respectively), and AEs (4.4% and 0%, respectively). Adverse events causing 4 patients (4.4%) to discontinue in the IAI group were metastatic breast cancer, traumatic cataract, and increased intraocular pressure, in 1 patient each, and small bowel obstruction and central pelvis abscess in 1 patient. Demographics and baseline characteristics of patients were similar in both treatment groups.[15] Of a maximum of 10 injections, eyes in the IAI group received a mean (standard deviation) of 9.0 (1.8) injections from baseline to week 48. A total of 9 eyes in the IAI group (9/85 eyes completing week 24 [10.6%]) received active laser rescue treatment at week 36. In the laser group, eyes received a mean (standard deviation) of 1.7 (0.5) laser treatments from baseline to week 20, of a maximum of 2 possible laser treatments. From week 24 to 48, 67 eyes in the laser group (67/83 eyes completing week 24 [80.7%]) received a mean of 4.4 IAI treatments. Of these, 44 eyes (44/83 eyes completing week 24 [53.0%]) received the maximum number of IAI treatments (5 injections) during this period. The median time (range) to the first IAI rescue treatment in the laser group was 24.9 weeks (23.1−48.4 weeks) from baseline. Overall, 16 eyes in the laser group (16/83 eyes completing week 24 [19.3%]) did not meet rescue criteria through week 52 and never received IAI injections. After week 24, the laser group is referred to as the laser/IAI group.

Efficacy

After a single IAI injection, 36.3% and 56.0% of eyes in the IAI group gained $\geq$15 and $\geq$10 in letter score at week 4, respectively, compared with 7.8% (difference IAI minus laser, 28.5%; 95% confidence interval, 17.2−39.8) and 17.8% (difference IAI minus laser, 38.3%; 95% confidence interval, 25.4−51.2) of eyes in the laser group. The percentage of eyes with improvement from baseline BCVA 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 (Fig 1A). The percentages of eyes that gained $\geq$10 or $\geq$5 in letter score were also higher in the IAI group compared with the laser/IAI group at week 52 (Table 1).

The mean change from baseline BCVA letter score in the IAI group compared with the laser/IAI group was 17.0 versus 6.9 ($P < 0.0001$) at week 24 and 17.1 versus 12.2 ($P = 0.0035$) at week 52 (Fig 1B). Eyes that had $\geq$10 disc areas of retinal nonperfusion were designated as nonperfused, and those with $<$10 disc areas of retinal nonperfusion were designated as perfused. In the IAI group, the mean change from baseline BCVA letter score was 13.7 in the perfused eyes and 20.0 ($P = 0.2402$) in the nonperfused eyes at week 52. The corresponding mean change from baseline BCVA letter score in the laser/IAI group was 11.9 and 15.6 ($P = 0.1491$) in the perfused and nonperfused eyes, respectively. The percentage of eyes with a visual acuity of $\geq$20/40 in the IAI and laser/IAI groups was 24.2% and 18.9% ($P = 0.3910$) at baseline, 82.4% and 46.7% ($P < 0.0001$) at week 24, and 84.6% and 67.8% ($P = 0.0054$) at week 52, respectively.

The mean reduction from baseline CRT in the IAI and laser/IAI groups was 280.5 versus 128.0 μm ($P < 0.0001$) at week 24, and 283.9 versus 249.3 μm ($P = 0.0218$) at week 52 (Fig 1C). The percentage of eyes with dry retina (absence of intraretinal and subretinal fluid) under the foveal center in the IAI and laser/IAI groups was 13.2% versus 15.6% at baseline, 90.1% versus 38.9% ($P < 0.0001$) at week 24, and 94.5% versus 84.4% ($P = 0.0303$) at week 52, respectively. The percentage of eyes with perfused retinas in the IAI and laser/IAI groups was 60.4% versus 68.9% at baseline, 80.2% versus 67.1% ($P = 0.0497$) at week 24, and 77.9% versus 78.0% ($P = 0.7742$) at week 52 (Table 2). The proportion of eyes with a decrease in retinal ischemia in the IAI and laser/IAI groups was 29.0% versus 17.6% ($P = 0.1012$) at week 24 and 34.7% versus 29.6% ($P = 0.4708$) at week 52 (Table 3).

