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CLINICAL INVESTIGATION

Treatment of macular edema due to branch retinal vein occlusion with single or multiple intravitreal injections of bevacizumab

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Abstract
Purpose We examined the predictive factors for final visual acuity (VA) with macular edema of branch retinal vein occlusion (BRVO) treated by intravitreal injection of bevacizumab (IVB) and examined the differences between patients without recurrent macular edema due to BRVO after a single IVB and patients treated with multiple IVB because of recurrent macular edema.
Methods In this retrospective study, 37 eyes of 37 patients with BRVO were treated with IVB and followed up for more than 24 weeks. Eighteen eyes showed no recurrence of macular edema after a single IVB (single IVB group). The remaining 19 eyes showed recurrent macular edema and underwent multiple IVB (multiple IVB group). VA and morphologic parameters of optical coherence tomography were examined.
Results Mean VA, central retinal thickness, and mean retinal thickness in a circular region of 1-mm diameter at the fovea improved significantly with IVB treatment in both groups. Final VA was correlated with baseline VA and integrity grade of the photoreceptor inner and outer segment (IS/OS) line beneath the fovea.
Conclusion Baseline VA and IS/OS line grade at 4 weeks may be predictive factors for final VA.

Keywords Macular edema · Branch retinal vein occlusion · Intravitreal injection · Bevacizumab · IS/OS line

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Introduction

Macular edema due to branch retinal vein occlusion (BRVO) is a major cause of visual loss. Macular grid laser photocoagulation, intravitreal injections of steroids, and vitrectomy were tried as treatments for macular edema secondary to BRVO [1–3]. Several studies report the effectiveness of intravitreal injections of bevacizumab (IVB) for macular edema secondary to BRVO [4–8]. Although the IVB had to be repeated whenever macular edema recurred, in some patients, BRVO-associated macular edema resolved with a single IVB [5–9]. Other studies examined the differences between responders and nonresponders to IVB [5, 10, 11], but little is known about the differences between patients who have no recurrence of macular edema after a single IVB and patients who require multiple IVB because of recurrent macular edema. In this study, we treated macular edema secondary to BRVO with IVB and retrospectively examined the differences in the recovery of visual acuity (VA) and the morphologic parameters of optical coherence tomography (OCT) between patients without recurrent macular edema after a single IVB and patients treated with multiple IVB because of recurrent macular edema.

Patients and methods

Patients

We retrospectively examined 37 eyes of 37 consecutive patients (22 women and 15 men) with macular edema due to BRVO at Toyama University Hospital from December 2008 to July 2009. All patients were naïve to treatment of macular edema and had BRVO with macular involvement

accompanied by decreased VA and macular edema. The macular edema was confirmed by OCT, which revealed a central macular thickness (CMT) >250 μm. Patients who had BRVO without the involvement of macular edema or without a decrease in VA were excluded. The research was conducted in accordance with the Institutional Guidelines of the University of Toyama and was approved by the Institutional Review Board. The procedures conformed to the tenets of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from each patient after provision of sufficient information about the procedures.

Primary treatment with intravitreal injections of bevacizumab

All patients in this study underwent IVB as a primary treatment on their first visit to our hospital, which was performed as follows. After topical anesthesia with 2% lidocaine, the eye was irrigated with 10% povidone–iodine. Then, 0.1–0.2 ml of 2% lidocaine was injected into the subconjunctival space around the anticipated injection site. At 3.5–4 mm from the limbus, 1.25 mg (50 μl) bevacizumab was injected into the vitreous cavity with a 29-gauge needle. Antibiotic eye ointment was applied to the cul-de-sac at the end of the injection. An antibiotic eye drop was given daily for several days after the IVB.

Follow-up examinations and retreatment

After the first IVB, all patients were followed every 4 weeks for at least 24 weeks with VA, ophthalmic, and OCT examinations (RTVue-100; Optovue Inc, Fremont, CA, USA). The OCT examinations included measurements of central retinal thickness (CRT) and mean retinal thickness (MRT) in a circular region of 1-mm diameter at the fovea. CRT was measured manually on OCT images. MRT was obtained using the EMM5 software for the RTVue-100. At 4 weeks after the first IVB, the junction line between the inner and outer segments of the photoreceptors (IS/OS) beneath the fovea was divided into three categories following the method reported in a previous study [12]: grade 0, IS/OS line not visible; grade 1, abnormal or discontinuous IS/OS line; grade 2, normal or well-preserved IS/OS line. Decimal VA was converted to the logarithm of the minimum angle of resolution (logMAR) units and used for statistical analyses. When recurrence of macular edema was detected by a >20% increase in CRT compared with that in the previous examination, another IVB (1.25 mg) was given as a retreatment in the same manner. All patients who showed a recurrence of macular edema were treated, and the IVB treatment was completed when a recurrence of macular edema was not observed during the follow-up term.

