

Two-year Results of Intravitreal Ranibizumab Injections Using a Treat-and-extend Regimen for Macular Edema due to Branch Retinal Vein Occlusion

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We investigated the effectiveness of a treat-and-extend regimen (TAE) of intravitreal ranibizumab injections for macular edema (ME) due to branch retinal vein occlusion (BRVO). We retrospectively examined 2-year results of 32 eyes of 32 patients who underwent TAE to treat ME due to BRVO. The patients whose treatment interval extended to ≥ 12 weeks were switched to a pro re nata regimen (PRN). For the patients whose treatment interval was < 12 weeks, TAE was continued. At 2 years, 10 eyes had required no additional injections after the initial treatment period [recurrence(-) group], whereas the other 22 eyes required additional treatment [recurrence(+) group]. Among the recurrence(+) patients, 11 eyes (34.4% of total) were eventually switched from TAE to PRN; the other 11 eyes (34.4%) continued TAE for 2 years. Visual acuity and central retinal thickness were significantly improved in both the recurrence(+) and (-) groups, and there was no significant between-group difference in visual acuity at 2 years. Univariate analyses revealed significant differences in visual acuity ($p=0.004$), age ($p=0.014$), and vessel occlusion site ($p=0.018$) between these groups. Our results suggest that TAE may be effective for BRVO patients with lower visual acuity, older age, and occlusion of a major vein.

Key words: branch retinal vein occlusion, macular edema, anti-vascular endothelial growth factor, ranibizumab, treat-and-extend regimen

Several large clinical trials have demonstrated that anti-vascular endothelial growth factor (VEGF) therapy is an effective and safe treatment for macular edema (ME) due to branch retinal vein occlusion (BRVO) [1-6], and anti-VEGF therapy is currently the first-line treatment for ME due to BRVO. However, an appropriate treatment protocol for this therapy has not been established [7]. One reason for this problem is that the required frequency of anti-VEGF injections varies greatly from patient to patient. Although there have

been reports that ME resolves spontaneously in 18-41% of BRVO cases [8,9], it has also been reported that 50% of cases require continued anti-VEGF treatment even after 4 years of anti-VEGF therapy [9].

Several clinical trials have used a protocol that includes switching to a pro re nata regimen (PRN) after 6 months of monthly administrations of anti-VEGF therapy [1,3,5]. However, even the first six monthly injections can lead to overtreatment and a serious patient burden. To further complicate matters, a PRN regimen can be insufficient to treat some patients with

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ME due to BRVO. Therefore, in order to minimize the number of treatments and reduce the burden on the patient, an individualized administration regimen is desirable.

A treat-and-extend regimen (TAE) is an individualized administration method which aims to reduce the number of consultations by determining the optimal treatment interval [10-12]. TAE regimens have mainly been used for the administration of anti-VEGF therapy to treat age-related macular degeneration, but these regimens have also been used to treat ME due to BRVO [13,14]. We conducted a study of the 1-year results following a TAE regimen for ME due to BRVO, and we observed that TAE regimens were effective and that there were large individual differences in reactivity to anti-VEGF treatment [15]. In the present study, we report the 2-year therapeutic results of a TAE regimen of anti-VEGF injections for ME due to BRVO.

Patients and Methods

Patient sample and study design. We retrospectively reviewed the medical records of 32 eyes of 32 consecutive patients (14 men, 18 women; mean age \pm SD, 71.3 ± 11.2 years) with treatment-naïve ME due to BRVO who were treated at Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences. The patients began treatment between October 2013 and November 2014 and were each administered intravitreal injections of ranibizumab (0.5 mg; Lucentis, Genentech/Novartis, San Francisco, CA, USA) according to a TAE regimen. All patients continued treatment with this regimen for ≥ 2 years. This study was approved by the Institutional Review Board of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (approval No. 1506-043) and was conducted in accordance with the tenets of the Declaration of Helsinki. Each patient was informed of the risks and benefits of treatment and gave written informed consent to participate.