The mean change from baseline NEI VFQ-25 total score for the IAI and laser/IAI groups was similar at week 52 (9.4 versus 8.3; $P = 0.0986$). In the IAI versus the laser/IAI groups, the mean change in subscale scores between baseline and week 52 was 12.0 versus 8.4 ($P = 0.1060$) for near activities, 10.9 versus 5.7 ($P = 0.0061$) for distance activities, and 4.8 versus 7.7 ($P = 0.9757$) for visual dependency.

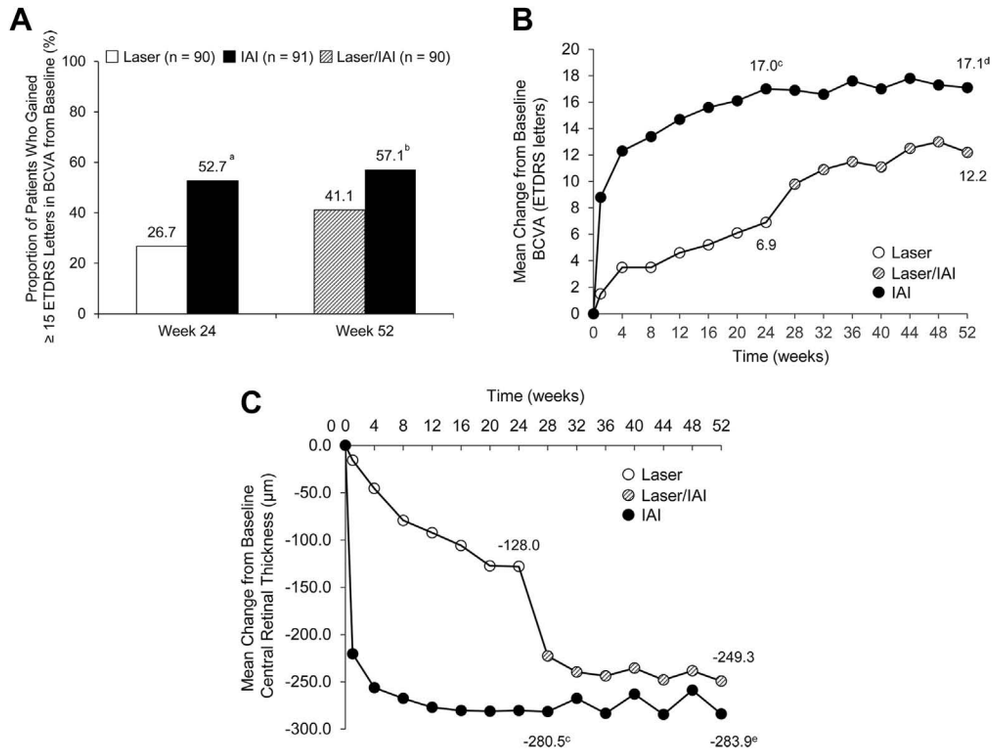

Figure 1. Visual and anatomic outcomes. The percentage of eyes that gained ≥15 in letter score from baseline to weeks 24 and 52 **(A)**, and the mean change from baseline in best-corrected visual acuity (BCVA) **(B)** and central retinal thickness (CRT) **(C)** over 52 weeks are shown. Full analysis set. Missing data were imputed using the last observation carried forward method. [a]$P = 0.0003$, [b]$P = 0.0296$, [c]$P < 0.0001$, [d]$P = 0.0035$, and [e]$P = 0.0218$ versus laser. ETDRS = Early Treatment Diabetic Retinopathy Study; IAI = intravitreal aflibercept injection.

