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RETINAL BLOOD FLOW AFTER INTRAVITREAL BEVACIZUMAB IS A PREDICTIVE FACTOR FOR OUTCOMES OF MACULAR EDEMA ASSOCIATED WITH CENTRAL RETINAL VEIN OCCLUSION

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Purpose: To investigate whether retinal blood flow levels after intravitreal bevacizumab (IVB) treatment are correlated with the outcomes of patients with macular edema secondary to central retinal vein occlusion.

Methods: This retrospective observational case study enrolled 44 cases nonischemic central retinal vein occlusion. In each patient, visual acuity, central retinal thickness, and mean blur rate, which was measured by laser speckle flowgraphy and represents retinal blood flow velocity, were examined.

Results: At the end of the follow-up period (19.8 ± 8.8 months), 4 of 44 eyes (9.1%) converted to the ischemic type (converted group), whereas 40 (90.9%) remained unchanged (nonischemic group). Mean central retinal thickness significantly decreased and mean visual acuity significantly improved at 1 month after the first IVB injection in each group. Mean mean blur rate in the nonischemic group significantly increased, whereas it was unchanged in the converted group. The difference between the two groups was already significant after the first IVB injection. Subsequently, visual acuity worsened in the converted group. Multiple linear regression analysis indicated that the strongest correlation was between the last visual acuity and the last mean blur rate.

Conclusion: Blood flow measurements are useful for evaluating IVB treatments. Blood flow after IVB can predict outcomes in patients with central retinal vein occlusion.

RETINA 38:283–291, 2018

In central retinal vein occlusion (CRVO), the degree of ischemia varies among individual cases and according to the actual stage of the disease.[1] Visual function loss because of CRVO is strongly dependent on the extent of the macular edema and the development of retinal ischemia. Visual outcomes have historically been reported to be good in nonischemic CRVO and poor in ischemic CRVO.[1,2] Vascular endothelial growth factor (VEGF) is the primary mediator of the retinal angiogenesis and macular edema.[3–5] Therefore, the anti-VEGF agent, bevacizumab (Avastin; Roche, Reinach, Switzerland), has been used as an off-label indication for treating macular edema associated with CRVO.

Many studies have suggested that intravitreal bevacizumab (IVB) injections can lead to a significant reduction of the macular edema and improve the visual acuity.[6,7] However, the therapeutic benefit of this approach is often temporary or ineffective, despite patients receiving multiple intravitreal injections.[8] More recently, clinical trials that have examined anti-VEGF

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Supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture (25861638), and by the Japan National Society.

None of the authors have any conflicting interests to disclose.

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agents, such as ranibizumab (CRUISE[9]) and aflibercept (COPERNICUS,[10] GALILEO[11]), have led to the approval of treatments for macular edema related to CRVO.

Ocular blood flow measurements are a commonly used parameter for a variety of ophthalmic diseases. Color Doppler imaging,[12] laser Doppler velocimetry,[13] laser speckle flowgraphy (LSFG) (LSFG-NAVI; Softcare Co, Ltd, Fukuoka, Japan),[14–20] and the retinal functional imager methodologies[21] have all been used as noninvasive techniques to evaluate the ocular blood flow. The LSFG is a new technique that has been used for visualizing blood flow distributions in the ocular fundus. The LSFG is convenient for measuring blood flows and can be used for clinical applications.

The aim of the present study was to determine whether retinal blood flow levels are correlated with the outcomes in IVB-treated patients with macular edema related to CRVO.

Methods

This retrospective observational case series study was conducted in accordance with the Declaration of Helsinki. After approval by the Review Committee of the Institutional Research Board of Nagasaki University Hospital, consecutive patients with macular edema related to CRVO were enrolled in the study and underwent IVB treatment at Nagasaki University Hospital between June 2010 and August 2013. Subjects were excluded if proper measurements could not be obtained (e.g., in patients with cataracts with severe opacity, vitreous hemorrhage, poor mydriasis, or corneal opacity), if they had previous vitreoretinal surgery, if they were classified as ischemic type, or if they had been observed for <12 months. After obtaining informed consent from the patients, an IVB injection (1.25 mg, 0.05 mL) was performed via the pars plana using a 30-gauge needle. Injections were performed at 3.5 mm posterior to the limbus.

