REBOUND OF MACULAR EDEMA AFTER INTRAVITREAL BEVACIZUMAB THERAPY IN EYES WITH MACULAR EDEMA SECONDARY TO BRANCH RETINAL VEIN OCCLUSION

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Purpose: To determine the incidence of rebound macular edema after intravitreal bevacizumab in eyes with macular edema secondary to branch retinal vein occlusion and to identify the pretreatment factors that were significantly associated with the rebound.

Methods: The changes in the foveal thickness after the intravitreal bevacizumab (1.25 mg/0.05 mL) were studied in 65 eyes of 65 patients with macular edema secondary to branch retinal vein occlusion. A rebound of macular edema was defined as a ≥110% increase in the foveal thickness or a foveal thickness ratio of ≥110% (foveal thickness at the recurrence/foveal thickness at the baseline × 100). Multivariate logistic regression analyses and subgroup analyses were performed to determine which pretreatment factors were associated with the rebound.

Results: Seven of 65 eyes (10.8%) showed a rebound (≥110% of baseline thickness). Subgroup analyses showed that a thinner pretreatment fovea and a shorter interval between symptom onset to the initiation of the intravitreal bevacizumab were significantly associated with a rebound of macular edema ($P < 0.01$). The interval from symptoms onset to the initiation of treatment was <8 weeks in all 7 eyes with a rebound macular edema.

Conclusion: These results suggest that a rebound of macular edema in eyes with branch retinal vein occlusion was more likely to occur when the intravitreal bevacizumab therapy is initiated before the macular edema reaches the maximum level. Rebound of macular edema may be effectively avoided by waiting at least 8 weeks after the onset of symptoms to begin the intravitreal bevacizumab.

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Macular edema is one of the most common complications and major cause of visual decrease in eyes with branch retinal vein occlusion (BRVO).[1–3] The Branch Vein Occlusion Study Group reported on the long-term visual prognosis of 35 untreated patients with macular edema after BRVO and a decrease of visual acuity to ≤20/40. They found that two thirds of these eyes had a visual acuity <20/40 after 3 years.[4] Although macular grid laser photocoagulation[4–6] is still the gold standard treatment for macular edema secondary to BRVO, other treatment methods have been advocated including intravitreal injections of steroids[7–10] and vitrectomy with or without sheathotomy.[11–14]

Recently, an intravitreal injection of bevacizumab (Avastin; Genentech, Inc, South San Francisco, CA), a full-length recombinant monoclonal antibody against human vascular endothelial growth factor (VEGF), has been used to treat macular edema secondary to BRVO.[15–18] This therapy is widely accepted because it is known that the VEGF plays an important role in the pathogenesis of macular edema.[19–22] Long-term follow-up studies[23–26] also suggested that intravitreal

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bevacizumab (IVB) therapy is an effective treatment for macular edema secondary to BRVO.

In 2007, Matsumoto et al[27] reported on 3 patients with macular edema secondary to retinal vein occlusion whose edema initially responded to bevacizumab, but then showed a rebound of the macular edema. In these three patients, the degree of macular edema was greater than that before the initial bevacizumab administration. However, very little is known about the exact incidence of this rebound phenomenon and which pretreatment factors are related to this unique phenomenon.

Thus, the purpose of this study was to determine the incidence of rebound macular edema in eyes that received an IVB for macular edema secondary to BRVO. We also wanted to identify the pretreatment factors that were significantly associated with the rebound.

Subjects and Methods

Subjects

We reviewed the medical records of all patients with macular edema secondary to BRVO who had received IVB therapy at the Nagoya University Hospital from July of 2006 to April of 2009 and were followed-up for more than 6 months. Eyes that had received other treatments, for example, vitrectomy, grid laser photocoagulation, or drug injections including triamcinolone acetonide, were excluded.

The procedures used conformed to the tenets of the World Medical Association's Declaration of Helsinki. An informed consent for the IVB therapy was obtained from each of the patients before the IVB, and afterward, they were provided sufficient information on the procedures to be used. The Nagoya University Hospital Ethics Review Board approved (#09-28) this retrospective analysis of the patients' data.

