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Foveal Thickness Fluctuation in Anti-VEGF Treatment for Branch Retinal Vein Occlusion: A Long-term Study

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Purpose: Branch retinal vein occlusion (BRVO) causes macular edema (ME), which can be controlled with anti-VEGF treatments. However, these treatments are not curative, necessitating additional anti-VEGF treatments at recurrence. Long-term results, optimal anti-VEGF treatment regimens, and the comprehensive effects of ME recurrence are largely unknown. Thus, we aimed to examine the effects of foveal thickness (FT) fluctuation (FTF) on the visual and morphologic outcomes of anti-VEGF treatments for BRVO-ME administered via a pro re nata regimen.

Design: A retrospective, observational case series.

Subjects: This study analyzed 309 treatment-naïve patients (309 eyes) with BRVO-ME between 2012 and 2021 at a multicenter retinal practice.

Methods: The FT was assessed using OCT at each study visit.

Main Outcome Measures: We evaluated the logarithm of the minimal angle of resolution (logMAR) best corrected visual acuity (BCVA) and the defect length of the foveal ellipsoid zone (EZ) band using OCT.

Results: At baseline, the mean logMAR BCVA was 0.30 ± 0.30 and the mean FT was 503 ± 162 μm. The number of anti-VEGF injections for BRVO-ME was 5.8 ± 4.6 during the mean follow-up period (50.6 ± 22.2 months). At the final examination, the mean logMAR BCVA and FT values were significantly improved compared with those at the baseline. Multiple regression analyses showed that age, baseline logMAR BCVA, and FTF were significantly associated with the final logMAR BCVA ($\beta = 0.20$, 0.35, and 0.30, respectively). Foveal thickness fluctuation (divided into groups 0−3 in ascending order of FTF) was significantly associated with logMAR BCVA and the defect length of the foveal EZ band at the final examination. The defect lengths of the foveal EZ band were longitudinally shortened in groups 0 and 1 and were slightly prolonged in groups 2 and 3. The logMAR BCVA showed improvements in groups 0 and 1 and worsened slightly in groups 2 and 3.

Conclusions: Foveal thickness fluctuation was significantly associated with visual acuity and foveal photoreceptor status. Thus, the morphologic and functional prognoses of eyes with BRVO may improve with the identification of the characteristics of eyes with greater FTF and consequently controlling the FTF more strictly. *Ophthalmology Retina 2022;6:567-574 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.ophthalmologyretina.org.

Branch retinal vein occlusion (BRVO) is the second-most commonly occurring retinal circulatory disease, causing retinal hemorrhage, edema, and ischemia in the affected area.[1,2] When these pathological changes involve the macula, this symptomology results in significant visual impairment. However, with the advent of anti-VEGF therapy, most of the resulting macular edema (ME) can be rapidly resolved.[3,4] Consequently, the visual prognoses of patients with BRVO have improved substantially compared with that in the era before the availability of anti-VEGF therapy.[3,5,6] Nevertheless, because anti-VEGF agents do not act directly on obstructive mechanisms in the affected retinal veins, BRVO-ME often recurs as intravitreal concentrations of anti-VEGF agents decrease.[7−12]

In the clinical management of BRVO-ME recurrence, an additional anti-VEGF injection at each ME recurrence is considered standard.[13−16] This treatment regimen is termed as a pro re nata (PRN) injection. The PRN regimen is commonly used because it is difficult to predict ME recurrence in each patient,[4,17,18] BRVO-ME occasionally disappears during the natural course of the disease,[1,2,18−20] and the PRN regimen for treating ME recurrence has been evaluated and validated in prior clinical trials.[21,22] However, most prior trials using anti-VEGF treatments with the PRN regimen aimed to

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examine the short-term outcomes of 1 or 2 years.[22] The long-term outcomes of ≥2 years are, thus, not fully understood.

In recent investigations evaluating anti-VEGF treatments for age-related macular degeneration (AMD), patients with greater foveal thickness (FT) fluctuation (FTF) had worse final visual acuity during a 24-month observation period as well as more severe foveal fibrosis and atrophy compared with those with lesser fluctuations.[23,24] However, to the best of our knowledge, no prior studies have evaluated the associations between FTF and BRVO. Therefore, in this study, we examined the long-term results of anti-VEGF treatments for recurrent ME as well as the effects of FTF on visual and morphologic outcomes in patients with BRVO.