Safety

From baseline to week 52, 49.5% of eyes in the IAI group and 47.8% of eyes in the laser/IAI group experienced at least 1 ocular AE in the study eye. The most common ocular AE occurring in the IAI and laser/IAI groups was conjunctival hemorrhage (24.2% versus 15.2%, respectively). During the 52 weeks of the study, 4 eyes, all in the laser/IAI group, developed retinal neovascularization (3 eyes before week 24 and 1 eye after week 24). Of 3 eyes that developed retinal neovascularization before week 24, 2 eyes were treated with scatter laser photocoagulation. One eye that developed retinal neovascularization after week 24

Table 1. Eyes with Vision Gains and Losses from Baseline at Week 52

	Laser/IAI (n = 90)	IAI (n = 91)	*P* Value
Vision gain, n (%)			
≥30 letters	7 (7.8)	13 (14.3)	0.1128
≥15 letters	37 (41.1)	52 (57.1)	0.0296
≥10 letters	53 (58.9)	73 (80.2)	0.0021
≥5 letters	67 (74.4)	80 (87.9)	0.0248
≥0 letters	78 (86.7)	84 (92.3)	0.2426
Vision loss, n (%)			
>0 letter	12 (13.3)	7 (7.7)	0.2426
≥5 letters	6 (6.7)	5 (5.5)	0.8181
≥10 letters	3 (3.3)	3 (3.3)	0.9700
≥15 letters	1 (1.1)	2 (2.2)	0.5611

Full analysis set. Last observation carried forward.
IAI = intravitreal aflibercept injection.

Table 2. Retinal Perfusion Status at Baseline, Week 24, and Week 52

	Laser/IAI (n = 90)	IAI (n = 91)
Baseline, n (%)		
Perfused	62 (68.9)	55 (60.4)
Nonperfused	16 (17.8)	20 (22.0)
Cannot grade	10 (11.1)	16 (17.6)
Missing	2	0
Week 24, n* (%)		
Perfused	55/82 (67.1)	65/81 (80.2)[†]
Nonperfused	27/82 (32.9)	16/81 (19.8)
Missing	8	10
Week 52, n* (%)		
Perfused	64/82 (78.0)	67/86 (77.9)[‡]
Nonperfused	18/82 (22.0)	19/86 (22.1)
Missing	8	5

Full analysis set. Last observation carried forward.
IAI = intravitreal aflibercept injection.
*Denominators included only nonmissing assessments.
[†]$P = 0.0497$ compared with the laser/IAI group.
[‡]$P = 0.7742$ compared with the laser/IAI group.

Table 3. Proportion of Eyes with a Decrease in Retinal Ischemia from Baseline at Weeks 24 and 52

	Laser/IAI (n = 90)	IAI (n = 91)	*P* Value
Week 24, n* (%)	12/68 (17.6)	20/69 (29.0)	0.1012
Week 52, n* (%)	21/71 (29.6)	25/72 (34.7)	0.4708

Full analysis set. Last observation carried forward.
IAI = intravitreal aflibercept injection.
*Denominators included only nonmissing assessments.

had received IAI and was treated with scatter laser photocoagulation. None of the eyes in either treatment group developed anterior segment neovascularization. There were no cases of endophthalmitis. Traumatic cataract in 1 eye (1.1%) in the IAI group was the only ocular SAE. One eye (1.1%) in the laser/IAI group had mild intraocular inflammation between weeks 24 and 52.

