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Changes in retinal blood flow in patients with macular edema secondary to branch retinal vein occlusion before and after intravitreal injection of bevacizumab.

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CHANGES IN RETINAL BLOOD FLOW IN PATIENTS WITH MACULAR EDEMA SECONDARY TO BRANCH RETINAL VEIN OCCLUSION BEFORE AND AFTER INTRAVITREAL INJECTION OF BEVACIZUMAB

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Running title: RBF AND BEVACIZUMAB IN BRVO

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Abstract

Purpose: To investigate the effect of intravitreal bevacizumab (IVB) injections for macular edema secondary to acute branch retinal vein occlusion (BRVO) on the retinal microcirculation.

Design: Prospective, interventional case series.

Methods: We measured central macular thickness using spectral-domain optical coherence tomography and retinal blood flow (RBF) in untreated eyes with macular edema secondary to acute BRVO in occluded (V1) and opposite venules in affected eyes (V2) and the equivalent venules in contralateral eyes (V3), using laser Doppler velocimetry during follow-up and after IVB injection.

Results: In 33 eyes with acute BRVO of less than 2 months duration at the first visit, we observed changes in the retinal microcirculation for 1 month; the macular edema improved spontaneously and the RBF was unchanged in 15 of 33 eyes, and the RBF increased by 23.3% in 18 eyes with persistent macular edema. Twenty-four eyes received an IVB injection (1.25 mg/0.05 mL). The RBF did not change significantly during follow-up. In eight (33%) of 24 eyes with improved macular edema 3 months after treatment, the average RBF values before injection were significantly higher compared with eyes with recurrent edema.

Conclusions: One IVB injection might have little effect on the retinal microcirculation in patients with macular edema secondary to acute BRVO at least 3 months after injection. However, the increased RBF in the occluded venules before injection might be associated with improved macular edema after the IVB injection.

Key Words

anti-VEGF therapy, branch retinal vein occlusion, macular edema, intravitreal injection, retinal blood flow.

Summary Statement

One intravitreal injection of bevacizumab (IVB) does not affect the retinal blood flow (RBF) in patients with macular edema secondary to retinal vein occlusion. Measuring the RBF might predict the efficacy of the IVB injections.

Branch retinal vein occlusion (BRVO) is one of the most common retinal vascular disorders in elderly patients, and macular edema is the most frequent cause of visual impairment in BRVO. In addition to macular grid laser,[1] some studies have compared the effect of intravitreal injection of triamcinolone acetonide (IVTA)[2] with intravitreal bevacizumab (IVB) on macular edema secondary to BRVO. Although some studies have reported no differences between the two drugs,[3,4] it appears that IVB might provide greater benefit than IVTA for macular edema associated with BRVO, because of the cataract progression and increased intraocular pressure (IOP) associated with IVTA.[5]

However, some case reports have shown that IVB is associated with retinal ischemic disorders,[6] suggesting that IVB might affect the retinal circulation. Recently, some studies have reported that intravitreal injection of an anti-vascular endothelial growth factor (VEGF) treatment might change the ocular blood flow. Bonnin et al. reported that the velocity of the retrobulbar blood flow measured using color Doppler imaging decreased 4 weeks after one IVB injection (1.25 mg/0.05 ml) in patients with age-related macular degeneration (AMD).[7] Other studies also reported that the retinal arterioles constricted in response to intravitreal injection of ranibizumab in patients with AMD.[8] In addition, Fontaine et al. also reported that three repeated IVB injections caused significant vasoconstriction of the retinal arterioles but did not change retinal blood flow (RBF) measured by bi-directional laser Doppler flowmeter.[9] In contrast, only one study examined the effect of anti-VEGF treatment on the retinal circulation in patients with macular edema secondary to BRVO. Sacu et al. reported vasoconstriction in the veins and arteries of the affected eyes measured by retinal vessel analyzer and a significant