Methods

This retrospective study adhered to the tenets of the Declaration of Helsinki and was approved by the ethics committee of Saneikai Tsukazaki Hospital (Hyogo, Japan), the Kyoto University Graduate School of Medicine (Kyoto, Japan), the Tokushima University Faculty of Medicine (Tokushima, Japan), and the Kagawa University Faculty of Medicine (Kagawa, Japan). Written informed consent was not obtained from all the subjects because of the retrospective nature of this study. Instead, a home page was created, presenting information on the purpose of this study for subjects to read. It was emphasized that any subject could opt out of the study at any time via telephone, fax, or email.

This study enrolled patients with BRVO-ME who presented with a symptom duration of <3 months before their initial treatment and had visited 1 of the 4 aforementioned facilities between August 2012 and February 2021. At the initial visit, none of the patients had received any treatment for BRVO-ME. The other study inclusion criteria were a baseline FT of > 300 μm, determined using OCT, and a minimum follow-up period of 24 months from baseline. At the initial visit, all eyes (100%) showed retinal hemorrhage and ME, with some showing serous retinal detachment at the fovea.

The patients received intravitreal anti-VEGF injections of ranibizumab (0.5 mg/0.05 mL, Lucentis; Novartis Pharma AG) or aflibercept (2.0 mg/0.05 mL, Eylea; Bayer Pharma AG) for the treatment of ME and serous retinal detachment at the fovea according to different regimens adhered to by each institute. In total, we evaluated 309 eyes from 309 consecutively presenting patients with unilateral and treatment-naïve acute BRVO (mean age: 67.5 ± 10.0 years; 118 men and 191 women). Twenty-eight eyes received 1 initial intravitreal anti-VEGF injection, and 281 eyes received 1 intravitreal anti-VEGF injection per month for the initial 2 months (from baseline to Month 2). None of the patients received treatment other than ranibizumab and aflibercept for ME (e.g., bevacizumab injection, grid laser photocoagulation, steroid treatment, and surgical intervention). After the administration of the initial injections at each facility, PRN injections were administered only when ME or serous retinal detachment was evident at the fovea on OCT sections and the patient's informed consent could be obtained. The same anti-VEGF agents were used for the initial and subsequent injections for each patient.

Study Examinations

Retinal specialists at each facility diagnosed acute BRVO based on a medical interview regarding the onset of visual impairment as well as fundus examinations, including slit-lamp biomicroscopy and OCT (Spectralis HRA + OCT, Heidelberg Engineering; RS-3000, Nidek; and 3D OCT-1, Topcon). To assess the retinal circulatory status, we performed fluorescein angiography (FA; Optos 200Tx Imaging System, Optos PLC) in, essentially, all the patients. However, FA was not performed in the following patient categories: patients who had shown allergic reactions to the dye used in FA and those who did not provide their consent for the FA examination. Additionally, we did not always perform FA for patients with macular BRVO, in which the affected retinal area was limited within the retinal vascular arcade. Moreover, FA was reperformed around 1 year after the start of the anti-VEGF treatment or when an increase in fresh retinal hemorrhage, peripheral white vessels, or neovascular changes was detected via routine examinations using ophthalmoscopy.

At each facility, we assessed the sex, age, BRVO subtypes (major BRVO or macular BRVO),[1,2,20] smoking history, hypertension, dyslipidemia, diabetes mellitus, ischemic heart disease, glaucoma, and posterior vitreous detachment at the initial visit. At each follow-up visit, we measured the patients' best-corrected visual acuity (BCVA) using the Landolt chart and measured their FT using OCT. Similarly, we measured the defect length of the foveal ellipsoid zone (EZ) band at each visit, except for the baseline visit. We examined the status of the affected eye at the baseline and at the 3-, 6-, and 12-month follow-up visits during the first year of the observation period. We subsequently conducted examinations every 12 months.