Bevacizumab Injection

The eyes were anesthetized with 1% topical tetracaine, and the fornices of the eyes were irrigated with 10% povidone–iodine. Each patient received an intravitreal injection of 1.25 mg/0.05 mL bevacizumab using a 30-gauge needle inserted 3.5 mm from the limbus. Antibiotics drops were given for 3 days after the IVB.

All patients received a single intravitreal injection of bevacizumab, and the effects were evaluated monthly by the best-corrected visual acuity (BCVA) and the foveal thickness determined by optical coherence tomography (OCT).

Best-Corrected Visual Acuity

The BCVA was measured by a standard Japanese decimal visual acuity chart at 5 m. The decimal values were converted to the logarithm of the minimum angle of resolution units for statistical analyses.

Foveal Thickness

The foveal thickness was determined by OCT (Stratus or Cirrus model; Carl Zeiss Meditec, Dublin, CA). The same OCT machine was used on the same patient. After the patients' pupils were fully dilated with 0.5% tropicamide and 0.5% phenylephrine (Mydrin-P; Santen Co, Osaka, Japan), 6 mm vertical and horizontal scans were made through the fovea. The average foveal thickness of the vertical and horizontal scans was used as the foveal thickness. We used a manual method to place the cursors on the OCT images to measure the foveal thickness[28,29] because it has been reported that the automatic measurements of the foveal thickness often failed to identify the outer border of the neural retina, especially when the Stratus model of OCT was used.[30] We have also found that our manual method is more useful when two different OCT systems were used in the same study.[31]

Definition of Effectiveness, Recurrence, and Rebound of Macular Edema

A treatment was defined as effective when the OCT-determined foveal thickness had decreased by $>30\%$ after the initial bevacizumab injection. A recurrence of macular edema was defined as an increase of foveal thickness of $>30\%$ after an initial decrease of foveal thickness. A rebound of macular edema was defined as when the recurrence foveal thickness ratio (foveal thickness at the recurrence/foveal thickness at the baseline $\times$ 100) became $\geq 110\%$ after an initial decrease of foveal thickness (Figure 1).

According to these definitions, we classified our 65 eyes into 4 groups (Figure 1). Group 1 included 3 eyes in which the initial bevacizumab injection was not effective. Group 2 included 21 eyes in which the initial bevacizumab injection was effective without any recurrence. Group 3 included 34 eyes in which the initial bevacizumab injection was effective, then a recurrence occurred with the recurrence ratio $<110\%$. And Group 4 included 7 eyes in which the initial bevacizumab injection was effective, then a recurrence occurred with the recurrence ratio $\geq 110\%$, that is, a rebound.

Additional injections of bevacizumab were given only when a recurrence of macular edema or a worsening of the BCVA by ≥ 0.2 logarithm of the minimum angle of resolution units developed or the results of the initial injection did not reach the level considered to be effective.

