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Comparison of the Short-term Efficacy of Intravitreal Aflibercept and Ranibizumab for Macular Edema Caused by Branch Retinal Vein Occlusion

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We compared the efficacy of an initial intravitreal aflibercept injection（IVA）followed by pro re nata（additional injection as needed）with that of intravitreal ranibizumab injection（IVR）for the treatment of naive patients with macular edema（ME）due to branch retinal vein occlusion（BRVO）. Thirty-four consecutive patients（IVA group, n = 20; IVR group, n = 14）were reviewed retrospectively. A significant improvement in best-corrected visual acuity（BCVA）and reduction in central retinal thickness（CRT）from baseline at all time points was noted in both the groups but not between the groups. The rate of ME recurrence at 3 months was significantly smaller in the IVA group than in the IVR group, and the time between initial IV and the first ME recurrence was also significantly longer in the IVA group. In the early stages of ME caused by BRVO, aflibercept might have a sustained effect on ME suppression than ranibizumab.

Keywords: anti-VEGF therapy, aflibercept, ranibizumab, branch retinal vein occlusion, macular edema

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INTRODUCTION

Branch retinal vein occlusion（BRVO）is the second most leading retinal vascular disease after diabetic retinopathy, and macular edema（ME）is the most frequent cause of visual impairment in BRVO［1, 2］. Retinal ischemia after vascular occlusion can elevate the levels of both vitreous and aqueous vascular endothelial growth factor（VEGF）［3, 4］. Increased levels of VEGF in the vitreous cavity have been reported to result in higher vascular permeability, resulting in ME in patients with BRVO［5-7］. Therefore, the use of anti-VEGF agents, which directly inhibit intraocular VEGF, seems to be a promising therapeutic modality in ME, in addition to anti-inflammatory treatments with dexamethasone implant［8-11］. Two major anti-VEGF agents are currently available for intravitreal injection treatment for ME secondary to BRVO: ranibizumab（Lucentis™, Genentech, Inc., South San Francisco, CA, USA）and aflibercept（Eylea™, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA, and Bayer Pharma AG, Berlin, Germany）.

The BRAVO study and VIBRANT study demonstrated the efficacy of ranibizumab and aflibercept for the treatment of ME secondary to BRVO, respectively［12, 13］. In June 2015, aflibercept was submitted for approval for use in ME secondary to BRVO in Japan. A comparison of the efficacy

of bi-monthly intravitreal ranibizumab (IVR) and bi-monthly intravitreal aflibercept (IVA) injections in ME patients secondary to central retinal vein occlusion (CRVO) showed no significant difference in visual improvement in the IVA group compared with the IVR group; however, in the IVA group, the aqueous VEGF concentration was strongly suppressed at 2 months after the initial injection compared with the IVR group [14]. To our knowledge, few studies have directly compared the efficacy of IVA with that of IVR for ME secondary to BRVO. In this study, we compare the efficacy of IVA and IVR for ME secondary to BRVO.

MATERIALS AND METHODS

This study was a part of the research protocol "Epidemiologic Study of Ocular Morphology and Function" approved by the Ethics Committee of Shimane University Hospital approved. The study protocol complied with the tenets of the Declaration of Helsinki. In accordance with the provisions of the Japanese Guidelines for Epidemiologic Study issued by the Japanese Government, the ethics committee exempted the requirement of patients' informed consent and their medical record data. Instead, the protocol was posted at the outpatient clinic to inform the participants of the study. From April 2014 to September 2016, we conducted a retrospective study at the Department of Ophthalmology, Shimane University Hospital. We included 34 eyes of 34 patients naive to anti-VEGF therapy with ME due to BRVO who could be followed over 3 months after the initial intravitreal injection (IV). There are no specific drug selection criteria, however, aflibercept was approved in Japan in June 2015 for the treatment of ME secondary to BRVO, thus, ranibizumab was used before approval and aflibercept after approval. Therefore, the consecutive cases were recruited for each period in each group.