Table 1. Clinical Characteristics of All Patients with Branch Retinal Vein Occlusion

Variables	Counts (men/women)	*P* value
Total N	309 (191/118)	
Baseline		
Age (yrs), range (yrs)	67.5 ± 10.0 (40-91)	
Systemic hypertension	158 (51.3%)	
Dyslipidemia	72 (23.5%)	
Diabetes mellitus	33 (10.7%)	
Smoking	75 (25.3%)	
Ischemic heart disease	14 (4.6%)	
Clinical subtype; major BRVO/macular BRVO (n, %)	205 (66.3%)/104 (33.7%)	
Posterior vitreous detachment (n, %)	112 (36.4%)	
Glaucoma	39 (12.7%)	
Best-corrected visual acuity (logMAR)	0.30 ± 0.30	
Foveal thickness (μm)	503.1 ± 162.4	
Height of subretinal fluid at the fovea (μm)	99.0 ± 119.1	
Duration of observation period (mos)	50.6 ± 22.2	
Total number of injections	5.8 ± 4.6	
Vitreous hemorrhage (n, %)	12 (3.9%)	
Neovascular glaucoma (n, %)	0 (0.0%)	
Final		
Best-corrected visual acuity (logMAR)	0.09 ± 0.28	<0.001*
Foveal thickness (μm)	287.1 ± 103.3	<0.001*
Defect length in the foveal EZ band (μm)	189.0 ± 427.0	

*Comparisons between the parameters at the initial and final examinations were evaluated using paired t-tests.

BRVO = branch retinal vein occlusion; EZ = ellipsoid zone; logMAR = logarithm of the minimum angle of resolution.

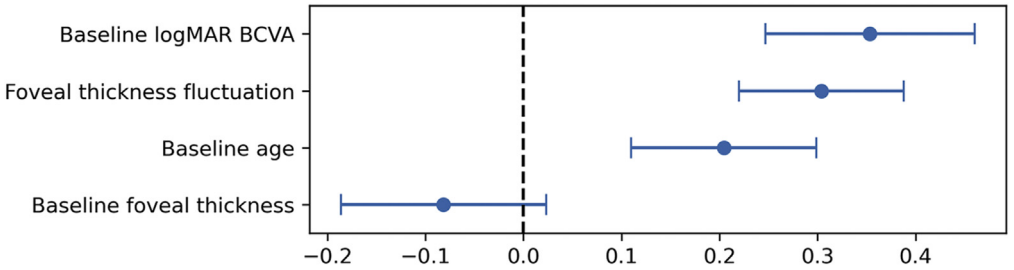

Figure 1. Multiple regression analyses determining the factors associated with the final logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity (BCVA). The multiple regression analyses showed that baseline foveal thickness was not associated with the final logMAR BCVA ($\beta = -0.08$), with an associated 95% confidence interval (CI) of −0.19 to 0.02 ($P = 0.126$). However, age, baseline logMAR BCVA, and foveal thickness fluctuation were statistically significantly associated with the final logMAR BCVA ($\beta = 0.20, 0.35, 0.30$, respectively), with associated 95% CIs of 0.11 to 0.30 ($P < 0.01$), 0.25 to 0.46 ($P < 0.01$), and 0.22 to 0.39 ($P < 0.01$), respectively. The vertical axis shows the explanatory variables, and the horizontal axis shows the regression coefficients. The blue lines indicate 95% CIs. We defined explanatory variables, wherein the 95% CIs do not include 0 as statistically significant.

Measurements of FT and the Defect Length of the Foveal EZ Band

We quantified the disruption in the foveal EZ band within the central 2 mm of OCT images horizontally and vertically dissecting the center of the fovea. We evaluated the signal intensity of the foveal EZ band on the OCT images using the plot profile function in ImageJ software (National Institutes of Health). This measurement method has been reported in prior studies.[25,26] We calculated the average value of the defect lengths of the foveal EZ band on the horizontal and vertical OCT sections. The defect lengths of the foveal EZ band were truncated to an upper limit of 2000 µm at the measurement stage.

We measured the FT using the OCT images of each eye based on a methodology described in a prior study.[23] More specifically, we created a thickness map of the whole retina using volume OCT scanning of the macula. Within the central subfield of the ETDRS grid, we defined FT as the mean distance between the vitreoretinal interface and the retinal pigment epithelium.