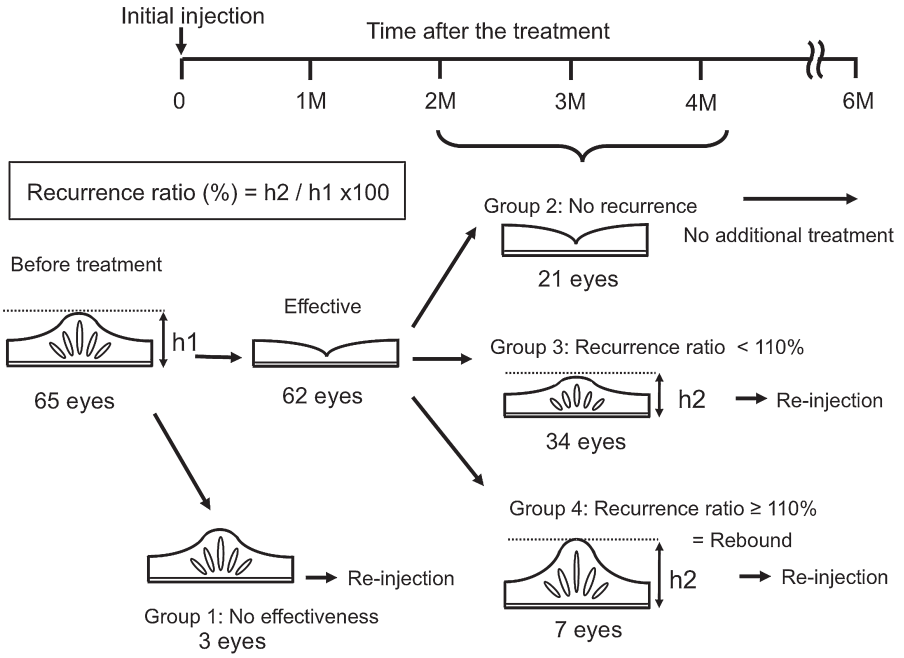

Fig. 1. Classification of macular edema according to the course of macular morphology obtained by OCT after IVB. Group 1 included the eyes in which the initial bevacizumab injection was not effective. Group 2 included the eyes in which the initial bevacizumab injection was effective without any recurrence thereafter. Group 3 included the eyes in which the initial bevacizumab injection was effective, and then a recurrence occurred with the recurrence ratio <110%. Group 4 included the eyes in which the initial bevacizumab injection was effective, and then a recurrence occurred with the recurrence ratio ≥110%, that is, a rebound.

Statistical Analyses

To identify the pretreatment factors that might influence the rebound of macular edema after the initial IVB, multivariate logistic regression analyses were performed with rebound macular edema as the dependent variable. The independent variables included patient's age, gender, presence of systemic complications, for example, hypertension, hypercholesterolemia, diabetes mellitus, pretreatment logarithm of the minimum angle of resolution visual acuity, pretreatment foveal thickness, and period from symptoms onset to the IVB.

We also performed subgroup analyses comparing the pretreatment factors presented above between Group 3 and Group 4. Differences in the patient's age, pretreatment logarithm of the minimum angle of resolution visual acuity, pretreatment foveal thickness, and period from symptoms onset to the IVB were compared using the nonparametric Mann–Whitney *U*-test. The significance of differences in gender and presence of hypertension, hypercholesterolemia, and diabetes mellitus were determined by chi-square tests.

The SPSS version 17.0J for Windows (SPSS, Inc, Chicago, IL) was used for all these statistical analyses. A P value <0.05 was considered significant.

Results

Intravitreal bevacizumab therapy was performed on 65 eyes of 65 consecutive patients (35 men and 30 women) whose mean ± SD age was 62.3 ± 8.6 years (range, 39–85 years). Forty-four of these patients had systemic hypertension, seven patients had diabetes mellitus without diabetic retinopathy, and six patients had hypercholesterolemia. The decimal BCVA at baseline ranged from 0.01 to 0.6, and the mean BCVA was 0.64 ± 0.33 logarithm of the minimum angle of resolution units. The mean foveal thickness was 585 ± 177 μm with a range from 244 μm to 1106 μm. The mean interval between the onset of symptoms and the IVB was 10.0 ± 8.3 weeks with a range of 2 weeks to 52 weeks. No serious systemic or local bevacizumab-related adverse events were observed in our 65 patients.

The course of macular edema after the initial IVB therapy in all 65 eyes is summarized in Figure 1. The initial injection of bevacizumab was effective in 62 of 65 eyes and was not effective in 3 eyes (4.6%; Group 1). Twenty-one eyes (32.3%) had no recurrence of macular edema after the initial reduction of the macular edema (Group 2). Thirty-four eyes (52.3%) had a recurrence of macular edema after the initial reduction of the macular edema but with a recurrence ratio <110% (Group 3). Seven eyes (10.8%) had a recurrence of macular edema after the initial reduction of the macula, and the recurrence ratio was ≥110% (Group 4). For patients in Groups 1, 3, and 4 (44 eyes, 67.7%), a second injection of IVB was performed as soon as appropriate unless the patient did not agree to a second injection.