We excluded patients with a medical history of prior trauma, diabetic retinopathy, vitreomacular traction, epiretinal membrane and previous treatment of intravitreal anti-VEGF agent injection, retinal or macular laser photocoagulation, or ocular surgery except for uneventful phacoemulsification. Patients underwent clinical examination including best-corrected visual acuity (BCVA), slit-lamp examination, intraocular pressure measurement, fundus examination, and standard spectral-domain optical coherence tomography (SD-OCT) scan. The SD-OCT (3D OCT-2000, Topcon, Tokyo, Japan) scans (128 horizontal scan lines composed of 512 A-scans, 6 × 6 mm) with high resolution and a 16.2-megapixel fundus photo were taken of all eyes before and after treatment. Central retinal thickness (CRT) was measured from the thickness map of the SD-OCT platform and defined as the average thickness of the radius 1-mm circle of the fovea on OCT images. ME was defined as a CRT >300 μm detected by SD-OCT.

After the patients provided written informed consent, 20 eyes were treated with IVA and 14 eyes with IVR. Following the administration of topical anesthesia and disinfection of the eyelid and conjunctiva, aflibercept (2 mg/0.05 mL) or ranibizumab (0.5 mg/0.05 mL) was injected into the vitreous cavity using a 30-gauge needle inserted through the inferotemporal pars plana, at 4 mm posterior to the limbus. Afterward, the IV was repeated in eyes with recurrence of ME with CRT >300 μm or with persistent macular cysts or submacular fluid that affected vision, even if the CRT was <300 μm. This is an administration method called 1 + pro re nata (1 + PRN), in which administration is repeated as necessary after the initial administration. Recurrence of ME was defined as an increase in CRT from the CRT at the previous return visit after the first month of treatment. Improvement in BCVA, reduction in CRT measured by OCT before and after treatment, the rate of ME recurrence, the time between initial IV and the first ME recurrence, and the total number of IVs over a 9-month period were evaluated.

The within-group comparisons of changes in CRT and BCVA were assessed using the Wilcoxon signed-rank test, and comparisons between groups were assessed using the Mann–Whitney U test. Fisher's exact test and chi-squared test were used to evaluate the clinical variables between groups. $P < 0.05$ was considered statistically significant.

RESULTS

There was no statistical difference between the

data of the two groups, including age, gender, incidence of patients with diabetes and hypertension, presenting BCVA and CRT, and duration from onset at baseline ($P > 0.05$; Table 1). At baseline and months 1, 3, 6, and 9, logMAR visual acuity was 0.53, 0.19, 0.16, 0.23, and 0.16 ($P = 0.0001$–0.0078 vs. baseline) in the IVA group and 0.59, 0.37, 0.37, 0.31, and 0.36 ($P = 0.0005$–0.031 vs. baseline) in the IVR group, respectively (Figure 1). CRT was 485.2, 245.6, 270.4, 281.3, and 319.0 mm ($P = 0.0001$–0.0078 vs. baseline) in the IVA group and 535.6, 287.3, 367.4, 279.0, and 238.8 mm ($P = 0.0001$–0.0039 vs. baseline) in the IVR group, respectively (Figure 2). All patients had improved vision and decreased CRT with resolution of macular cysts or submacular fluid after 1 month of treatment compared with pre-IV. At all points of the evaluation, BCVA ($P = 0.16$–0.80) and CRT ($P = 0.073$–0.94) were not significantly different between the two groups (Table 1). The numbers of

Table 1. Characteristics at baseline, 1 month, 3 months, 6 months, and 9 months by participation in the comparison between the intravitreal aflibercept group and ranibizumab group for macular edema caused by branch retinal vein occlusion