At each visit, every patient underwent measurements that included best-corrected visual acuity, central retinal thickness (CRT) measured by optical coherence tomography, retinal blood flow measured by LSFG, along with ophthalmic examinations performed by slit-lamp biomicroscopy. Patients also underwent fluorescein angiography at their first visit and whenever it was deemed appropriate. According to the Central Retinal Vein Occlusion Study Group,[22] ischemic type is defined as a case with more than 10 disc areas of nonperfusion. In the current study, when fluorescein angiography identified a case as the ischemic type, we immediately performed panretinal photocoagulation. If the macular edema persisted at 1 month after the first treatment (CRT $\geq$ 300 μm), patients underwent a repeat treatment. When the macular edema resolved (CRT $<$ 300 μm), we then performed follow-up examinations every month until the macular edema recurred. Recurrence of macular edema was treated in all instances. Intravitreal bevacizumab treatments were decided based on the period of the first recurrence. When macular edema recurred or persisted (CRT $\geq$ 300 μm), patients were given IVB. Repeat examinations were performed at 1 month after every treatment.

We retrospectively observed and divided the cases into two groups based on the clinical course. Nonischemic type cases at their first visit were classified according to whether they converted to the ischemic type (converted group) or remained as a nonischemic type (nonischemic group) on the final day of observation.

Laser Speckle Flowgraphy Blood Flow Measurements

Measurements were obtained using the LSFG system (LSFG-NAVI; Softcare Co, Ltd, Fukuoka, Japan) (Figure 1). As has been previously described,[14,15] use of the LSFG technique makes it possible to measure the optic disc. The most recent iteration of the instrument uses a fundus camera that is equipped with a diode laser (wavelength, 830 nm) and a highly sensitive charge-coupled device camera (750 × 360 pixels), which has a scanning speed of 30 frames per second. Blood flow observations in the fundus are performed by using a wide laser spot to illuminate the area of interest. As a result, the back-scattered laser from the spot forms a speckled pattern in the image plane of the fundus. The charge-coupled device camera is then used to detect the intensity variation of the pattern. In the human fundus, the

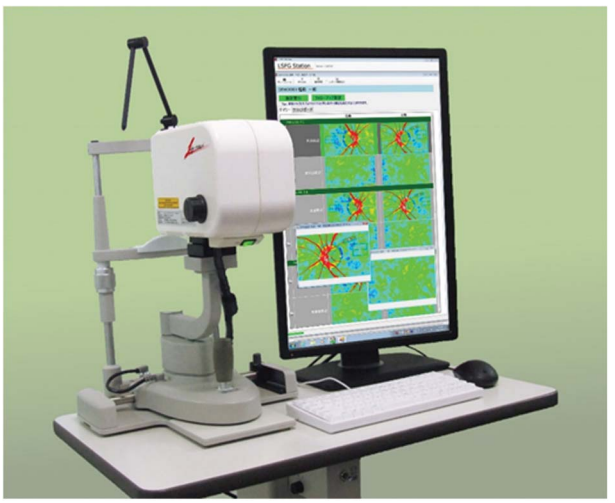

Fig. 1. Appearance of LSFG.

viewable area corresponds to a field of 8 mm × 3.8 mm (21° visual angle of the fundus camera).

We evaluated microcirculation at the optic nerve head by measuring the mean blur rate (MBR) of the optic disc, as per previous reports.[23–25] The blood flow velocity evaluated by the MBR was expressed in arbitrary units and displayed as a 2-dimensional color-coded map. After demarcating a circle around the optic disc by hand using an oval band, we then investigated the MBR of the major vessels (arteries and veins) within the area of this circle.

Figure 2 shows a composite map (A) within the optic disc and its histogram (B). The vertical axis corresponds to the number of pixels, whereas the horizontal axis corresponds to the MBR in the histogram. The appropriate threshold between the tissue and vessel areas was automatically determined by the software. The histogram seen in Figure 2D shows the division between the tissue and vessel areas that was determined from the image shown in Figure 2C. The area to the left of the threshold line corresponds to the tissue area of the optic disc (black area in Figure 2C), whereas the area to the right corresponds to the vessel area of the optic disc (white area in Figure 2C). Since the MBR in the vessel area includes the choroidal blood flow, we subtracted the mean MBR in the tissue area from the mean MBR in the vessel area. Thus, the MBR used to evaluate the blood flow in the retinal vessel excluded the choroidal blood flow. All measurements were performed three times, with the average used as the MBR value. The coefficient of variation was 8.2 ± 4.2%. Because the eye positions were recorded by performing the LSFG measurements with an auto tracking function, this made it possible to capture the same area during each of the subsequent examinations with high reproducibility.