Statistical analyses

Statistical analyses were performed with JMP® 9 (SAS Institute, Cary, NC, USA). Follow-up data were compared with baseline data by a paired *t* test. Comparisons between the two groups were done by analysis of variance (ANOVA) for continuous variables or by χ^2 test for categorical variables. Because the number of samples was not sufficient for multiple regression analysis, we used Spearman's correlation coefficient by rank test to examine correlations. A P value <0.05 was considered statistically significant.

Results

Baseline characteristics and follow-up

Baseline VA and OCT parameters are summarized in Table 1. Mean follow-up was 33.6 ± 14.0 (range 24–72) weeks. Patients were retrospectively divided into a single or multiple IVB group based on responses to IVB. During the follow-up after the first IVB, 18 eyes (48.6%) of 18 patients showed a resolution of macular edema without recurrence (single IVB group). Nineteen eyes (51.4%) of 19 patients showed a recurrence of macular edema after a couple of months and underwent another IVB (multiple IVB group). Mean VA and CRT were not significantly different between groups, though only MRT was significantly different at baseline ($P < 0.05$) (Table 1).

Table 1 Baseline characteristics of single and multiple intravitreal injection of bevacizumab (IVB) groups

	Single IVB group ($n = 18$)	Multiple IVB group ($n = 19$)	P value
Age (years)	66.5 ± 15.0	66.8 ± 12.5	0.4384
Gender (M:F)	6:12	9:10	0.1994
Mean visual acuity (logMAR units) (range)	0.54 ± 0.42 (0.05–1.4)	0.48 ± 0.27 (0.05–1.0)	0.3092
CRT (μm) (range)	401.1 ± 117.7 (250–648)	400.0 ± 107.5 (272–638)	0.4881
MRT (μm) (range)	461.9 ± 82.9 (261–606)	541.1 ± 140.8 (352–876)	0.0403

logMAR logarithm of the minimum angle of resolution, *CRT* central retinal thickness, *MRT* mean retinal thickness in a circular region of 1 mm diameter at the fovea

Because it was difficult to evaluate the IS/OS line beneath the fovea in the OCT images prior to the injections, the IS/OS line beneath the fovea was evaluated in the OCT images at 4 weeks after the first IVB and categorized into three groups. The single IVB group included five eyes classified as grade 0, eight as grade 1, and five as grade 2. The multiple IVB group was divided into seven eyes classified as grade 0, ten as grade 1, and two as grade 2. There was no statistical difference in the number of eyes in each grade between groups ($P = 0.06$). The mean number of IVB replications in the multiple IVB group was 2.52 ± 0.69 (range 2–4), and the mean period of recurrence of macular edema after the first IVB in the multiple IVB group was 13.1 ± 4.2 (range 7.1–21.4) weeks. In the multiple IVB group, eight of 19 eyes were evaluated at 24 weeks' follow-up within 12 weeks after the last IVB. No severe ophthalmic or systemic complications, such as endophthalmitis, retinal detachment, or cerebral infarction, were observed.

Mean visual acuity

Data on mean VA are shown in Fig. 1. Mean VA improved significantly from the baseline after IVB in both groups. Mean VA of the single IVB group was 0.21 ± 0.29 at 4 weeks ($P < 0.01$), 0.13 ± 0.24 at 12 weeks ($P < 0.01$), and 0.08 ± 0.25 at 24 weeks ($P < 0.01$). Mean VA of the multiple IVB group was 0.31 ± 0.31 at 4 weeks ($P < 0.01$), 0.25 ± 0.22 at 12 weeks ($P < 0.02$), and 0.24 ± 0.24 at 24 weeks ($P < 0.05$). Mean VA was not significantly different between groups at any time point.