Definition and Classification of FTF

To evaluate the degree of BRVO-ME recurrence during the observation period, we calculated the standard deviation (SD) in the FT for each patient based on the FT values evaluated at each visit (except for the baseline visit). We divided the included patients evenly into 4 groups in ascending order of the SDs, ranging from group 0 (minimum SD) to group 3 (maximum SD), and compared the clinical parameters among the groups. The range of SD was 0 to 9.14, 9.14 to 34.31, 34.31 to 84.07, and 84.07 to 1 117 for group 0, 1, 2, and 3, respectively. This methodology has been previously reported in investigations conducted among patients with AMD.[23,24]

Statistical Analysis

All data were statistically analyzed using Python Statsmodels (https://www.statsmodels.org), the scikit-learn package (https://scikit-learn.org/), and Py4Etrics (https://github.com/Py4Etrics/py4etrics). The data are presented as means ± SDs. The visual

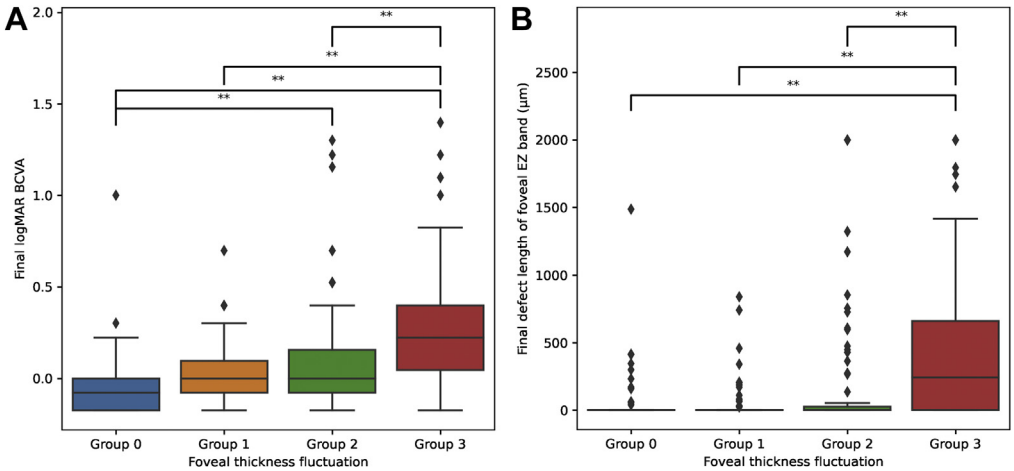

Figure 2. Associations of foveal thickness fluctuation (FTF) with the final logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity (BCVA) and the defect length of the foveal ellipsoid zone (EZ) band. Patients with greater FTF (group 3) had a statistically significantly poorer final logMAR BCVA than those with lesser FTF (groups 0, 1, and 2). **A,** Patients in group 3 had a statistically significantly longer defect of the foveal EZ band at their final examination than those with lesser FTF (groups 0, 1, and 2). **B,** Foveal thickness fluctuations were statistically significantly associated with both the logMAR BCVA and the defect length of the foveal EZ band at the final examination.