To compare the MBR in different eyes and among different patients, we also evaluated the rate of change during the treatment, with the values obtained before the treatment designated as 100%.

Retinal Thickness Analysis

Central retinal thickness determinations were performed by optical coherence tomography (Cirrus TM HD-OCT; Carl Zeiss Meditec, Dublin, CA) using the Macular Cube 512 × 128 scanning protocol, which measured the mean retinal thickness in the central 1,000-μm diameter area.

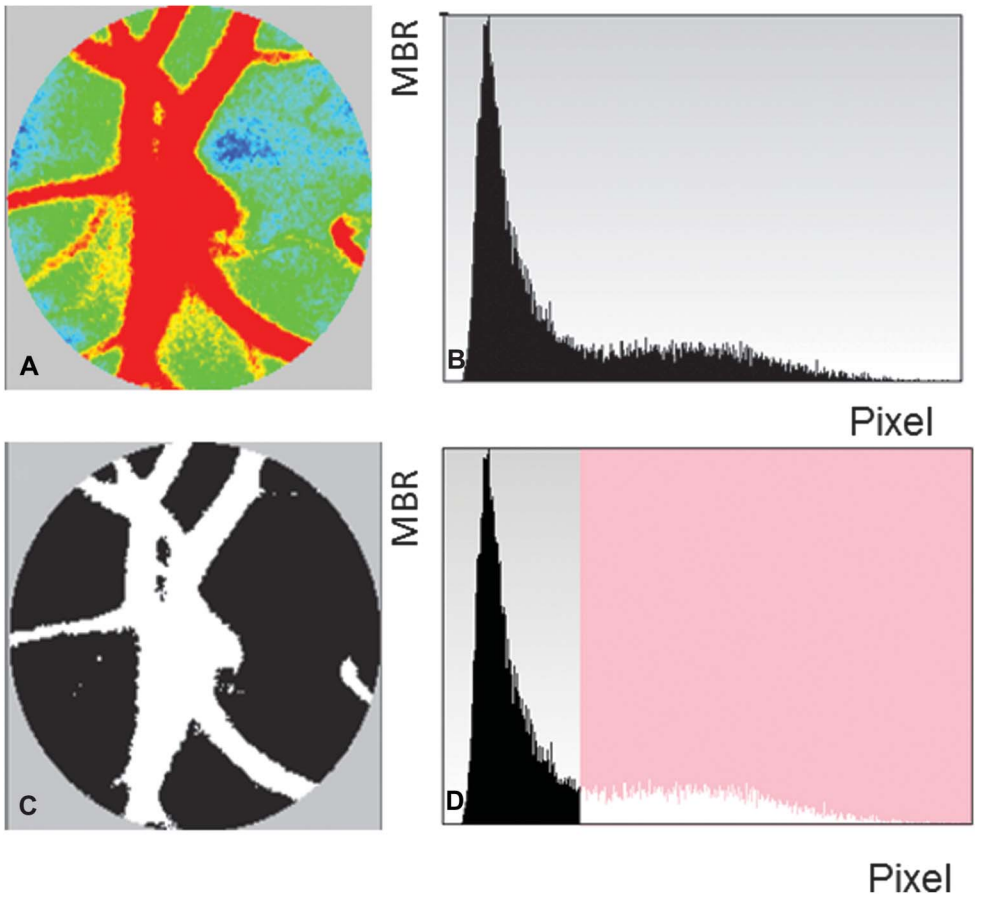

Fig. 2. A composite map and a histogram within the optic disc that was produced when using the LSFG. A false-color composite map within the optic disc is shown (**A**). Red indicates a faster blood flow, whereas blue indicates a slower blood flow. A histogram within the optic disc is shown (**B**). The vertical axis corresponds to the number of pixels, whereas the horizontal axis corresponds to the MBR. Representative binary format images for segmentation between the vessel (white area) and the tissue (black area) are shown (**C**). The histogram was analyzed using image viewer software that uses an automated definitive threshold (**D**). The area to the left of the threshold line corresponds to the tissue of the optic disc (black area in **C**), whereas the area to the right of the line corresponds to the vessel of the optic disc (white area in **C**).