Ophthalmological examination. All patients underwent comprehensive ophthalmologic examinations at all visits, including the measurement of his or her best-corrected visual acuity (BCVA) with refraction using the 5-m Landolt C acuity chart and indirect and contact lens slit lamp biomicroscopy. The patients' BCVA values were recorded as decimal values and con-

verted to logarithm of the minimum angle of resolution (logMAR) units for the statistical analyses. The diagnoses of ME due to BRVO were based on the results of fundus examinations, fluorescein angiography (TRC50DX; Topcon Medical Systems, Tokyo), and optical coherence tomography (OCT) (Cirrus: Carl Zeiss Meditec, Jena, Germany and DRI OCT-1 Atlantis: Topcon Medical Systems). We defined ME as a central retinal thickness (CRT) measurement $> 300 \mu\text{m}$, as determined by OCT. Patients with a history of thromboembolic events were excluded from this study.

The treat-and-extend regimen. Intravitreal injections of ranibizumab were administered to all 32 patients as described [15]. Briefly, the patients were examined and injected with ranibizumab every 4 weeks until no sign of ME was found. If there was no sign of ME, a new injection was given, and the time interval until the next treatment was extended by 4 weeks at a time, to a maximum interval of 12 weeks. If an OCT examination revealed recurrence, defined as a CRT $> 300 \mu\text{m}$, the interval was shortened by 2 weeks at a time until the CRT became $\leq 300 \mu\text{m}$. Patients whose treatment interval was extended to 12 weeks were subsequently switched from the TAE regimen to a PRN regimen.

Thus, if a patient's ME did not recur at all after the initial injection, the treatment regimen was shifted to a PRN regimen after four doses, *i.e.*, 6 months after the initial injection (Fig. 1). Patients who showed a retinal non-perfusion area > 10 optic discs area (DA) at 6 months after the initial injection were treated with retinal photocoagulation.

Outcome measures. The main outcome measures were as follows: (1) the individualized therapeutic protocols; (2) changes in the BCVA, CRT, and the annual number of intravitreal ranibizumab injections; and (3) predictive factors for the recurrence of ME.

Statistical analyses. Both the BCVA and CRT were compared at baseline, 1 month, 6 months, 1 year, and 2 years after the initial injection by a one-way analysis of variance (ANOVA) with a Bonferroni correction. To explore the predictive factors for the absence of ME recurrence following intravitreal ranibizumab treatment by a modified TAE regimen, we analyzed clinical characteristics including age, disease duration, BCVA, and CRT by unpaired *t*-tests. The site of occlusion, the presence/absence of a 10-DA nonperfusion area, the presence/absence of serous retinal detachment, and the

presence/absence of hypertension at baseline were analyzed using Pearson's chi-square tests. Probability values <0.05 were considered significant. All statistical analyses were performed using SPSS for Windows ver. 17.0 (SPSS, Chicago, IL, USA). Unless otherwise noted, the data are presented as means ± standard deviation.

Results

Thirty-two eyes of 32 Japanese patients were analyzed. The patients' baseline characteristics are summarized in Table 1. Figure 1 provides a summary of the individualized treatment protocols for all patients during the 2-year study period. At 2 years, 10 eyes (31.3%) had not shown any recurrence of ME after the initial injection; these patients comprised the recurrence(-) group. The other 22 eyes (68.7%) did show a recurrence of ME and required additional treatment; these patients were the recurrence(+) group.

In the recurrence(+) group, 11 of the total 32 eyes (34.4%) were able to eventually change from the TAE regimen to a PRN regimen, and the other 11 recurrence(+) eyes of the total 32 eyes (34.4%) continued the TAE regimen for 2 years. Ten of the 15 eyes in which

ME did not recur for 6 months after the initial injection did not show any recurrence throughout the follow-up period, and the remaining 5 eyes showed a recurrence of ME; the interval of the recurrence was 16-28 weeks after the initial injection.