Improvement or deterioration of VA was defined by changes in >0.3 logMAR units from baseline values. VA in patients with changes <0.3 logMAR units of VA was considered to be maintained. VA improved in 11 (66%) and maintained in seven (34%) eyes at 24 weeks in the single IVB group, whereas eight eyes (44%) improved, ten (51%) were maintained, and one (5%) deteriorated at 24 weeks in the multiple IVB group. Ratios of VA improvement were not significantly different between groups ($P = 0.22$). Baseline VA was significantly correlated with final VA in both the single ($r = 0.761$, $P < 0.0003$) and multiple ($r = 0.694$, $P < 0.002$) IVB groups.

Morphologic parameters of OCT

CRT

Mean CRT of the single IVB group was 401.6 ± 116.9 μm at baseline, 209.3 ± 49.2 μm at 4 weeks ($P < 0.01$), 205.7 ± 42.2 μm at 12 weeks ($P < 0.01$), and 194.1 ± 23.6 μm at 24 weeks ($P < 0.01$) (Fig. 2). It decreased significantly after 4 weeks, and this reduced CRT was maintained in the single IVB group until 24 weeks. Mean CRT of the multiple IVB group was 400.0 ± 107.5 μm at baseline, 243.8 ± 100.8 μm at 4 weeks ($P < 0.01$), 281.8 ± 91.6 μm at 12 weeks ($P < 0.01$), and 307.4 ± 135.2 μm at 24 weeks ($P < 0.02$). It decreased significantly from baseline at each of these time points. However, it increased gradually, and at 12 and 24 weeks after the first IVB, mean CRT of the multiple IVB group was significantly greater than that of the single IVB group ($P < 0.01$) (Fig. 2).

There was no correlation between the CRT at baseline and the final VA.

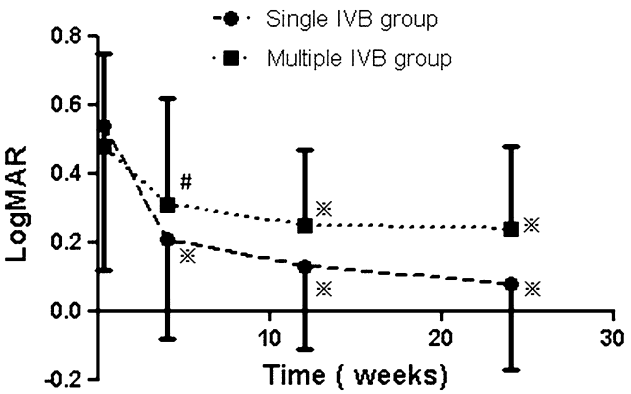

Fig. 1 Mean visual acuity (VA) improved significantly until 24 weeks after intravitreal injection of bevacizumab (IVB) treatment both in the single and multiple IVB groups. Mean VA was not significantly different between groups ($^{\#}P < 0.05$, $*P < 0.02$, ※$P < 0.01$)

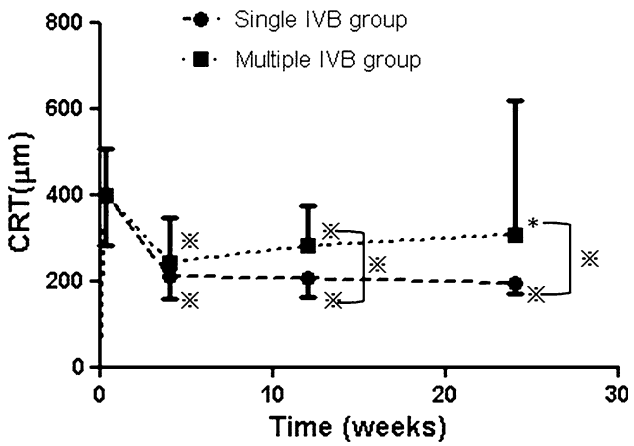

Fig. 2 Mean central retinal thickness (CRT) after intravitreal injection of bevacizumab (IVB) treatment. Both groups showed a significant decrease after the first IVB until 24 weeks. At 12 and 24 weeks, CRT in the single IVB group was significantly decreased compared with that in the multiple IVB group ($*P < 0.02$, ※$P < 0.01$)