Statistical Analysis

The primary objective of this study was to determine whether a correlation existed between the retinal blood flow levels and the outcomes of patients treated with IVB for macular edema secondary to CRVO. In the first step, we compared the outcomes between the nonischemic and converted groups, with the Mann–Whitney *U* test and Pearson chi-square test used for the comparisons. A Dunnett test was used to compare the posttreatment and pretreatment values for the mean CRT and the mean MBR in each group. We also performed linear regression analysis to evaluate the last logarithm of the minimum angle of resolution (logMAR) visual acuity and other factors, along with tests of the regression. We performed the multiple regression analysis using the 37 cases that had complete data. All statistical analyses were carried out using Statflex ver. 6.0 software (Artech Co, Ltd, Osaka, Japan). Results are expressed as mean ± standard deviation, unless otherwise indicated. *P*-values < 0.05 were considered to indicate statistical significance.

Results

This study assessed a total of 44 eyes in 44 consecutive nonischemic type patients with CRVO (25 men and 19 women), with a mean age of 66.1 ± 11.9 years. None of these patients had any previous treatments for macular edema related to CRVO. Of the total number of patients, 28 had hypertension, 8 had diabetes mellitus, 1 had cardiovascular disease, and 8 had no past clinical history.

Of the 44 nonischemic eyes, 4 (9.1%) eyes converted to the ischemic type during the study. Duration from CRVO onset to the first IVB treatment was 4.6 ± 7.0 months. The follow-up period was 19.8 ± 8.8 months.

Based on the clinical course, we divided these patients into two groups: the nonischemic group and the nonischemic → ischemic type group (converted group). Table 1 presents the characteristics of each group. There were no significant differences observed between the two groups for sex, age, duration from CRVO onset to the first IVB injection, and history. However, a significant difference was observed for the number of IVB treatments (nonischemic group: 4.3 ± 3.2 times, converted group: 13.0 ± 7.2 times, $P = 0.02$, Mann–Whitney *U* test).

Figure 3 shows the changes in the mean visual acuity (Snellen visual acuity ratio equivalent to mean logMAR visual acuity calculated) for each group. Significant improvement was observed for the mean visual acuity of the nonischemic group (before treatment: 20/100, 1 month after the first IVB injection: 20/50, at the final visit: 20/40) (before treatment: 0.69 ± 0.41, 1 month after the first IVB injection: 0.39 ± 0.42, $P < 0.01$, and at the final visit: 0.30 ± 0.37, $P < 0.01$, Dunnett test in logMAR visual acuity, respectively). However, a worsening of the mean visual acuity was observed for the converted group (before treatment: 20/200, 1 month after the first IVB injection: 20/70, at the final visit: 20/400; before treatment: 1.01 ± 0.46, 1 month after the first IVB injection: 0.50 ± 0.24, and at the final visit: 1.33 ± 0.37 in logMAR visual acuity, respectively). There was a significant difference for the mean logMAR visual acuity between the two groups at the final visit (Mann–Whitney *U* test).

Figure 4 presents the changes in the mean CRT found in each group. In the nonischemic group, there was a significant decrease observed in the mean CRT (before treatment: 596 ± 166 μm vs. 1 month after the first IVB injection: 326 ± 118 μm, $P < 0.01$, at the final visit: 279 ± 57, $P < 0.01$, Dunnett test). Similarly, the mean CRT after the first IVB injection and at the final visit in the converted group was also significantly lower than that observed before treatment (before treatment: 700 ± 174 μm vs. 1 month after the first IVB injection: 287 ± 36 μm, $P < 0.05$, at the final visit: 334 ± 266, $P < 0.05$, Dunnett test).

The change in the mean MBR in each group is shown in Figure 5A. In the nonischemic group, the mean MBR significantly increased (before treatment: 21.1 ± 10.5 vs. 1 month after the first IVB injection: 25.9 ± 12.9, $P < 0.05$, at the final visit: 30.8 ± 12.0,

Table 1. Group Characteristics (n = 44)

	Nonischemic Group	Converted Group	*P*	All
No. (male/female)	40 (22/18)	4 (3/1)	0.44	44 (25/19)
Age	65.7 ± 12.3	70.5 ± 7.3	0.21	66.1 ± 11.9
Duration from CRVO onset to the first IVB injection, months	4.3 ± 7.1	7.5 ± 6.5	0.09	4.6 ± 7.0
No. of IVB injection	4.3 ± 3.2	13.0 ± 7.2	0.02	5.1 ± 4.4
History, n (%)				
Hypertension	25 (62.5)	3 (75.0)	0.62	28 (63.6)
Diabetes mellitus	8 (20.0)	0	0.33	8 (18.2)
Cardiovascular disease	1 (2.5)	0	0.75	1 (2.3)