Seventeen eyes showed a recurrence of ME during the first 6 months after the initial injection, and 11 (65%) of these 17 cases required repeated injections at intervals of <12 weeks throughout the second year. The treatment intervals at 2 years for all cases are shown in

Table 1 Baseline patient characteristics

Cases	32
Age (years)	71.3 ± 11.2
Sex (male/female)	14/18
Time period from onset of BRVO to initial injection (months)	1.9 ± 1.6
Major BRVO/Macular BRVO	20/12
NPA ≥ 10DA (eyes (%))	11 (34.4)
SRD (eyes (%))	14 (43.8)
Hypertension (eyes (%))	20 (62.5)

Data are presented as the mean ± standard deviation
BRVO, branch retinal vein occlusion; NPA, non-perfusion area; DA, discs area; SRD, serous retinal detachment.

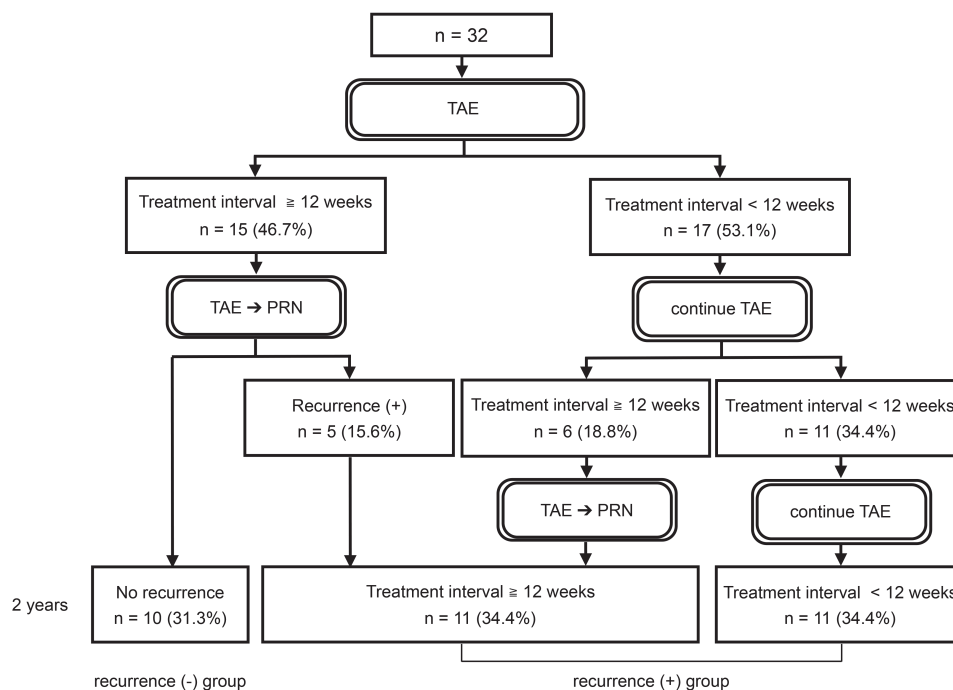


Fig. 1 Summary of the therapeutic protocol for all patients during the 2-year study period. TAE, treat-and-extend; ME, macular edema; PRN, pro re nata.

Fig. 2.

The patients' BCVA (logMAR) improved significantly, from a mean of 0.40 ± 0.34 at baseline to 0.10 ± 0.22 and 0.07 ± 0.19 at 1 year and 2 years, respectively (both $p < 0.001$, Fig. 3). Further, the mean BCVA (logMAR) improved significantly in both the recurrence(-) group and the recurrence(+) group. In the recurrence(-) group, the mean BCVA (logMAR) improved from 0.22 ± 0.10 at baseline to -0.01 ± 0.12 and -0.02 ± 0.11 at 1 year and 2 years, respectively (both $p < 0.001$, Fig. 3). The mean BCVA (logMAR) for the recurrence(+) group improved from 0.49 ± 0.37 at