The incidence of nonocular AEs through week 52 in the IAI and laser/IAI groups was 67.0% versus 68.5%, respectively. Nonocular AEs that occurred in ≥5% of patients in the IAI or laser/IAI group were hypertension (11.0% and 16.3%), nasopharyngitis (8.8% and 8.7%), bronchitis (6.6% and 2.2%), increased blood pressure (4.4% and 5.4%), and urinary tract infection (3.3% and 7.6%). Nonocular SAEs were reported in 14.3% of patients in the IAI group and 10.9% of patients in the laser/IAI group. Nonocular SAEs that occurred in more than 1 patient were acute renal failure (1 patient [1.1%] in each treatment group), pneumonia (2 patients [2.2%] in the IAI group and 1 patient [1.1%] in the laser/IAI group), hypertension (1 patient [1.1%] in each treatment group), anemia (2 patients [2.2%] in the IAI group), and dehydration (2 patients [2.2%] in the laser/IAI group). One death due to pneumonia (1.1%) and 1 Anti-Platelet Trialists' Collaboration–defined event of nonfatal stroke (1.1%) occurred during the first 24 weeks of study in the laser group before receiving any IAI. One Anti-Platelet Trialists' Collaboration–defined event of nonfatal myocardial infarction (1.1%) occurred after week 24 in a patient in the laser group who had received IAI.

Discussion

The VIBRANT study previously demonstrated that eyes with macular edema after BRVO treated with IAI every 4 weeks had a significantly better visual outcome at week 24 compared with those treated with grid laser photocoagulation in terms of both the percentage of eyes that gained ≥15 in letter score (52.7% versus 26.7%, $P = 0.0003$) and the mean change from baseline BCVA letter score (17.0 versus 6.9, $P < 0.0001$).[15] Between weeks 24 and 48, eyes in the IAI group received IAI every 8 weeks. Nine eyes (10.6%) in the IAI group met rescue criteria at week 36 and received macular grid laser treatment. At week 52, the percentage of eyes in the IAI group that showed improvement from baseline BCVA letter score ≥15 was 57.1%, and the mean change from baseline BCVA letter score was 17.1. Thus, visual outcomes obtained in eyes with macular edema after BRVO with injections of intravitreal aflibercept every 4 weeks for 24 weeks were well maintained during a subsequent 24 weeks in which the duration of injections was extended to every 8 weeks in all eyes and rescue grid laser was given in approximately 10% of eyes. The mean CRT reduction of 280.5 μm at week 24 after IAI every 4 weeks was also maintained in the IAI groups with administration of IAI every 8 weeks (plus grid laser in ~10% of eyes) between weeks 24 and 52, at which point the reduction in CRT was 283.9 μm. At week 52, there was no difference between the treatment groups in the mean change from baseline NEI VFQ-25 total score, likely because of a combination of factors including good vision in the fellow eye in almost all patients and IAI rescue treatment in the study eye in most patients in the laser group.

At week 24 and beyond, eyes in the laser/IAI group received IAI if rescue criteria were met, which occurred in 67 of 83 eyes (80.7%). Eyes that met rescue criteria received 3 injections 4 weeks apart followed by IAI every 8 weeks. Eyes in the laser/IAI group that met rescue criteria at week 24 could have received 5 injections of aflibercept, whereas eyes that did not meet rescue criteria at week 24, but did at a subsequent visit, received fewer than 5 injections. Overall, a majority of eyes in the laser group met rescue criteria with IAI at week 24, and the mean number of IAI from week 24 to week 52 was 4.4. Between weeks 24 and 52, there was improvement in visual outcomes in the laser/IAI group. Compared with the 26.7% of eyes that gained ≥15 in letter score between baseline and week 24, 41.1% gained ≥15 in letter score between baseline and week 52. The mean change from baseline BCVA letter score was 12.2 at week 52 compared with 6.9 at week 24. However, despite the substantial visual gains between weeks 24 and 52, and reduction in edema comparable to that in the IAI group, visual outcomes in the laser/IAI group were statistically inferior to those in the IAI group at week 52. These findings suggest that early treatment after presentation of macular edema after BRVO might be important for optimal visual outcomes with IAI. This is consistent with the 12-month results in the BRAVO trial.[24]