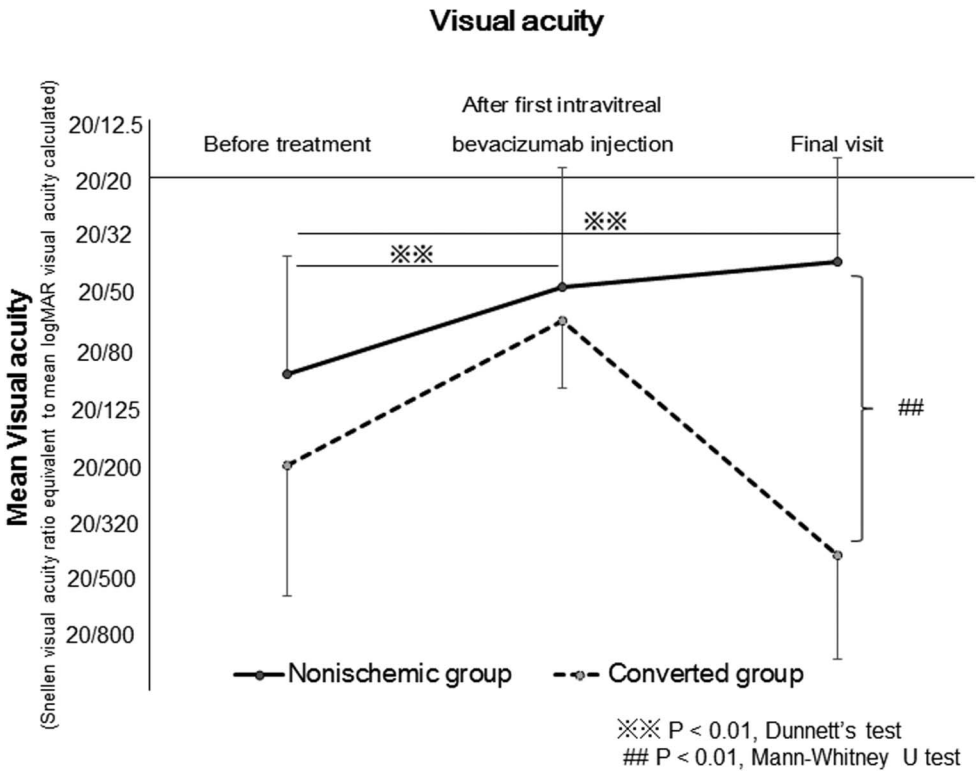

Fig. 3. Changes of the mean visual acuity that occurred in each group. Significant improvement was observed for the mean visual acuity of the nonischemic group (before treatment: 20/100, 1 month after the first IVB injection: 20/50, at the final visit: 20/40) (before treatment: 0.69 ± 0.41, 1 month after the first IVB injection: 0.39 ± 0.42, $P < 0.01$, and at the final visit: 0.30 ± 0.37, $P < 0.01$, Dunnett test in logMAR visual acuity, respectively) (n = 40). However, a worsening of the mean visual acuity was observed for the converted group (before treatment: 20/200, 1 month after the first IVB injection: 20/70, and at the final visit: 20/400) (before treatment: 1.01 ± 0.46, 1 month after the first IVB injection: 0.50 ± 0.24, and at the final visit: 1.33 ± 0.37 in logMAR visual acuity, respectively) (n = 4). There was a significant difference for the mean logMAR visual acuity between the 2 groups at the final visit (20/40 and 20/400 in Snellen visual acuity ratios, respectively).

$P < 0.01$, Dunnett test). In the converted group, however, the MBR was unchanged (before treatment: 13.7 ± 7.4, 1 month after the first IVB injection: 10.3 ± 5.5, at the final visit: 11.9 ± 4.7). The differences between the mean MBR values after the IVB injection in the nonischemic versus the converted group were