	IVA (n = 20)	**IVR (n = 14)**	***P* value**
Baseline			
Age, years	69.9 ± 11.6	69.8 ± 14.9	0.82[a]
Gender (female)	7	6	0.64[b]
Duration from onset, weeks	10.4 ± 18.7	3.6 ± 2.5	0.67[a]
Best-corrected visual acuity (logMAR)	0.53 ± 0.32	0.59 ± 0.44	0.76[a]
Central retinal thickness, μm	485.2 ± 84.8	535.6 ± 132.1	0.18[a]
Diabetes	1	3	0.14[b]
Hypertension	6	6	0.44[b]
1 month			
Completed month 1 visit (persons)	20	14	
Best-corrected visual acuity (logMAR)	0.19 ± 0.21	0.37 ± 0.46	0.35[a]
Central retinal thickness, μm	245.6 ± 45.0	287.3 ± 104.7	0.20[a]
Rate of ME recurrence (%)	0/20 (0%)	0/14 (0%)	
3 months			
Completed month 3 visit (persons)	20	14	
Best-corrected visual acuity (logMAR)	0.16 ± 0.17	0.37 ± 0.47	0.16[a]
Central retinal thickness, μm	270.4 ± 82.2	367.4 ± 181.6	0.10[a]
Rate of ME recurrence (%)	5/20 (25%)	9/14 (64%)	0.022[b]
Time between initial IV and the first ME recurrence, months	2.8 ± 0.4 (n = 5)	2.0 ± 0.9 (n = 9)	0.13[a]
6 months			
Completed month 6 visit (persons)	16	9	
Best-corrected visual acuity (logMAR)	0.23 ± 0.19	0.31 ± 0.40	0.80[a]
Central retinal thickness, μm	281.3 ± 92.6	279.0 ± 97.9	0.94[a]
Rate of ME recurrence (%)	10/16 (62.5%)	8/9 (88.9%)	0.16[b]
Time between initial IV and the first ME recurrence, months	3.8 ± 1.3 (n = 11)	2.3 ± 1.0 (n = 12)	0.015[a]
9 months			
Completed month 9 visit (persons)	8	8	
Best-corrected visual acuity (logMAR)	0.16 ± 0.19	0.36 ± 0.46	0.46[a]
Central retinal thickness, μm	319.0 ± 114.4	238.8 ± 38.5	0.073[a]
Rate of ME recurrence (%)	6/8 (75%)	7/8 (87.5%)	1.0[c]
Time between initial IV and the first ME recurrence, months	4.2 ± 1.5 (n = 13)	2.3 ± 1.0 (n = 12)	0.0051[a]
Injection number	2.0 ± 0.8	2.5 ± 0.8	0.23[a]

Abbreviations: IVA, intravitreal aflibercept injection; IVR, intravitreal ranibizumab injection; LogMAR, logarithmic minimum angle of resolution; ME, macular edema; IV, intravitreal injection.

[a]Statistical significance was calculated using Mann–Whitney *U* test.

[b]Statistical significance was calculated using chi-squared test.

[c]Statistical significance was calculated using Fisher's exact test.