reduction in flow velocities in the retrobulbar central retinal artery measured using color Doppler imaging in the BRVO eyes over time after three intravitreal injections of ranibizumab.[10] However, because no study has examined the effect of IVB on the RBF by simultaneously measuring the vessel diameter and blood velocity of the retinal vessels in both eyes of patients with BRVO and macular edema, we did so in untreated eyes with macular edema secondary to acute (less than 6 months in duration) BRVO using a Canon laser Doppler velocimetry (LDV) system (Canon Laser Blood Flowmeter, model CLBF 100, Canon, Tokyo, Japan). We also tested the hypothesis that measuring the RBF might predict the efficacy of IVB for treating macular edema secondary to BRVO.

Materials and Methods

Subjects

This study adhered to the tenets of the Declaration of Helsinki and followed the guidelines approved by the ethics committee of our institution. All patients were native Japanese who provided written informed consent to treatment. Forty-eight consecutive previously untreated eyes of 48 patients (21 men, 27 women; age, mean ± standard deviation [SD], 61.8 ± 6.3 years) with macular edema secondary to BRVO were enrolled prospectively between April 2008 and March 2009. The inclusion criteria were the presence of macular edema that involved the fovea secondary to untreated acute BRVO. All patients were affected unilaterally. The duration of symptoms before inclusion ranged between 1 and 5 months. Patients with diabetes were excluded because the RBF might be impaired in patients with diabetes and no retinopathy.[11] Twenty-three patients had controlled systemic

hypertension with no change in treatment during this study. Patients with uncontrolled hypertension (blood pressure >160/100 mmHg) were excluded from this study.

The patients underwent comprehensive ophthalmologic examinations, including measurement of the best-corrected visual acuity (BCVA), slit-lamp biomicroscopy with a noncontact fundus lens, color fundus photography, fluorescein angiography (FA), and optical coherence tomography (OCT) (RTVue-100, Optovue Inc., Fremont, CA). Two retina specialists (KS, AY) diagnosed the BRVO based on the findings of the fundus examination and FA. No eyes had an ischemic retinal vein occlusion. The BCVA was measured with a Landolt chart and converted to the logarithm of the minimum angle of resolution (logMAR). FA was performed using a confocal laser scanning system (HRF-2, Heidelberg Engineering, Heidelberg, Germany). Spectral-domain OCT was used to assess the macular edema. Study eyes were required to have a central foveal thickness of 300 μm or more at baseline.

RBF Measurements

The RBF was measured after the ocular examination. The subjects abstained from drinking coffee for at least 12 hours before the test. The LDV system was used to estimate the blood flow in the superior branch of the first-order major temporal retinal venules. The detailed methodology of this system was reported previously.[12] The retinal LDV system allows noninvasive measurement of the absolute values of the red blood cells flowing in the centerline of the vessel, based on the bi-directional LDV.[12] The mean retinal blood velocity (V_{mean}) was defined as the V of the average maximal speed during one cardiac cycle. The

diameter of the retinal venules was determined automatically by computer analysis of the signal produced by the vessel image on the array sensor using the half height of the transmittance profile to define the vessel edge.

The RBF measurements were performed on the temporal venules, i.e., the occluded venule (V1) and the opposite venule (V2), in the affected eye and the equivalent venule (V3) in the contralateral eye. The measurement sites were within 1 disc diameter of the optic disc margin. In all cases, we measured the first bifurcation of the retinal venules. If it was difficult to perform reliable RBF measurements in the occluded venules due to poor VA or a massive retinal hemorrhage, those eyes were excluded from this study. Every RBF measurement was performed at the same time in the morning as the first measurement.