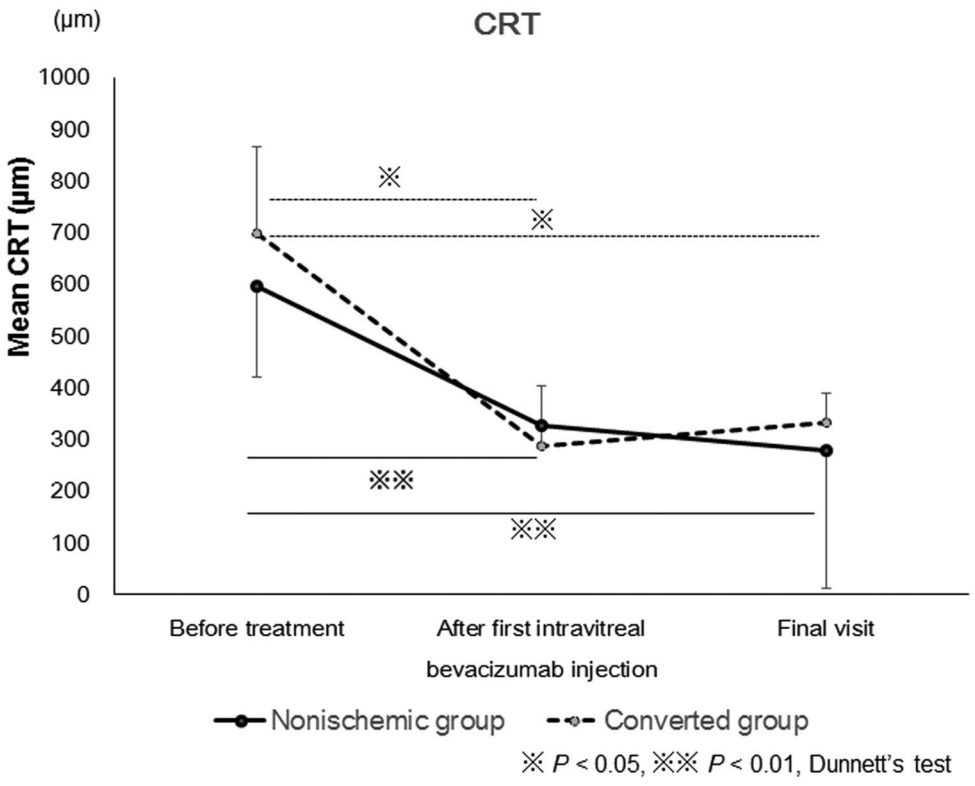

Fig. 4. Changes of the mean CRT in each group (the nonischemic group: n = 40, the converted group: n = 4). The mean CRT after the first IVB injection and at the final visit in each group was significantly lower than that observed before treatment.

statistically significant ($P < 0.01$, Mann–Whitney U test). Figure 5B shows the changes in the mean MBR ratio in each group, with a significant increase noted for the MBR ratio in the nonischemic group after the IVB (before treatment: 100% vs. 1 month after the first IVB injection: 130 ± 56%, $P < 0.01$, at the final visit: 162 ± 65%, $P < 0.01$, Dunnett test). In the converted group, however, the MBR ratio was unchanged after the IVB (before treatment: 100%, 1 month after the first IVB injection: 78 ± 34%, at the final visit: 93 ± 29%). Significant differences were found between the mean MBR ratio after the IVB in the nonischemic versus the converted group (1 month after the first IVB injection, $P < 0.05$; at the final visit, $P < 0.05$, t-test). There were no significant differences in the intraocular pressure and the ocular perfusion pressure between the two groups or between the same group before and after the IVB injection (Table 2).