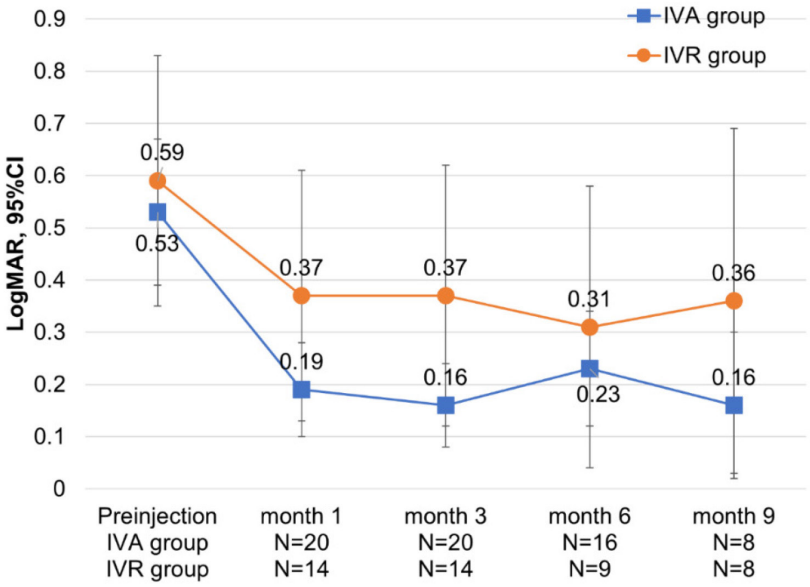

Figure 1. Improvements in best-corrected visual acuity from baseline to month 9 in patients with macular edema caused by branch retinal vein occlusion treated using intravitreal aflibercept or ranibizumab. Abbreviations: logMAR, logarithmic minimum angle of resolution; CI, confidence interval; IVA, intravitreal aflibercept injection; IVR, intravitreal ranibizumab injection; N, number.

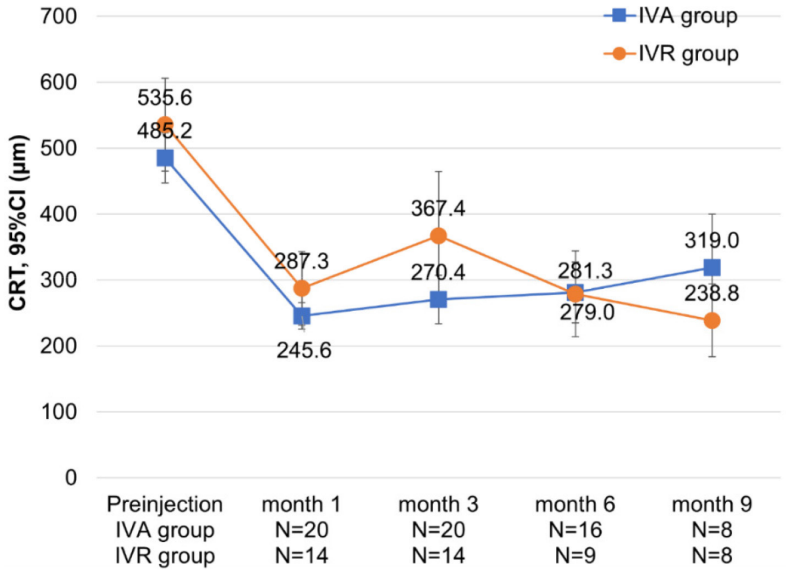

Figure 2. Improvements in central retinal thickness from baseline to month 9 in patients with macular edema caused by branch retinal vein occlusion treated using intravitreal aflibercept or ranibizumab. Abbreviations: CRT, central retinal thickness; CI, confidence interval; IVA, intravitreal aflibercept injection; IVR, intravitreal ranibizumab injection; N, number.

eyes with recurrent ME at 3, 6, and 9 months were 5 eyes (25%), 10 eyes (62.5%), 6 eyes (75%) in the IVA group and 9 eyes (64%), 8 eyes (88.9%), and 7 eyes (87.5%) in the IVR group, respectively. The rate of ME recurrence after 3 months of IVA was significantly lower than that of IVR (P = 0.022), but there was no difference at the other observation points. The time between initial IV and the first ME recurrence was significantly longer in the IVA group than in the IVR group (IVA: 4.2 months, IVR: 2.3 months, P = 0.0051). The total number of IVs over the 9-month period was not significantly different between the two groups (IVA: 2.0, IVR: 2.5, P = 0.23; Table 1). During the 9-month period after the baseline injection, 2 eyes (25%) in the IVA group and 1 eye (12.5%) in the

IVR group required no additional IV.

No serious adverse ocular events, including endophthalmitis, retinal detachment, vitreous hemorrhage, or elevated intraocular pressure, were observed in any of the patients. A side effect that was commonly observed was local hyperemia or subconjunctival hemorrhage at the injection site. No systemic adverse events were noted.