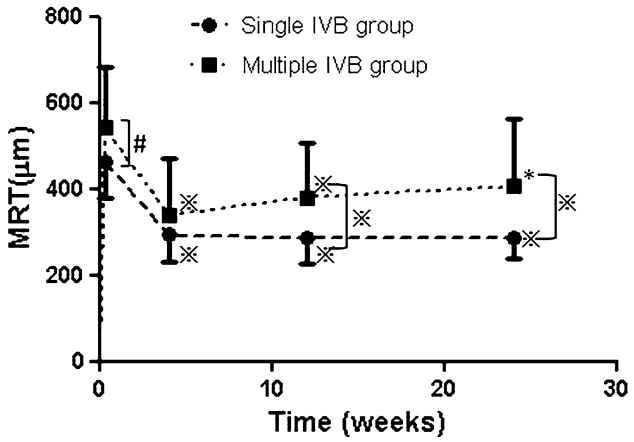

Fig. 3 Mean retinal thickness (MRT) in a circular region of 1-mm diameter at the fovea after intravitreal injection of bevacizumab (IVB) treatment. MRT decreased significantly until 24 weeks in both groups. At baseline and 12 and 24 weeks, MRT in the single IVB group was significantly smaller than that in the multiple IVB group ($^{\#}P < 0.05$, $^{*}P < 0.02$, $※P < 0.01$)

MRT

MRT in a circular region of 1-mm diameter at the fovea in the single IVB group was 461.9 ± 82.9 μm at baseline, 292.9 ± 61.1 μm at 4 weeks ($P < 0.01$), 285.1 ± 57.9 μm at 12 weeks ($P < 0.01$), and 286.8 ± 48.4 μm at 24 weeks ($P < 0.01$) (Fig. 3). It decreased significantly after 4 weeks, and the reduced value was maintained until 24 weeks in the single IVB group. MRT in the multiple IVB group was 541.1 ± 140.8 μm at baseline, 338.9 ± 132.7 μm at 4 weeks ($P < 0.01$), 380.2 ± 125.9 μm at 12 weeks ($P < 0.01$), and 405.8 ± 157.8 μm at 24 weeks ($P < 0.01$). It was also significantly decreased after 4 weeks in the multiple IVB group, but thereafter, it gradually increased until 24 weeks (Fig. 3). It was significantly greater in the multiple IVB group than in the single IVB group at baseline ($P < 0.05$), 12 weeks ($P < 0.01$), and 24 weeks ($P < 0.01$), respectively (Fig. 3).

There was no correlation between MRT at baseline and final VA.

IS/OS line

We examined the effects of the IS/OS line on VA in both groups and found clear difference. Patients with the grade 2 IS/OS line always showed better VA than those with the other grades in the single IVB group (Fig. 4a); however, in the multiple IVB group, patients with the grade 2 IS/OS line showed better VA at baseline, and there was no difference among the three grades after 12 weeks (Fig. 4b). Mean VA seemed to depend on the integrity of the IS/OS line in the single IVB group. In a comparison of mean VA of patients with the same IS/OS grades between the two

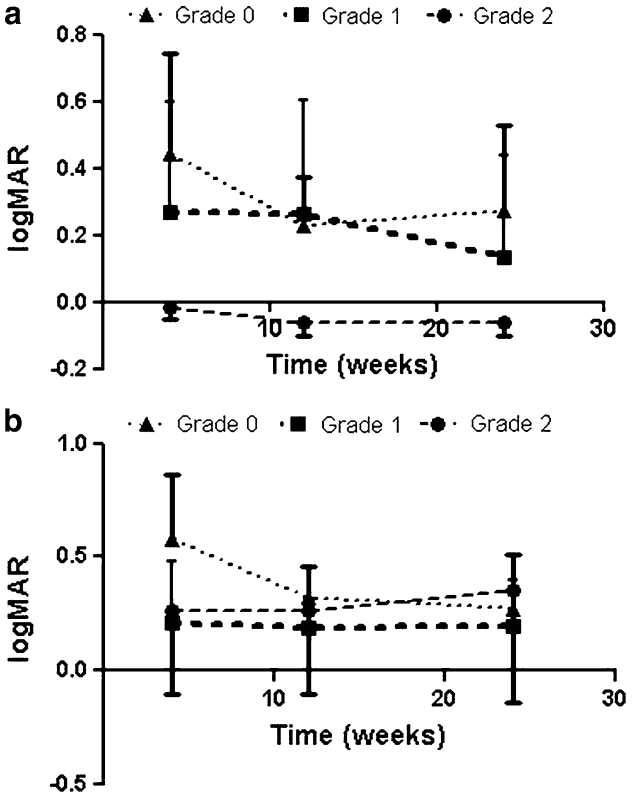

Fig. 4 **a** Single intravitreal injection of bevacizumab (IVB) group mean visual acuity (VA) logarithm of the minimum angle of resolution (logMAR) after treatment for the single IVB group in each grade of the inner and outer segment (IS/OS) line. **b** Multiple IVB group mean VA (logMAR) after IVB treatment of the multiple IVB group in each grade of the IS/OS line

groups, only the mean VA of grade 2 at 24 weeks was significantly better in the single IVB group than in the multiple IVB group ($P < 0.05$).