Intravitreal Injection of Bevacizumab

It is widely recommended that treatment of macular edema secondary to BRVO should be initiated at least 2 to 3 months after symptom onset because macular edema can resolve spontaneously within this period.[1] Therefore, in the current study, the BRVO had to have started more than 3 months before the treatment started. We did not administer IVB if the eyes showed evidence of spontaneous improvement during the baseline follow-up period, as determined by an improvement of more than 15 letters of vision or by thinning of the central macular thickness (CMT) by more than 20% from the initial measurement. In contrast, if the patients first visited our hospital with BRVO of 3 to 6 months duration, we injected bevacizumab during the first visit.

IVB was administered in a sterile manner (1.25 mg/0.05 mL) using a 30-gauge needle.

Topical antibiotics were applied prophylactically for 3 days after the IVB injection. Patients were re-examined 2 weeks after the injection and then monthly for the first 3 months. All patients were treated with one IVB injection, with no additional treatment for 3 months after the first injection. Recurrent macular edema was defined as increases in the CMT that exceeded 100 μm over the minimal value after administration of the IVB injection.

Calculations

The RBF was calculated as RBF = V_{mean} x area, where V_{mean} is calculated as V_{mean} = V of the average maximal speed/2, and area is the cross-sectional area of the retinal venules at the laser Doppler measurement site.[12] The mean arterial blood pressure (BP) was determined by the formula: diastolic BP + (systolic BP – diastolic BP)/3.

Statistical Analysis

All values are expressed as the mean ± SD. The assumption of data normality was assessed using the Shapiro-Wilk test. We used one-way analysis of variance followed by a post-hoc comparison with Tukey-Kramer's procedure. We analyzed the standardized regression coefficients from multiple regression analyses of the RBF in relation to various factors. $P < 0.05$ was considered significant.

Results

Study 1: Follow-up Study

Nine of 48 patients were excluded from this study due to poor VA and/or a massive

retinal hemorrhage that prevented obtaining a reliable RBF measurement. In 33 of the remaining 39 eyes with acute BRVO of less than 2-months duration after symptom onset at the first visit, we observed the natural course of the changes in the retinal microcirculation for 1 month with no treatment. The other six eyes for which more than 3 months passed after symptom onset were treated with IVB at the first visit. The average coefficients of variation (CVs) (mean ± SD) of the vessel diameter, blood velocity, and RBF of five baseline measurements obtained from all 39 eyes were 1.7% ± 1.2%, 10.2% ± 4.5%, and 10.3% ± 5.0% in V1; 1.8% ± 1.5%, 11.7% ± 5.8%, and 11.7% ± 4.9% in V2; and 1.7% ± 1.3%, 10.7% ± 5.1%, and 11.2% ± 5.1% in V3, respectively, at the first visit. There were no significant differences in the CVs among V1, V2, and V3 at the first visit and between the first and second visits (data not shown).

One month after the first visit, the macular edema improved spontaneously in 15 (45%) eyes of 33 eyes. The RBF in V1 was unchanged in 15 eyes with spontaneous resolution but significantly ($P<0.05$) increased by 23.3% in 18 eyes with persistent macular edema during this baseline follow-up period (Table 1).

Study 2: Effect of Intravitreal Injection of Bevacizumab on Retinal Circulation

Twenty-four eyes were treated with one IVB injection and followed at 2 weeks and 1, 2, and 3 months after the injection. No endophthalmitis, retinal detachment, or any other severe procedure-related complications developed (Table 2). The IOP did not exceed 21 mmHg during follow-up in any patient. No obvious bevacizumab-related ocular or systemic adverse events developed. No patient developed any neovascular complications or needed peripheral sectorial laser photocoagulation during the follow-up period.

The logMAR VA increased and the CMT decreased significantly during the follow-up period after IVB. The RBF did not change significantly in V1, V2, or V3 during the follow-up period (Table 3). Recurrent macular edema was defined as increases in the CMT that exceeded 100 μm over the minimal value after administration of the IVB injection. In 16 (67%) of 24 eyes, the macular edema recurred 3 months after injection, whereas the macular edema did not recur until 3 months after IVB in the other eight (33%) of 24 eyes. In these patients, the vessel diameter and RBF in V1 were significantly higher compared with the eyes with recurrent edema before IVB (Table 4). There were no significant differences in the changes in diameter, velocity, or RBF between the groups at any time point after administration of the IVB injection (data not shown). There also were no significant correlations between the changes in diameter, velocity, or RBF and logMAR or CMT at any time point after IVB in all patients (n=24) (data not shown).