DISCUSSION

In this study, both IVA and IVR were similarly effective for improving BCVA and the reduction of CRT as measured by OCT in the treatment against ME secondary to RVOs, as indicated in previous reports [12, 13, 15-17]. However, the rate of ME recurrence at 3 months was significantly smaller in the IVA group than in the IVR group, and the duration to the first ME recurrence of the IVA group was significantly longer than that of the IVR group in the present study. Thus, aflibercept may have a longer ME-suppressant effect than ranibizumab did. The network meta-analysis also demonstrated that several anti-VEGF agents, including ranibizumab and aflibercept, had comparable effects on BCVA improvement and anatomical recovery at 6 months in eyes with BRVO or CRVO [18]. However, to the best of our knowledge, there are few reports directly comparing the clinical outcomes between IVA and IVR for patients with ME secondary to BRVO. Comparing the efficacy of a PRN (additional injection as needed) treatment regimen of aflibercept and ranibizumab in ME secondary to BRVO, no statistical difference between the two groups in terms of number of injections required and visual acuity gains was observed with either aflibercept or ranibizumab at 12-month follow-up [19]. In contrast, in ME due to BRVO, another recent study showed that aflibercept was more effective in improving CRT and BCVA than ranibizumab from baseline to month 3; however, those differences disappeared in the subsequent 9 months [20]. Moreover, in Japanese patients with ME secondary to BRVO, a change in treatment from ranibizumab to aflibercept prolonged the interval of IV with no anatomical or functional deterioration [21]. Therefore, the results of the present study corroborate the findings of previous reports and suggest the superiority of IVA over IVR in terms of short-term sustained efficacy.

Several studies reported the use of different regimens for ME treatment secondary to BRVO. The previously studied, large, multicenter, randomized clinical trials investigating the efficacy of ranibizumab have shown the use of 3–6 monthly injections in the induction phase. Monthly injections in the induction phase ranged from three in the BRIGHTER trial [22] to six in the BRAVO [23] and RELATE [24] trials. However, the 1+PRN and 3+PRN, in which administration is repeated as necessary after the initial three consecutive administrations regimens were reported to have similar functional outcomes at 12 months, with the mean total number of IVR injections of 3.8 in the 1 + PRN group and 4.6 in the 3 + PRN group [25]. Therefore, it was concluded that the 1 + PRN regimen can significantly reduce the physical and economic burden on patients by reducing the overall number of injections without interfering with the vision-improving effects of ranibizumab [25]. Similarly, a retrospective, single-center study of 1 + PRN and 3 + PRN regimens reported no significant differences in anatomic and functional results at 12 months, with the mean total number of IVR injections of 2.8 in the 1 + PRN group and 4.2 in the 3 + PRN group [26]. Moreover, a recent study demonstrated that 1 + PRN ranibizumab is safe and effective in untreated patients with ME caused by BRVO, and that concomitant laser therapy does not improve the functional prognosis or reduce the number of IVR injections needed [27]. However, the VIBRANT study showed that a 6+bimonthly aflibercept regimen maintained control of ME after BRVO and visual benefits through week 52 [13]. Moreover, a recent research showed that a 1+PRN aflibercept regimen was effective over 24 months for ME due to BRVO, with mean number of 2.2 IVAs in the first year [28]. Moreover, the frequent and prolonged administration of anti-VEGF drugs can lead to systemic adverse events [29, 30]. Therefore, the 1 + PRN regimen was clinically selected to minimize the risk of systemic adverse events and the financial burden on patients as much as possible by reducing the number of anti-VEGF drugs IV. In addition, we considered the 1 + PRN regimen to be optimal for assessing the duration of