There was a significant correlation between grades of the IS/OS line and final VA in the single IVB group ($r = 0.6508$, $P = 0.0034$) but not in the multiple IVB group ($r = 0.07468$, $P = 0.7468$).

Discussion

Vascular endothelial growth factor (VEGF) increases vascular permeability and is associated with macular edema due to BRVO [13]. Many groups show that anti-VEGF therapy is effective for macular edema due to BRVO [4–11]. In previous studies on IVB treatment, macular edema due to BRVO recurred frequently after IVB; however, in some patients, the condition was resolved with a single IVB [5–9]. Therefore, we treated all patients with macular edema due to BRVO and decreased VA with IVB and retrospectively divided the patients into two groups (single and multiple IVB) based on responses. First, we

confirmed that IVB could significantly improve VA and macular edema due to BRVO in both groups. We treated all patients with IVB at their first visit if VA had decreased and a macular edema >250 μm was detected, because the period of decreased VA was not accurate in some patients. Therefore, this study might have included some patients in whom macular edema due to BRVO had spontaneously resolved. However, we still do not have enough information to distinguish between spontaneously resolving and persistent macular edema. As persistent macular edema is a major cause of VA loss in BRVO [2], it is important to treat macular edema due to BRVO in the early phase.

Kondo et al. [5] show that macular edema resolved in 28% of their BRVO patients with a single IVB. Other authors report fewer patients in whom macular edema was resolved by a single IVB [9]. However, the characteristics of BRVO patients who can be successfully treated with a single IVB are not fully understood. In our retrospective study, we found that MRT in a circular region of 1-mm diameter was significantly smaller in the single than in the multiple IVB group at baseline, even though CRT and mean VA were not significantly different at baseline. These results indicate that MRT might reflect the degree of macular edema more accurately than CRT and mean VA. Analyses of these morphologic parameters might be helpful for developing a strategy for macular edema treatment.

In this study, a significant correlation was detected between IS/OS grades and final VA in the single IVB group only. Integrity of the IS/OS line at this time may be a predictive factor of final VA in the single IVB group. Because macular edema in the single IVB group resolved and became stable, the integrity of the IS/OS line might directly result in the final VA. We also showed that preoperative VA was correlated with the final VA in the multiple IVB group ($P < 0.002$). As, because of the small number of patients, we had to employ Spearman's correlation coefficient by rank test, further studies using multiple regression tests are needed to clarify predictive factors. Previous studies show several prognostic factors in BRVO, such as preoperative VA and macular thickness, early gainers of VA after IVB, presence of macular ischemia, and integrity of the IS/OS line beneath the fovea [11, 14]. Ach et al. [9] found no predictive factors for the effectiveness of bevacizumab therapy. As we did not perform fluorescein angiography in all patients, we could not evaluate the factor of macular ischemia. In addition, none of the other morphologic parameters (CRT and MRT) at baseline was correlated with final VA in this study.

We examined the morphologic parameters of CRT and MRT to evaluate the effects of IVB on macular edema due to BRVO. Kriechbaum et al. [15] show that mean retinal thickness responded slowly and less impressively to anti-VEGF treatment. Our results of MRT showed similar responses to CRT with IVB treatment. This might have been due to the fact that they measured mean retinal thickness and retinal volume in an area of 20° × 20°, with the midpoint centered on the fovea, whereas we obtained MRT from a smaller area, a circular region of 1-mm diameter at the fovea. The IS/OS line is accepted as the reflection of photoreceptor integrity and is more useful in predicting visual outcomes than are other morphologic parameters of OCT in macular diseases.

In summary, we retrospectively divided BRVO patients into single and multiple IVB groups and showed that the single group had less MRT at baseline and better final VA, although MRT were not correlated with the final VA. The IS/OS line at 4 weeks after IVB and baseline VA might be a predictive factor for macular edema resolved with a single IVB treatment in BRVO, but further studies involving more cases are needed to identify the predictive factors in the treatment of macular edema due to BRVO.

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