Discussion

The current findings suggested that one IVB injection might have little effect on the retinal microcirculation of the occluded vessels and the unoccluded vessels in the fellow eyes in patients with macular edema secondary to acute BRVO at least 3 months after injection. However, the increased RBF in the occluded venules during the 1-month observation period before injection might be associated with improved macular edema in response to IVB. The current results also suggested that measuring the RBF before the injection might predict the efficacy of IVB in patients with acute BRVO with macular edema.

Because several case reports have indicated that intravitreal anti-VEGF therapy might be associated with severe RBF disturbances,[13] it is clinically relevant to evaluate the effect of IVB on the retinal circulation in humans. In the current study, we did not observe any significant changes in vessel diameter, blood velocity, or blood flow in either the occluded or unoccluded venules in the affected eye in response to one IVB injection in patients with macular edema secondary to BRVO during 3 months. In contrast, multiple intravitreal injections of ranibizumab, another anti-VEGF drug, significantly constricted the retinal veins and arteries of the affected eyes in patients with macular edema secondary to BRVO.[10] Unfortunately, those authors did not measure the blood velocity in the retinal vessels, so they could not adequately evaluate the effect of ranibizumab on the RBF in patients with BRVO with macular edema. Moreover, this discrepancy might have resulted from a difference between one IVB injection and multiple injections of ranibizumab.

Regarding the effect of bevacizumab on the retinal circulation, a recent clinical trial found that the RBF did not change significantly, whereas the diameter of the retinal arteriolar vessels decreased after the first injection and persisted until the end of the study in patients with AMD.[9] In contrast, Soliman et al. reported that the changes in the vessel diameters (arteries and veins) after 4 months of IVB injections were not significant in patients with diabetic macular edema (DME).[14] Taken together, it appears that the effect of anti-VEGF treatment on the retinal microvessels might vary depending on the treatment (bevacizumab or ranibizumab) and ocular vascular diseases (AMD, DME, or macular edema secondary to RVO).

Although some investigators did not observe substantial changes in the retrobulbar

ocular blood flow in the untreated fellow eyes,[7] one recent clinical trial reported that injection of IVB might affect the retrobulbar ocular blood flow in the injected and the untreated fellow eyes of patients with neovascular AMD.[15] However, the current findings clearly showed that the IVB injections did not significantly affect the RBF in the untreated eye (Table 3). Our results seemed to agree with previous studies that reported no or a minimal effect of the IVB injections on the untreated fellow eyes.[16,17]

In the current study, we observed the natural course of RBF for 1 month until 3 months after the onset of BRVO with no treatment (study 1). During this baseline follow-up period, the RBF was unchanged in the eyes in which the macular edema spontaneously resolved without an injection, whereas the RBF and blood velocity increased with no change in vessel diameter in eyes with persistent macular edema, which required treatment later (Table 1). These findings suggested that the increased RBF observed before IVB injection might be associated with persistent macular edema. Because VEGF per se seems to increase the RBF,[18] probably via production of nitric oxide,[19] which plays an important role in vasodilation of the retinal microvessels[20] especially in the vessels that were smaller than those we measured using LDV and/or the capillaries, the increased blood velocity and RBF with no change in vessel diameter in patients with persistent macular edema might be associated with dilation of the smaller vessels and/or capillaries in response to nitric oxide production due to increased VEGF and/or tissue hypoxia. In addition, although we did not perform repeated FA in the current study, we need to consider another possibility, i.e., that the development of peripheral arteriovenous shunting might be associated with increased blood velocity and RBF

without any change in vessel diameter in eyes with persistent macular edema during the follow-up period. Further clinical study using repeated FA is warranted.