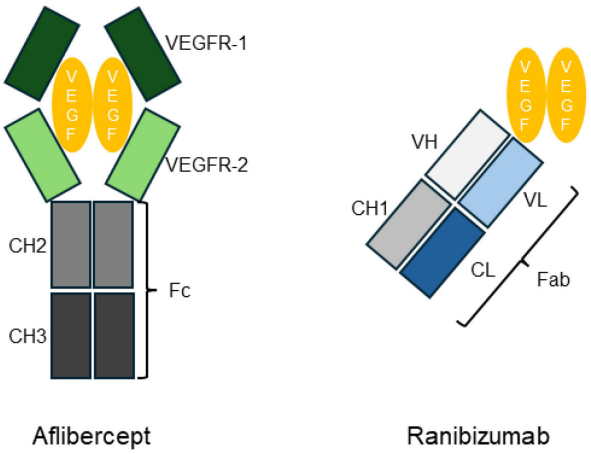

Figure 3. Comparison of molecular structure of aflibercept and ranibizumab. Aflibercept possesses 2nd Ig domain of VEGFR-1 and 3rd Ig domain of VEGFR-2 fused to the Fc portion of human IgG1. Ranibizumab is a Fab fragment of humanized IgG monoclonal antibody. Aflibercept can bind to both sides of the VEGF dimer, forming an inert 1:1 complex. On the other hand, ranibizumab can bind to a single VEGF molecule, but only on one side. Abbreviations: VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; CH, constant heavy chain; Fc, fragment crystallisable region; VH, variable heavy chain; VL, variable light chain; CL, constant light chain; Fab, fragment antigen binding region.

the pharmacologic effects of a single anti-VEGF injection.

Aflibercept and ranibizumab have been found to be considerably different both in terms of molecular interactions and stabilizing energy due to their different molecular structures (Figure 3) [31]. A previous study in rabbit and monkey eyes reported the half-life and the suppression time of VEGF-A concentrations in vitreous after IVA was longer than after IVR [32-34]. A recent report compared and confirmed the half-life of the agents [35]. Similarly, in the aqueous humor of neovascular AMD patients, the average period during which VEGF-A concentration was suppressed below the lower limit of quantification (<4 pg/mL) continued at 34 days using IVR injection and at 67 days using IVA injection ($P < 0.001$) [36]. In patients with CRVO, the aqueous VEGF levels were strongly suppressed by IVA compared with IVR at month 2 after the initial injection [14]. Furthermore, in patients with CRVO, bimonthly IVR injections may not completely neutralize the aqueous VEGF levels in the eye [14]. Thus, IVA seems to suppress both aqueous and vitreous VEGF and have an ME-suppressant effect that is longer than that of IVR. Moreover, aflibercept has an Fc fragment which is taken up by retinal pigment epithelial (RPE) cells and retinal endothelial cells [37] [38], whereas ranibizumab has no Fc fragment and is rapidly eliminated from the circulation once the drug enters the bloodstream [39]. Indeed, compared to ranibizumab, aflibercept is known to have a longer period of VEGF inhibition and more VEGF suppression in the serum [29], and the area under the curve is greater than that of ranibizumab because aflibercept reaches the peak serum concentrations 2 days after IV, one day later than ranibizumab, and then gradually cleared from the circulation [40]. Additionally, aflibercept significantly reduced the serum and plasma VEGF levels at 1 month after injection, whereas ranibizumab had no significant effect on both the serum and plasma VEGF levels [41]. Furthermore, numerous retinal cell types, including RPE cells, pericytes, endothelial cells, glial cells, choroidal fibroblasts, Müller cells, and ganglion cells can synthesize VEGF [42]. Thus, aflibercept might have shown longer effectiveness because of its bidirectional effects (i.e., vitreous cavity and blood). Moreover, the ability to bind the placental growth factor (PlGF) peculiar to aflibercept may be a factor of the longer suppression time of ME recurrence as compared with ranibizumab. An increase in the PlGF concentration was also reported in eyes of BRVO patients compared with control eyes [8]. Miyamoto *et al.* indicated that PlGF-increased RPE permeability was also associated with accumulation of subretinal fluid and retinal edema in human RPE cell culture [43, 44]. Aflibercept has high affinity for VEGF-A, VEGF-B, and PlGF and should neutralize their intraocular levels [45, 46]. However, because one study reported that both ranibizumab and aflibercept achieved similar significant reductions in the aqueous humor levels of VEGF and PlGF in patients with CRVO, this point will need to be verified in patients with BRVO in the future [47].