In VIBRANT, a higher percentage of eyes in the grid laser group than those in the IAI group had ≥10 disc areas of retinal nonperfusion at week 24. Between weeks 24 and 52, approximately 80% of patients in the laser/IAI group received treatment with intravitreal aflibercept, and there was no longer a between-group difference in retinal nonperfusion at week 52 (Table 2). Consistent with these findings, a higher proportion of patients in the IAI group had a decrease in retinal ischemia by week 24 compared with the laser control. By week 52, the difference between the treatment groups still favored the IAI group, although the proportion of patients with a decrease in retinal ischemia in the laser/IAI group increased between weeks 24 and 52 after many of these patients received rescue with IAI (Table 3). The BRAVO study included only patients with <10 DA of nonperfusion, and retinal perfusion was not evaluated in this study. However, similar results were seen with ranibizumab in a retrospective analysis of prospectively collected data from BRAVO patients who had <10 DA of nonperfusion. In the retrospective analysis, patients who were originally randomized to receive sham injections showed progression of retinal nonperfusion between

baseline and month 6, which was reduced in patients randomized to receive monthly injections of 0.3 mg or 0.5 mg of ranibizumab.[4] Between months 6 and 12, patients in the sham group were able to receive ranibizumab, and the difference in retinal nonperfusion was no longer present at month 12.[4] Taken altogether, these findings suggest that neutralization of VEGF not only prevents progression of retinal nonperfusion but also seems to reverse its underlying process in eyes with macular edema after BRVO.

In conclusion, IAI is an effective treatment for macular edema due to BRVO. After 6 IAI given every 4 weeks, edema was controlled, and visual outcomes were substantially improved. These outcomes were maintained during a subsequent 24-week period in which injections were extended to every 8 weeks. The visual benefits were significantly better in eyes treated with IAI every 4 weeks for 24 weeks compared with those treated with grid laser therapy. Administration of IAI after 24 weeks in the laser/IAI group resulted in substantial improvements in BCVA and CRT, but outcomes were still significantly inferior to those seen in the IAI group at week 52. These data support the use of IAI every 8 weeks after a 24-week period of IAI every 4 weeks in eyes with macular edema after BRVO.

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[1] Palmetto Retina Center, West Columbia, South Carolina.

[2] Retina-Vitreous Associates Medical Group, Beverly Hills, California.

[3] Ophthalmic Consultants of Boston, Boston, Massachusetts.

[4] Retina Consultants of Houston, The Methodist Hospital, Houston, Texas.

[5] Wills Eye Hospital, Philadelphia, Pennsylvania.

[6] Regeneron Pharmaceuticals, Inc, Tarrytown, New York.

[7] Department of Ophthalmology, The Johns Hopkins School of Medicine, Baltimore, Maryland.

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Author Contributions:

Conception and design: Clark, Boyer, Heier, Brown, Haller, Vitti, Kazmi, Berliner, Erickson, Chu, Soo, Cheng, Campochiaro

Data collection: Clark, Boyer, Heier, Brown, Vitti, Kazmi, Berliner, Erickson, Chu, Soo, Campochiaro

Analysis and interpretation: Clark, Boyer, Heier, Brown, Haller, Vitti, Kazmi, Berliner, Erickson, Chu, Soo, Cheng, Campochiaro

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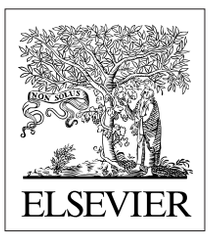
Abbreviations and Acronyms:
AE = adverse event; **BCVA** = best-corrected visual acuity; **BRVO** = branch retinal vein occlusion; **CRT** = central retinal thickness; **IAI** = intravitreal aflibercept injection; **ME** = macular edema; **NEI VFQ-25** = National Eye Institute Visual Function Questionnaire-25; **OCT** = optical coherence tomography; **SAE** = serious adverse event; **VEGF** = vascular endothelial growth factor.

Correspondence:
Peter A. Campochiaro, MD, 815 Maumenee, The Wilmer Eye Institute, The Johns Hopkins Hospital, 600 N. Wolfe Street, Baltimore, MD 21287. E-mail: pcampo@jhmi.edu.



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