Although only one injection was administered in the current study with a short follow-up period, we also found that the macular edema resolved until 3 months after one IVB injection in eight (33%) of 24 eyes and that the vessel diameter and RBF at baseline (before injection) were significantly higher compared with eyes with recurrent edema in these patients. If the increased RBF was associated with the increased retinal VEGF level as discussed previously, the RBF should decrease after IVB. However, we could not find any significant decreases in the retinal circulatory parameters after IVB compared with baseline (Table 4). Moreover, the patients with improved macular edema had greater RBF compared with those with recurrent macular edema before and after one IVB injection. It recently was reported that vitreous fluid levels of not only VEGF but also inflammatory cytokines, such as soluble intercellular adhesion molecule 1, interleukin 6, and monocyte chemotactic protein 1, are correlated strongly with retinal vascular permeability and the severity of the macular edema in patients with BRVO.[21] Although the effect of these inflammatory cytokines on the retinal circulation remains unknown, we speculated that factors other than VEGF might be involved in the recurrence of macular edema after one IVB injection.

The study limitations included a small number of patients that could undergo subgroup analysis, a very short follow-up period for assessing the effect of anti-VEGF after one IVB injection, and no control group. The current study also enrolled only patients diagnosed with BRVO close to the time of enrollment, so it is unknown if these findings apply to patients with longstanding disease. Because we could not measure the

RBF in eyes with massive retinal hemorrhages and/or poor VA because of the methodologic limitations, we could not reach any conclusion about patients with severe visual impairment. Moreover, there was a selection bias in study 2 because we excluded 15 eyes in which the macular edema improved spontaneously during the follow-up period and also included another six eyes with a longer duration of macular edema (more than 3 months) that had not been included in study 1. Finally, because we enrolled 23 patients with controlled systemic hypertension in the current study, we considered the effect of systemic hypertension on our results. Although we found no significant difference in the RBF between those taking and not taking anti-hypertensive medications among our patients (data not shown), the effect of systemic medications on the retinal microcirculation in patients with BRVO should be studied in the future.

In summary, the current study provided the first evidence about the lack of change in the RBF after injection of IVB in patients with macular edema secondary to acute BRVO. However, the increased RBF in the occluded venules before injection might be associated with improved macular edema as a result of the IVB injection. The RBF before the injection might predict the efficacy of IVB in patients with acute BRVO with macular edema.

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Table 1. RBF Parameters in the Occluded Venules (V1) and CMT in Patients with and without Improved Macular Edema during the First and Second Visits before Treatment

	First Visit	Second Visit	*P* Value
Injection group (n=18)			
Diameter (μm)	143.4±4.5	144.2±23.3	0.51
Velocity (mm/sec)	21.4±7.1	23.2±6.3	0.04
RBF (μl/min, range)	10.8±5.0	12.0±5.5	0.03
LogMAR VA	0.45±0.23	0.39±0.20	0.07
CMT (μm)	496.7±121.8	520.6±116.3	0.41
Improved group (n=15)			
Diameter (μm)	137.9±20.1	138.2±19.9	0.84
Velocity (mm/sec)	21.9±7.8	22.8±5.4	0.48
RBF (μl/min, range)	10.2±5.3	10.7±5.2	0.63
LogMAR VA	0.21±0.36	0.08±0.23	0.00001
CMT (μm)	381.7±70.8	324.7±43.7	0.04

Values are expressed as means ± standard deviation.

RBF, retinal blood flow; CMT, central macular thickness; logMAR VA, logarithm of the minimal angle of resolution visual acuity.