Horizontal OCT images through the fixation point at baseline (left), at 4 weeks after the initial IVB

(middle), and at the recurrence of macular edema (right) for all 7 eyes of Group 4 are shown in Figure 2. All these 7 eyes had had an initial resolution of the macular edema at 4 weeks after the injection, but had a recurrence of the macular edema at 8 weeks to 12 weeks (mean, 9.1 weeks). The recurrence ratio (foveal thickness at the rebound/foveal thickness at the baseline × 100) ranged from 110% to 149%, and the mean was 124.6% for these 7 eyes. However, the recurrence ratio ranged from 39% to 102%, and the mean degree of recurrence was 74.7% for the 34 eyes of Group 3.

To identify the potential pretreatment factors that were associated with the rebound of macular edema, multivariate logistic regression analyses were performed on all 65 eyes, with rebound macular edema (recurrence rate ≥110%) as the dependent variable (Table 1). The results showed that a thinner pretreatment fovea (odds ratio, 0.98; 95% confidence interval, 0.96–1.00, $P = 0.063$) and a shorter interval from symptom onset to the initial injection (odds ratio, 0.47; 95% confidence interval, 0.21–1.05; $P = 0.067$) showed strong trends to be associated with the rebound of macular edema.

We next performed subgroup analyses comparing each pretreatment factor between Group 3 (recurrence rate <110%, n = 34) and Group 4 (recurrence rate ≥110, n = 7, Table 2). We found that the pretreatment fovea was significantly thinner ($P = 0.004$) in Group 4 (451 ± 70 μm) than in Group 3 (651 ± 179 μm). In addition, the interval from the symptom onset to the initiation of treatment in Group 4 (4.9 ± 2.2 weeks) was significantly shorter ($P = 0.007$) than that in Group 3 (9.1 ± 4.6 weeks). There was no significant difference in other pretreatment factors between the two groups.

To investigate the relationship between the recurrence ratio and the 2 pretreatment factors that were found to be associated with a rebound macular edema, we also plotted the recurrence ratio against the foveal