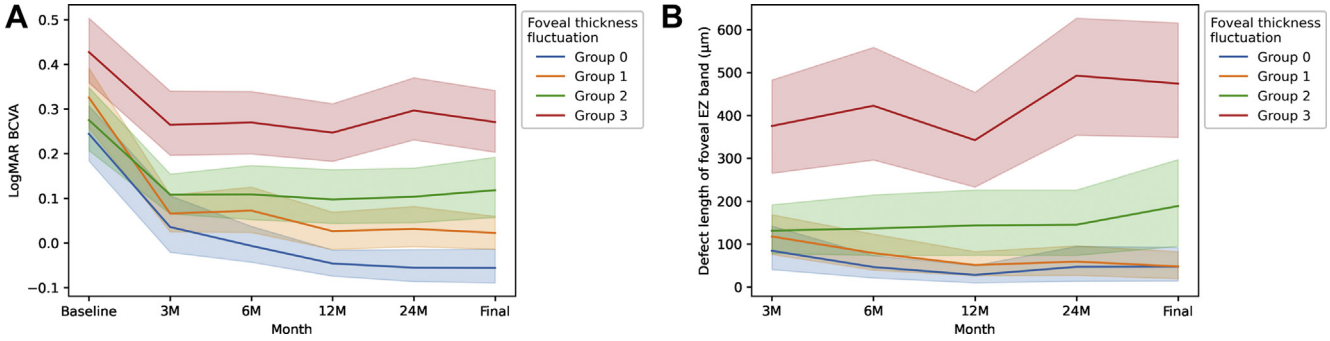

Figure 3. Longitudinal changes in the logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity (BCVA) and the defect length of the foveal ellipsoid zone (EZ) band according to foveal thickness fluctuation. **A,** The logMAR BCVA showed improvements in the smaller-foveal thickness fluctuation groups (groups 0 and 1), which worsened slightly in the larger-foveal thickness fluctuation groups (groups 2 and 3). **B,** The defect lengths of the foveal EZ band were longitudinally slightly shortened in groups 0 and 1 and slightly prolonged with time in groups 2 and 3.

acuities measured using the Landolt chart were converted to logarithm of the minimum angle of resolution (logMAR) units.

We performed multiple regression analyses using a linear model, in which the final logMAR BCVA was set as the objective variable; age, baseline logMAR BCVA, baseline FT, and FTF were set as explanatory variables based on the confirmation that there were no multicollinearities among these explanatory variables. Among the explanatory variables, continuous variables were standardized to a mean of 0 and a variance of 1. Additionally, we performed multiple comparisons of the final BCVA, final defect length of the foveal EZ band, and number of anti-VEGF injections among the groups. We used the Tukey honest significant difference method to compare the final BCVA and the defect length of the foveal EZ band and the Steel−Dwass method to compare the number of anti-VEGF injections required.

Missing values were calculated using the MissForest methodology.[18] This calculation was performed using the missingpy package (https://github.com/epsilon-machine/missingpy).

The statistical significance level for all the tests was set to 0.05.

Results

Table 1 shows the demographic data for all the included patients. At the baseline, the mean logMAR BCVA was 0.30 ± 0.30 and the mean FT was 503 ± 162 μm. The number of anti-VEGF injections for BRVO-ME was 5.8 ± 4.6 during a mean follow-up period of 50.6 ± 22.2 months.

At the final examination, the mean logMAR BCVA was 0.09 ± 0.28 and the mean FT was 287 ± 103 μm; these values were statistically significantly ameliorated compared with those at the baseline (both $P < 0.01$). We examined the associations between the final logMAR BCVA, baseline parameters, and FTF during the observation period to determine prognostic factors for the final BCVA (Fig 1). The multiple regression analysis showed that baseline FT was not statistically significantly associated with the final logMAR BCVA ($\beta = -0.08$), with an associated 95% confidence interval of −0.19 to 0.02 ($P = 0.126$). However, age, baseline logMAR BCVA, and FTF were statistically significantly associated with the final logMAR BCVA ($\beta = 0.20$, 0.35, 0.30, respectively), with associated 95% confidence intervals of 0.11 to 0.30 ($P < 0.01$), 0.25 to 0.46 ($P < 0.01$), and 0.22 to 0.39 ($P < 0.01$), respectively.

FTF, Visual Acuity, and Foveal Photoreceptor Status

We divided the included patients equally into 4 groups (groups 0−3) in ascending order of FTF during the observation period. The total number of anti-VEGF injections necessary during the observation period was statistically significantly greater in patients in groups 2 and 3 than in those in groups 0 and 1 (all $P < 0.01$; Fig S1, available at www.ophthalmologyretina.org).

Upon final examination, the defect length of the foveal EZ band was 47.2 ± 187 μm in group 0, 47.7 ± 144 μm in group 1, 188 ± 456 μm in group 2, and 474 ± 594 μm in group 3 (Fig 2). The final logMAR BCVA was −0.06 ± 0.17 in group 0, 0.02 ± 0.17 in group 1, 0.12 ± 0.30 in group 2, and 0.27 ± 0.33 in group 3. At the final examination, patients in group 3, who had the greatest FTF, had a statistically significantly longer defect of the foveal EZ band and a statistically significantly poorer logMAR BCVA than those in the other groups ($P < 0.01$; Fig 2). Foveal thickness fluctuation was statistically significantly and positively associated with logMAR BCVA and the defect length of the foveal EZ band in the final examination (Fig 2).