In the present study, though aflibercept had longer effectiveness for suppressing ME than ranibizumab did, the total mean number of IVAs over the 9-month period was lower than that of IVR but did not reach statistical significance. In routine clini-

cal practice in treating CRVO in the United States, there is no significant difference in the annual mean numbers of injections received in the first year and the mean interval between injections, regardless of whether patients started treatment with aflibercept or ranibizumab (IVA: 4.7, IVR: 4.4, $P = 0.38$). However, this retrospective study was based on an analysis of physician-level claims data in the United States, and the injection regimen, which varies by physician, was uncertain [48]. Another study showed that eyes with ME caused by CRVO that were switched from a minimum of three IVs of either intravitreal bevacizumab or ranibizumab to aflibercept were able to extend the injection interval [49]. In another study conducted in patients with chronic ME secondary to BRVO, changing the treatment from bevacizumab/ranibizumab to aflibercept was associated with a statistically significant extension of the retreatment interval [50]. In the former CRVO study, treatment schedules and injection intervals were left to the discretion of each retina specialist, whereas in the latter BRVO study, all IVs were administered according to a "treat and extend" regimen [51]; therefore, the difference in treatment regimens might have affected the injection interval.

In two previous studies of anti-VEGF IVs with a 1 + PRN regimen for ME secondary to BRVO, which did not directly compare the effectiveness of the two agents, the total mean number of IVR injections in the 1 + PRN group during the 12-month period was 3.8 ± 1.8 (n = 42) [24] and that of IVA was 2.12 ± 1.26 (n = 50) [52]. However, we were unable to perform a simple comparison of the two studies, and the total mean number of IVR injections in the 1 + PRN group during the 12-month period may be larger than that of IVA. In our study, the total mean number of IVR over the 9-month period was slightly higher than that of IVA, but there was no significant difference between the two groups (IVA: 2.0, IVR: 2.5, $P = 0.23$). The small sample size and the injection timing could mean that 9 months might have been the timing of the post-second IVA injection or pre-third IVR, considering the reinjection number of each agent in the prior reports [25, 52].

This study has some limitations, including a small sample size, retrospective nature, and short follow-up period. Moreover, the decision to treat with IVA or IVR depending on the timing of treatment initiation might be a selection bias of the study, however the impact of this limitation could be minimized because both groups were conducted on consecutive cases per period. A large prospective randomized study could further confirm the difference in treatment of ME in BRVO with a longer follow-up period. In addition, there are many kinds of treatment regimens that use an IV of anti-VEGF agents, so our findings should be restricted to only the 1 + PRN regimen.

CONCLUSION

In conclusion, this study provided a direct comparison of the treatment efficacy of a 1 + PRN ranibizumab or aflibercept injection regimen for ME secondary to BRVO in a clinical setting. IVA and IVR had similar functional and anatomical outcomes in BCVA and CRT. The lower rate of ME recurrence after 3 months of initial IV and the longer time required for the first ME recurrence from the initial IV of aflibercept than that of ranibizumab indicate that IVA may have a longer-lasting ME suppression effect than IVR, especially in the early stages of ME caused by BRVO. No serious systemic or ocular adverse events were reported.

Institutional Review Board Statement

The current study was part of the study protocol "Epidemiologic Study of Ocular Morphology and Function," that the Ethics Committee of Shimane University Hospital approved on October 27, 2008 (Identification code: 20080911-1), and adhered with the tenets of the Declaration of Helsinki.

Informed Consent Statement

In accordance with the regulations of Japanese Guidelines for Epidemiologic Study issued by the Japanese Government, the ethics committee exempted the study from the requirement of the patient's informed consent with respect to the use of their medical record data. Instead, the protocol was posted at the outpatient clinic to inform the paticipants about the study.

Author Contributions

All authors made conisderable contribution to the research work, in terms of the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors took part in drafting, revising, or critically reviewing the article; provided the final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the research.

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Conflicts of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the author upon request.

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