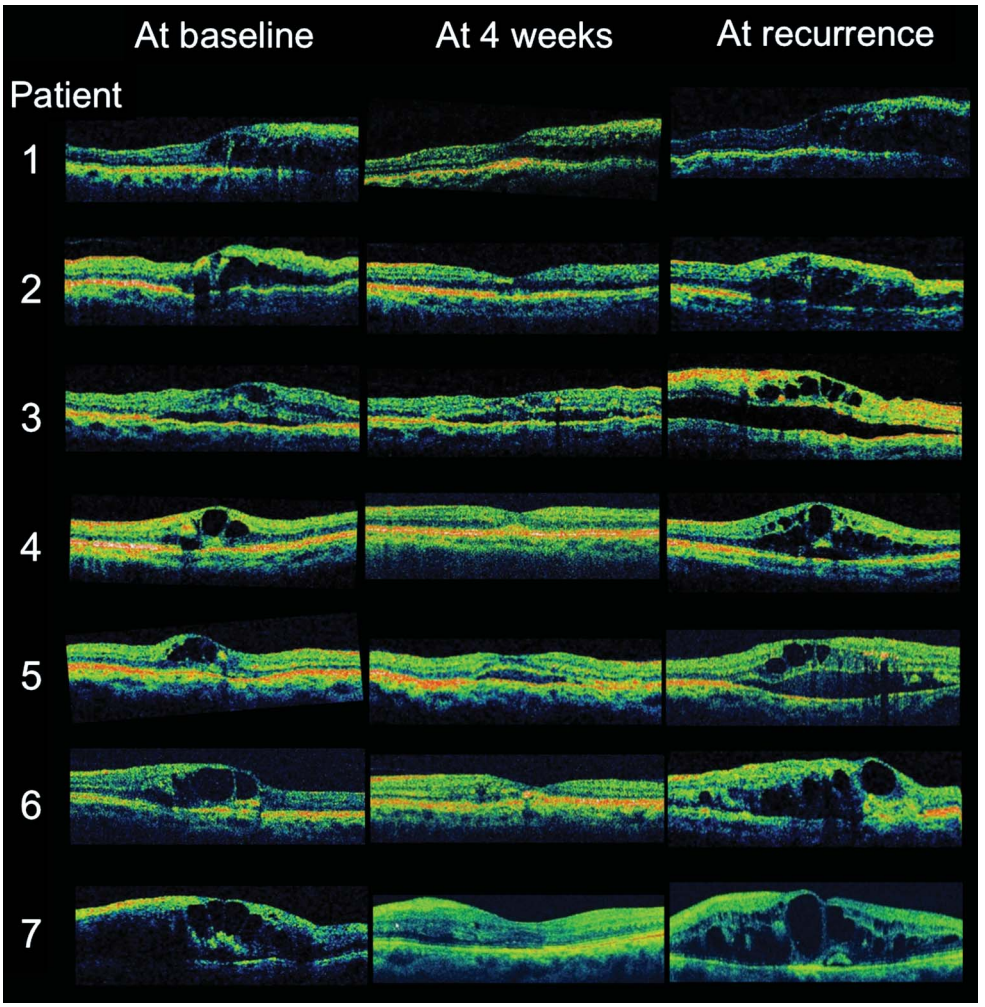

Fig. 2. Horizontal OCT images through the fixation point at baseline (left), at 4 weeks after initial bevacizumab injection (middle), and at the recurrence of macular edema (right) for all 7 eyes of Group 4 (recurrence rate ≥110%). These 7 eyes had an initial resolution of macular edema at 4 weeks after the injection but showed a recurrence of macular edema at 8 weeks or 12 weeks (mean, 9.1 weeks). At this time, their foveal thickness was ≥110% of the pretreatment thickness.

Table 1. Multivariate Logistic Regression Analysis of Pretreatment Factors Associated with the Rebound of Macular Edema Secondary to BRVO

Factor	Odds Ratio (95% CI)	*P*
Age (per year)	0.87 (0.68–1.12)	0.285
Gender (men vs. women)	30.09 (0.6401–1417.04)	0.083
Diabetes mellitus	20.04 (0.06–6268.55)	0.306
Hypertension	0.35 (0.07–17.89)	0.601
Hypercholesterolemia	<0.0001	0.999
Pretreatment visual acuity (logarithm of the minimum angle of resolution)	0.268 (0.01–143.60)	0.681
Pretreatment foveal thickness (μm)	0.98 (0.96–1.00)	0.063
Period from symptom onset to injection (weeks)	0.47 (0.21–1.05)	0.067

CI, confidence interval.

thickness in micrometers at the baseline (Figure 3A), and the interval from the symptom onset to the initiation of treatment in weeks (Figure 3B). In these figures, only the data of Groups 3 and 4 are plotted, because the eyes in Groups 1 and 2 did not show a recurrence of the macular edema. We found that the baseline foveal thickness for all 7 eyes with rebound (recurrence rate ≥110%) was ≤560 μm, and the interval from the symptom onset to the injection was ≤8 weeks for all 7 eyes. The intervals between the onset of symptoms and treatment in Groups 1 and 2 were 12.7 ± 10.3 and 12.5 ± 12.6 weeks, respectively.

Finally, to determine whether the rebound of macular edema resulted in a poorer post-IVB outcome, we compared the BCVA and foveal thickness at 6 months after the IVB and the total number of injections during the 6 months after the initial injection between Groups 3 and 4. The differences in these values between the 2 groups were not significant (Table 3). The reason for the low total number of injections during the 6 months in these 2 groups was that there were 14 patients (12 of Group 3 and 2 of Group 4) who did not want to receive a second injection mainly because their visual acuities were relatively maintained even though a recurrence of macular edema had occurred.