FTF and Longitudinal Changes in Visual Acuity and Foveal Photoreceptor Status

Next, we examined the longitudinal changes in logMAR BCVA and the defect lengths of the foveal EZ band in each group (Fig 3). The defect lengths of the foveal EZ band were longitudinally slightly shortened in the lesser-FTF groups (groups 0 and 1) and slightly prolonged with time in the larger-FTF groups (groups 2 and 3) (Fig 4). The logMAR BCVA showed improvements in groups 0 and 1 and worsened slightly in groups 2 and 3 (Fig 4).

Discussion

This multicenter study enrolled 309 patients with treatment-naïve acute BRVO. Herein, we examined the long-term results of anti-VEGF treatments for BRVO-ME. We administered an additional injection with an anti-VEGF agent at each ME recurrence. An average of 5.8 injections of anti-VEGF agents were necessary during the mean

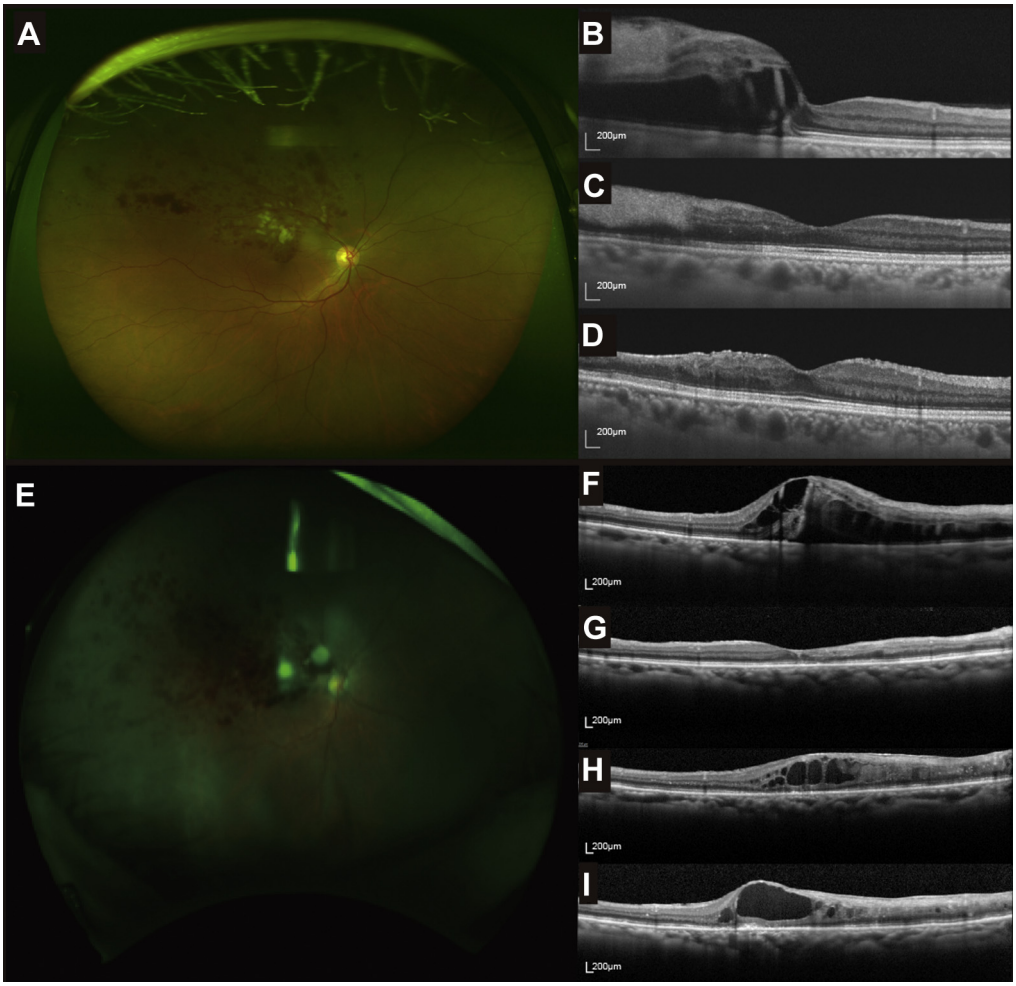

Figure 4. Representative cases with lesser and greater foveal thickness fluctuation (FTF) observed during the observation period. **A–D,** A representative case with less FTF occurring in a 64-year-old woman. **A,** A baseline ultrawide-field pseudo-color image showed temporal superior major branch retinal vein occlusion (BRVO). **B,** A baseline OCT image (a foveal vertical scan) showed macular edema (ME) of the superior side of the fovea. The patient's baseline best-corrected visual acuity (BCVA) was 20/50. Her baseline central foveal thickness (CFT) was 544 μm, and her baseline foveal ellipsoid zone (EZ) band defect length was 68.5 μm. **C,** An OCT image after 3 doses of intravitreal ranibizumab (IVR) demonstrated that the ME had disappeared. The patient's BCVA was 20/20, and her CFT was 242 μm. The patient's foveal EZ band defect length was 0.0 μm. **D,** A final OCT image 84M after the first injection. No recurrence of ME was observed after treatment with IVR. Her final BCVA was 20/20, and her final CFT was 240 μm. The final foveal EZ band defect length was 0.0 μm. **E–I,** A representative case with fluctuation in the right eye in an 83-year-old woman. **E,** A baseline ultrawide-field pseudo-color image showed temporal superior major BRVO. **F,** A baseline OCT image (foveal vertical scan) showed ME at the superior side of the fovea. Her baseline BCVA was 20/50, baseline CFT was 904 μm, and baseline foveal EZ band defect length was 342 μm. **G,** An OCT image after 3 doses of IVR. The patient's BCVA was 20/32, CFT was 262 μm, and foveal EZ band defect length was 267 μm. **H,** After 3 courses of IVR administered every few months, ME recurred in her fovea several times. **I,** A final OCT image 68M after the first injection (for a total of 10 doses of IVR) demonstrated that the patient's macula eventually developed cystoid macular degeneration. Her final BCVA was 20/100, final CFT was 653 μm, and final foveal EZ band defect length was 616 μm.