Table 2. Changes in Systemic and Ocular Parameters in 24 Eyes Treated with IVB

	Before Treatment	2 Weeks	4 Weeks	8 Weeks	12 Weeks	*P* Value
LogMAR VA	0.42±0.22	0.14±0.16*	0.09±0.13*	0.08±0.14*	0.14±0.22*	<0.0001
CMT (μm)	517.5±165.9	316.0±66.3*	308.0±91.3*	354.0±115.9*	402.1±149.6*	<0.0001
IOP (mmHg)	13.6±2.9	13.2±2.1	13.3±2.3	14.0±2.4	13.8±2.5	0.48
Systemic BP (mmHg)	145.8±17.6	141.8±19.8	137.3±15.5	140.4±21.6	133.9±19.7	0.28
Diastolic BP (mmHg)	81.8±10.5	77.7±12.2	77.5±10.4	80.6±13.3	78.1±13.3	0.66

Values are expressed as the means ± standard deviation.

*Significant vs. preinjection (P<0.05).

IVB, intravitreal bevacizumab; CMT, central macular thickness; logMAR VA, logarithm of the minimal angle of resolution visual acuity; IOP, intraocular pressure; BP, blood pressure.

Table 3. Changes in Retinal Circulatory Parameters in the Venules in 24 Eyes Treated with IVB

	Before Treatment	2 Weeks	4 Weeks	8 Weeks	12 Weeks	*P* Value
V1						
Diameter (μm)	146.2±22.0	142.8±22.2	141.8±21.9	142.20±21.1	142.5±18.6	0.23
Velocity (mm/sec)	22.8±5.9	21.9±7.1	21.8±5.9	23.6±7.7	21.3±4.9	0.35
RBF (μl/min)	12.0±5.1	11.0±5.2	10.9±5.4	11.6±5.1	10.7±4.1	0.27
V2						
Diameter (μm)	155.3±19.4	154.1±21.7	153.8±19.9	150.6±18.8	154.0±16.8	0.06
Velocity (mm/sec)	22.5±4.8	26.0±6.4	25.0±5.3	25.3±6.6	25.2±5.9	0.87
RBF (μl/min)	14.7±4.5	15.0±6.4	14.2±4.5	13.7±4.8	14.6±4.7	0.29
V3						
Diameter (μm)	141.6±13.9	142.4±13.4	144.4±18.1	142.1±18.1	143.7±18.2	0.16
Velocity (mm/sec)	25.5±6.5	26.7±8.0	26.4±7.1	26.4±7.1	24.9±5.7	0.30
RBF (μl/min)	12.1±3.6	12.8±4.3	13.2±4.9	13.2±4.9	12.3±4.9	0.19

Values are expressed as means ± standard deviation.

V, venule; RBF, retinal blood flow; IVB, intravitreal bevacizumab.

Table 4. Differences in the Changes in the Retinal Circulatory Parameters in the Occluded Venules (V1) between Groups with Improved and Recurrent Edema after IVB

	Before Treatment	2 Weeks	4 Weeks	8 Weeks	12 Weeks	*P* Value
Improved group (n=8 eyes)						
Diameter (μm)	159.5±9.7*	156.0±10.9	154.7±8.4	154.7±8.4	153.8±10.1	0.52
Velocity (mm/sec)	24.4±5.9	25.1±7.6	24.0±6.6	27.7±10.9	22.2±4.2	0.18
RBF (μl/min)	14.7±3.8*	14.0±2.6	13.5±4.1	15.2±5.3	12.5±1.9	0.20
Recurrence group (n=16 eyes)						
Diameter (μm)	139.5±23.6	137.1±23.7	134.6±23.7	136.3±22.5	136.9±19.5	0.51
Velocity (mm/sec)	22.0±6.0	20.4±6.7	20.7±5.4	21.5±4.6	20.9±5.3	0.91
RBF (μl/min)	10.6±5.2	9.7±5.8	9.6±5.6	9.8±4.0	9.9±4.7	0.71

Values are expressed as means ± standard deviation.

*Significant (P<0.05) vs. recurrence group.

RBF = retinal blood flow; IVB, intravitreal injection of bevacizumab.