Discussion

Our results showed that the incidence of a rebound of macular edema (recurrence ratio ≥110%) after an initial resolution after IVB was 10.8% (7 of 65 eyes). The degree of recurrence for these 7 eyes ranged from 110% to 149%, and 4 eyes had a recurrence ratio of ≥120% (Figure 3). These results indicated that the rebound of macular edema is not a rare phenomenon, and clinicians should be aware that this phenomenon can occur during the IVB therapy for macular edema associated with BRVO.

Because the rebound of macular edema is an unfavorable finding for both patients and clinicians, it is important to know what pretreatment factors were associated with the rebound. Our results using subgroup analyses demonstrated that a thinner pretreatment foveal thickness and a shorter interval from the symptom onset to the initiation of IVB were

Table 2. Comparison of Various Pretreatment Factors Between Group 3 and Group 4

Factor	Group 3	Group 4	*P*
Number of eyes	34	7	
Age (years)*	62.0 ± 7.4	57.7 ± 8.8	0.22
Gender (men/women)	19/15	5/2	0.37†
Diabetes mellitus	4	2	0.25†
Hypertension	25	4	0.39†
Hypercholesterolemia	5	0	0.28†
Pretreatment visual acuity (logarithm of the minimum angle of resolution)*	0.55 ± 0.24	0.68 ± 0.18	0.1
Pretreatment foveal thickness (μm)*	651 ± 179	451 ± 70	0.004
Period from symptom onset to injection (weeks)*	9.1 ± 4.6	4.9 ± 2.2	

Group 3 = eyes with recurrence ratio <110%. Group 4 = eyes with recurrence ratio. Differences between two groups were analyzed using a nonparametric Mann–Whitney *U*-test.

*Data are expressed as the mean ± SD.

†Differences between the two groups were analyzed using a chi-square test.

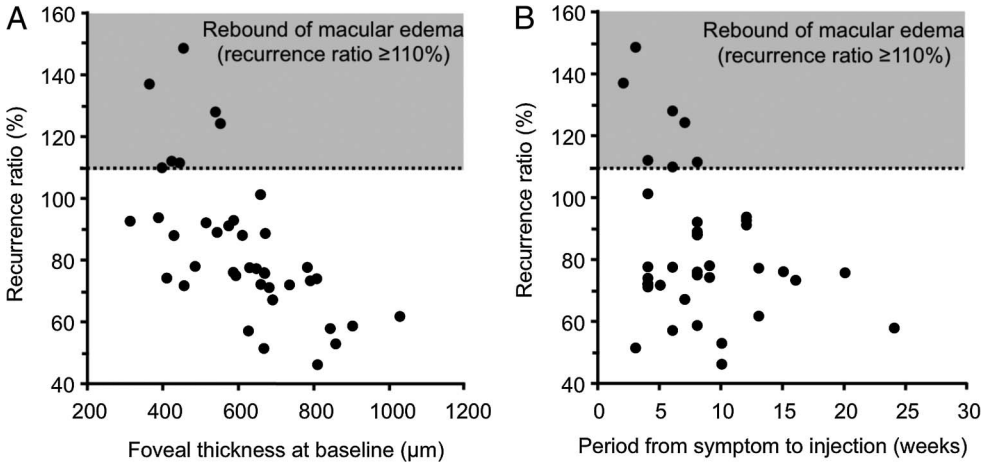

Fig. 3. Relationship between the recurrence ratio (foveal thickness at the rebound/foveal thickness at the baseline × 100) and 2 pretreatment factors for the 41 eyes of Groups 3 and 4. **A**. The recurrence ratio plotted against the foveal thickness at the baseline (in micrometers). **B**. The recurrence ratio plotted against the period from symptom onset to the initiation of treatment (weeks). Gray areas show the eyes with recurrence ratio ≥110%, that is, a rebound.

significantly associated with a rebound of macular edema. Interestingly, all 7 eyes that had a rebound of macular edema received the IVB therapy within 8 weeks of the onset of the symptoms (Figure 3B). These results suggest that the rebound of macular edema was more likely to occur when the IVB therapy was initiated at a relatively early stage of the macular edema before the edema had reached the maximum degree of edema in eyes with a BRVO. In other words, the rebound of macular edema may be more likely to occur in eyes in which the macular edema might have worsened if they had not received the IVB therapy during its natural course.