observation period of 50.6 months. Although the number of treatments was lesser than that in prior studies with a shorter duration of follow-up,[27,28] we found that the final BCVA improved substantially and that the mean final FT was statistically significantly decreased compared with those at the baseline (both $P < 0.01$; Table 1). These results suggest that the PRN regimen evaluated in this study achieved the same visual and morphologic outcomes as the results of prior studies with shorter follow-up periods[6,13,28–31] and that this regimen was effective during long-term follow-up.

Systemic pathologies, such as aging, hypertension, and atherosclerosis, are known risk factors for the development of BRVO.[7–10,12] In eyes with BRVO occurring at arteriovenous crossing sites, researchers have postulated that the thickening and stiffening of the retinal arterial wall leads to venous narrowing and turbulent flow within the adjacent retinal vein, resulting in endothelial damage and thrombus formation.[32–34] Downstream of these pathologies, intraocular VEGF is upregulated and ME can occur in the affected eyes. Vitreous injections of anti-VEGF agents suppress upregulated VEGF and contribute to the absorption of ME.

However, anti-VEGF agents do not act on obstructive mechanisms in the retinal veins. Therefore, ME often recurs as the intravitreal concentrations of the anti-VEGF agents decrease and the VEGF levels consequently increase.[35]

Prior studies have demonstrated that patients with diabetic ME and larger FTF had poorer BCVA.[36] Similarly, patients with neovascular AMD and larger FTF had poorer visual acuity as well as macular fibrosis and atrophy during an observation period of 2 years.[23] Moreover, in 30 eyes with chronic ME associated with retinal vein occlusion, Kurashige et al[37] examined the changes in foveal photoreceptor status during a mean observation period of 17.2 ± 5.5 months and found that neither visual acuity nor foveal photoreceptor status statistically significantly changed during the observation period, in contrast to what had previously been the conventional medical wisdom. However, because most of these eyes had undergone surgical and medical treatments before study inclusion,[37] the clinical significance of FTF was not well studied in treatment-naïve patients with acute BRVO. In the current study, we calculated the SDs in the FT for each patient using the FT values measured at each visit (except for those at the baseline) to evaluate the degree of BRVO-ME recurrence during the observation period (Figs 2 and 3).