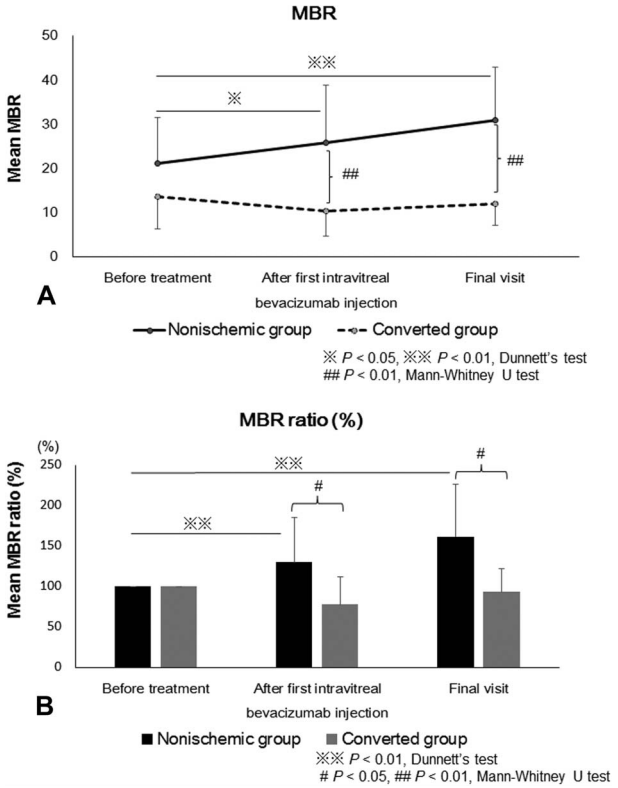

Fig. 5. A. Changes of the mean MBR (MV–MT) in each group. In the nonischemic group (n = 35), the mean MBR significantly increased. In the converted group (n = 4), however, the mean MBR decreased. The differences between the mean MBR values after the IVB injection in the nonischemic versus the converted group were statistically significant ($P < 0.01$). **B.** Changes of the mean MBR ratio in each group. A significant increase was observed for the MBR ratio in the nonischemic group (n = 34) after the IVB injection. In the converted group (n = 4), however, the MBR ratio decreased after the IVB injection. Significant differences were found between the mean MBR ratio after the IVB treatment in the nonischemic versus the converted group (1 month after the first IVB injection, $P < 0.05$, at the final visit, $P < 0.05$, t-test). MT, MBR in the tissue area; MV, mean MBR in the vessel area.

Our investigation into the correlation between the last logMAR visual acuity and other factors indicated that significant correlations were present. These results showed that there were correlations with the age (P = 0.01, r = 0.37 linear regression analysis), the logMAR visual acuity before the first IVB injection (P = 0.0000005, r = 0.67), the logMAR visual acuity at 1 month after the first IVB injection (P = 0.00002, r = 0.59), the CRT before the treatment (P = 0.009, r = 0.39), the MBR at 1 month after the first IVB injection (P = 0.004, r = −0.45), and the MBR at the final visit (P = 0.00009, r = −0.57). No statistically significant correlations were observed for the duration of the CRVO before the start of the IVB treatments, the CRT at 1 month after the first IVB injection, the CRT at the last visit, and the MBR before treatment. We performed a multiple regression analysis with the dependent factor defined as the logMAR visual acuity at the last visit, and the independent factors defined as the gender, age, lens states, duration from the CRVO onset to the first IVB injection, MBR, and CRT. Multiple linear regression analyses that examined the last logMAR visual acuity showed that the strongest correlation was between the MBR at the final visit and the last logMAR visual acuity (n = 37, because some MBR date and duration from the CRVO onset to the first IVB treatment date defect, standard partial regression coefficient: −0.55, P = 0.0001) (Table 3). The next strongest correlation was between the CRT before the first IVB and the last logMAR visual acuity (standard partial regression coefficient: 0.31, P = 0.02).

Discussion

Although off-label IVB can be very effective for the treatment of macular edema secondary to CRVO, previous reports have shown that it is not effective in all cases.[6–8,26] According to the RETAIN study,[27] in which patients were treated with ranibizumab with a mean follow-up of 49.7 months, the edema resolved in 14 of 32 patients with CRVO (44%). In our study, many cases experienced recurrence of macular edema.

A previous study by the Central Retinal Vein Occlusion Study Group reported the percentage of cases that converted from the nonischemic to the ischemic type at 4 months and 3 years was 15% and 34%, respectively.[1] The conversion percentage in our study was 9.1%, with a mean follow-up period of 19.7 ± 8.4 months. This decreased value might be related to the actual IVB treatment. The Rubeosis Anti-VEGF (RAVE) trial reported that the risk of neovascular complications was not ameliorated by VEGF blockade but rather was merely delayed.[28] Thus, the reason why

Table 2. Intraocular Pressure and Ocular Perfusion Pressure in Each Group

	Before the First IVB Injection	After the First IVB Injection	At the Final Visit
Intraocular pressure, mmHg			
Nonischemic group	13.8 ± 2.7	13.2 ± 3.2	13.8 ± 2.6
Converted group	13.6 ± 2.5	13.1 ± 3.2	13.6 ± 2.6
Ocular perfusion pressure, mmHg			
Nonischemic group	54.4 ± 20.7	51.9 ± 20.7	49.5 ± 15.9
Converted group	54.8 ± 18.6	51.8 ± 20.1	49.4 ± 16.3

Ocular perfusion pressure = 2/3 average artery pressure–intraocular pressure.

there were only a few cases that converted from the nonischemic to the ischemic type in our current study might be because the anti-VEGF therapy delayed the time to conversion to ischemia.

Advanced age is a known risk factor for CRVO.[29,30] Similarly, age has also been shown to be a risk factor for CRVO among those receiving bevacizumab therapy.[8] In our study, there was a strong and significant correlation between the last logMAR visual acuity and the age.