However, other factors may be involved in the mechanism for the rebound of macular edema after the IVB therapy, because 1 of 3 patients with rebound macular edema reported by Matsumoto et al[27] had received the IVB therapy 22 months after the diagnosis. They hypothesized that the inhibition of the VEGF pathway by IVB may upregulate VEGF receptors within the retina of the patients, and this upregulation may make the endothelial cells more sensitive to the VEGF that are already upregulated because of the underlying ischemic state.[27] Quantitative analysis of the changes in the expression of the VEGF receptors at various times after IVB therapy in an animal model of BRVO may answer this question.

We also studied whether there was any difference in the post-IVB outcomes between the eyes with and without rebound (Group 3 vs. Group 4), and we found that there was no significant difference in any of the post-IVB outcome values (Table 3). These findings suggest that the eyes with rebound macular edema do not necessarily result in poorer visual outcome than eyes without a rebound. However, we hesitate to draw this conclusion based on our results, because of the few eyes in Group 4 and the high withdrawal rate for additional injections in Groups 3 and 4. The reason for the high withdraw rate was because the decision to give additional injections was done not only by the data of foveal

Table 3. Comparison of Posttreatment Values Between Group 3 and Group 4

Posttreatment Values	Group 3	Group 4	*P*
BCVA at recurrence (logarithm of the minimum angle of resolution)	0.27 ± 0.21	0.44 ± 0.30	0.15
Changes in BCVA between baseline and recurrence (logarithm of the minimum angle of resolution)	0.33 ± 0.26	0.28 ± 0.19	0.85
Number of injections within 6 months	1.8 ± 0.7	2.0 ± 0.8	0.50
BCVA at 6 months after initial injection (logarithm of the minimum angle of resolution)	0.22 ± 0.21	0.35 ± 0.25	0.16
Changes in BCVA between baseline and 6 months after initial injection (logarithm of the minimum angle of resolution)	0.35 ± 0.27	0.33 ± 0.14	0.89
Foveal thickness at 6 months after initial injection (μm)	400 ± 150	375 ± 170	0.59

Data are expressed as mean ± SD. Differences between two groups were analyzed using a nonparametric Mann–Whitney *U*-test. VA, visual acuity.

thickness and visual acuity but also by the patient's approval. Thus, few eyes and high withdrawal rate for additional injections were limitations of our study.

The incidence of rebound macular edema in BRVO was 10.8%. However, this percentage may change because of the interval of the follow-up period. We followed-up our patients monthly and performed a second injection immediately when a recurrence was detected. It is possible that if our follow-up interval was shorter, for example, every week or every 2 weeks, then we might have detected a recurrence earlier and performed a second injection at an earlier stage of recurrence, resulting in lower incidence of rebound macular edema. The incidence of rebound macular edema can also change because of the period from symptom onset to the injection. If we initiated the IVB therapy after a 2- to 3-month observational period, then the incidence of rebound macular edema might have been lower than what we found (Figure 3B). In addition, the incidence of rebound macular edema can also change if multiple injections (e.g., three times monthly) had been adopted at the initial injection.

Finally, there is still discussion about when the IVB therapy should be initiated in eyes with macular edema secondary to BRVO. It is widely recommended that any invasive treatments for macular edema secondary to BRVO should be initiated at least 2 months to 3 months after the symptom onset because spontaneous resolution of macular edema can occur mostly within this period.[4,23,24] We did not set any observational window before the initiation of IVB. However, based on our results, we now believe that it is reasonable to wait at least 2 months after the onset to begin the IVB, because in addition to excluding eyes with spontaneous resolution, a rebound of macular edema may be avoided by waiting 2 months after the symptom onset.

Key words: branch retinal vein occlusion, macular edema, bevacizumab, vascular endothelial growth factor, rebound.

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