Patients with greater FTF had statistically significantly longer defects of the foveal EZ band and poorer BCVA at their final examination than those with lesser FTF (Fig 2). Moreover, we found that FTF affected the longitudinal changes in BCVA as well as foveal photoreceptor status similarly (Figs 3 and 4). These results may suggest that eyes with greater FTF promote the progression of foveal photoreceptor damage and visual impairment. We believe that the PRN regimen used in this study was useful in the long-term management of most patients with BRVO. However, there might be an indication for a more aggressive regimen than the PRN regimen while treating eyes with greater FTF. For example, for diabetic ME[38] and AMD,[39] the efficacy of anti-VEGF treatments using a treat-and-extend regimen has been reported in several clinical studies. As reported recently,[40] it is expected that the usefulness of the treat-and-extend regimen for BRVO-ME as well as the characteristics of patients receiving this or other regimens will be clarified more thoroughly and comprehensively in the future.

The current study had several limitations, the most significant of which was its retrospective design. Thus, the administered anti-VEGF agents and the duration of the follow-up varied among the enrolled patients. Second, because the current study was conducted in a multicenter setting, the examiners and imaging devices were not standardized, which might have caused a bias in the measurements. Third, some of the enrolled patients with BRVO had systemic and other ocular diseases, which might have affected the results. Fourth, we only measured the FTs at the time when the patients visited each facility. Hence, the actual status of ME during each visit interval is not precisely known.

The current study provides critically important, novel information based on comprehensive evaluations of the long-term results of anti-VEGF treatment with a PRN regimen for the treatment of BRVO-ME. Our findings showed that the baseline parameters, such as age and initial BCVA, were associated with the prognoses of visual acuity and foveal photoreceptor status. Additionally, our findings indicate that FTF during follow-up was involved in the longitudinal changes and final values of these parameters.

In conclusion, we may improve the morphologic and functional prognoses of eyes with BRVO by identifying the characteristics of eyes with greater FTF and consequently controlling the FTF more strictly. New, highly powered prospective studies will be needed to confirm the results of this investigation. Hence, our results can inform future research directions and, if confirmed, will directly inform medical guidelines regarding the treatment of BRVO.

Footnotes and Disclosures

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HUMAN SUBJECTS: This retrospective study adhered to the tenets of the Declaration of Helsinki and was approved by the ethics committee of Saneikai Tsukazaki Hospital (Hyogo, Japan), the Kyoto University Graduate School of Medicine (Kyoto, Japan), the Tokushima University Faculty of Medicine (Tokushima, Japan), and the Kagawa University Faculty of Medicine (Kagawa, Japan). Written informed consent was not obtained from all the subjects because of the retrospective nature of this study. Instead, a home page was created, presenting information on the purpose of this study for subjects to read. It was emphasized that any subject could opt out of the study at any time via telephone, fax, or email. All research complied with the Health Insurance Portability and Accountability Act of 1996 and adhered to the tenets of the Declaration of Helsinki.

No animals were used in this study.

Author Contributions:

Conception and design: Nagasato, Muraoka, Tsujikawa

Analysis and interpretation: Nagasato, Muraoka, Tanabe, Nishigori, Osaka, Mitamura, Tsujikawa

Data collection: Nagasato, Muraoka, Nishigori, Osaka, Mitamura, Tabuchi, Kadomoto, Murakami, Ooto, Suzuma, Tsujikawa

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **BRVO** = branch retinal vein occlusion; **EZ** = ellipsoid zone; **FA** = fluorescein angiography; **FT** = foveal thickness; **FTF** = foveal thickness fluctuation; **logMAR** = logarithm of the minimum angle of resolution; **ME** = macular edema; **PRN** = pro re nata; **SD** = standard deviation.

Keywords:
A long-term multicenter study, Anti-VEGF treatment, Branch retinal vein occlusion, Foveal thickness fluctuation.

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