Results of the analyses of the previous BRAVO and CRUISE clinical trials suggested that initial treatments should be immediately started in patients with CRVO.[31] Although our study did not find any significant differences for the evaluated groups, there was a longer duration from the CRVO onset to the first IVB in the converted (7.5 ± 6.5 months) versus the nonischemic (4.3 ± 7.1 months) group. This suggests that an earlier intervention might be better for the anti-VEGF treatments used for CRVO.

Our study also found that IVB treatments were more frequently performed in the converted group (nonischemic group: 4.3 ± 3.2 times, converted group: 13.0 ± 7.2 times, $P = 0.02$, Mann–Whitney U test). This suggested that the grade of ischemia does not necessarily improve in response to frequent IVB treatments. Additionally, it has been reported that anti-VEGF therapy can attenuate the increases in the areas of nonperfusion.[9,32–34] However, the RAVE clinical trial reported that the risk of neovascular complications was not ameliorated by VEGF blockade but was merely delayed.[28] Therefore, we speculate that this effect might be limited in accordance with the grade of the ischemia.

Table 3. Multiple Liner Regression (Dependent Factor: The LogMAR Visual Acuity at the Last Visit) (Except for Factors of Visual Acuity) (n = 37)

Independent Factor	Standard Partial Regression Coefficient	P
MBR at the final visit	−0.55	0.0001
CRT before the first IVB injection	0.31	0.02

As previously reported,[6,7] the mean CRT significantly decreased at 1 month after the initial IVB treatment in both groups. Thereafter, the CRT either decreased or persisted until after the last treatment. Although there was improvement in the mean visual acuity at 1 month after the first IVB treatment in both groups, a worsening of the mean visual acuity was observed in the converted group (1 month after the first IVB injection: 20/70, at the final visit: 20/400, 8 lines of worsening using ETDRS letter scores). Furthermore, there was also a significant difference between the nonischemic and the converted groups for the mean logMAR visual acuity at the final visit (Mann–Whitney U test).

In our previous study, we found that patients with a good response to IVB exhibited a decreased CRT and an increased MBR after treatment.[35] Although we found that there was no significant difference for the mean MBR before the treatment (nonischemic group: 21.1 ± 10.5, converted group: 13.7 ± 7.4, $P = 0.21$, Mann–Whitney U test) when we compared the 2 groups, we did find that there was a significant difference for mean MBR at 1 month after the first IVB injection (nonischemic group: 25.9 ± 12.9, converted group: 10.3 ± 5.5, $P = 0.003$, Mann–Whitney U test). In addition, there was a significant increase in the MBR value in the nonischemic group after the IVB injection. However, in the converted group, the MBR value was unchanged after the IVB injection. Thus, the MBR after an IVB injection might be a predictive factor for the outcomes of macular edema associated with CRVO.

Multiple linear regression analysis confirmed that there was a significant correlation between the visual acuity and retinal blood flow. These data suggest that we can predict outcomes in patients with CRVO by assessing blood flows after an IVB injection. Thus, patients who have an increase in the MBR after IVB might only require treatment with anti-VEGF therapy. However, additional treatments may be required for those patients who exhibit decreases in their MBR.

Rehak et al reported that early peripheral laser photocoagulation of a nonperfused retina improved

the vision in patients with CRVO.[36] Arvas et al reported that laser photocoagulation increased the retinal blood flow in eyes with CRVO.[37] Based on these reports, we can speculate that early photocoagulation might result in better outcomes.

There were several limitations for this study. Because this was a retrospective study, our patient numbers were limited, especially for the converted group, which only contained four patients. Thus, this rather few patients analyzed might make it difficult for a definitive statistical interpretation of our results. In addition, we only used one approach for the blood flow measurements. Laser Doppler instrumentation, like LSFG, is also noninvasive, and can be used to measure the absolute value of retinal blood flows.[13,38–40] Thus, ideally, different measurement methods (e.g., the use of laser Doppler instrumentation) should be used when undertaking these types of studies. Furthermore, bevacizumab was not used for the treatment of macular edema related to CRVO in our patient group because this is not the approved medication that is used to treat these types of patients at our institution at the present time. A further study that compares the responses between bevacizumab and other approved anti-VEGF agents (e.g., ranibizumab, aflibercept) would be of benefit and will need to be undertaken in the future.

In conclusion, blood flow measurements after an IVB injection can be used as one of the predictive factors for outcomes in patients with CRVO. When a decrease in the MBR value is observed after an initial treatment, additional therapy may be required in these patients.

Key words: bevacizumab, blood flow, central retinal vein occlusion.

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