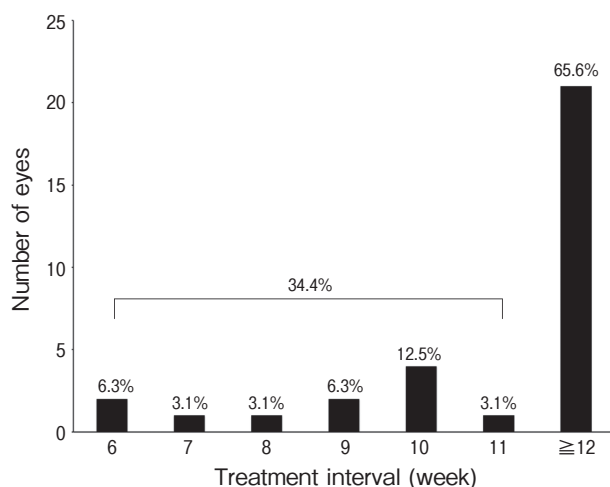


Fig. 2 Treatment interval at 2 years. Individual patients demonstrated a wide variation in the maximum treatment interval. At 2 years after the initial treatment, 21 eyes (65.6%) had achieved a treatment interval of ≥ 12 weeks, and the other 11 eyes (34.4%) required a treatment interval of < 12 weeks.

baseline to 0.15 ± 0.24 and 0.11 ± 0.20 at 1 year and 2 years, respectively (both $p < 0.001$, Fig. 3). There was no significant difference between the BCVAs of the 2 groups at 2 years (Table 2, Fig. 3).

The CRT decreased significantly, from a mean of $448.6 \pm 115.1 \mu\text{m}$ at baseline to $272.3 \pm 70.5 \mu\text{m}$ and $252.9 \pm 36.3 \mu\text{m}$ at 1 year and 2 years, respectively (both $p < 0.001$, Fig. 4). This significant decrease was seen in both the recurrence(-) group and the recurrence(+) group. In the recurrence(-) group, the mean CRT

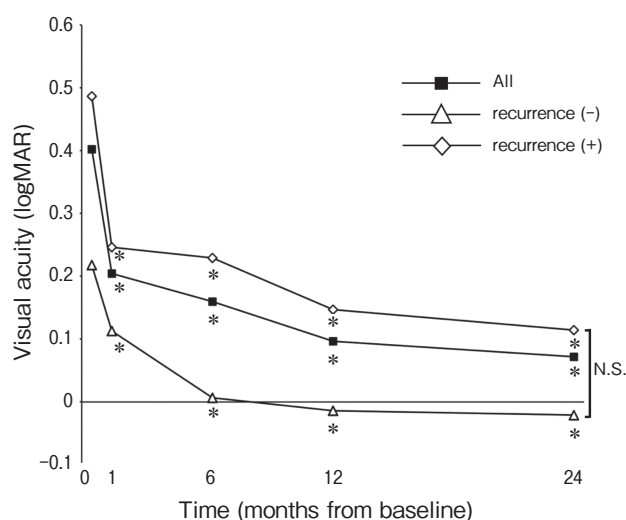


Fig. 3 Course of visual acuity. The mean BCVA measured at baseline, 1 month, 6 months, 1 year, and 2 years in the total patient group, the recurrence(+) group, and the recurrence(-) group. In each group, visual acuity was significantly improved at each time point compared to baseline. logMAR, logarithm of the minimum angle of resolution. * $p < 0.01$.

Table 2 Comparison of baseline characteristics between the no recurrence group and the recurrence group

	No recurrence (n = 10)	Recurrence (n = 22)	p value
Age (years)	62.0 ± 14.0	75.6 ± 6.5	0.014
Sex (male/female)	5/5	9/13	0.699
Time period from onset of BRVO to initial injection (months)	2.1 ± 1.9	1.9 ± 1.5	0.794
BCVA at baseline (logMAR)	0.22 ± 0.10	0.49 ± 0.37	0.004
CRT at baseline (μm)	460.9 ± 128.4	443.0 ± 111.4	0.692
Major BRVO/Macular BRVO	3/7	17/5	0.018
NPA $\geq 10\text{DA}$ (eyes (%))	1 (10.0)	10 (52.6)	0.106
SRD (eyes (%))	6 (60.0)	8 (42.1)	0.267
Hypertension (eyes (%))	7 (70.0)	11 (57.9)	0.703

Data are presented as the mean \pm standard deviation

TAE, treat-and-extend regimen; PRN, pro re nata; BRVO, branch retinal vein occlusion; BCVA, best-corrected visual acuity; CRT, central retinal thickness; NPA, non-perfusion area; SRD, serous retinal detachment.

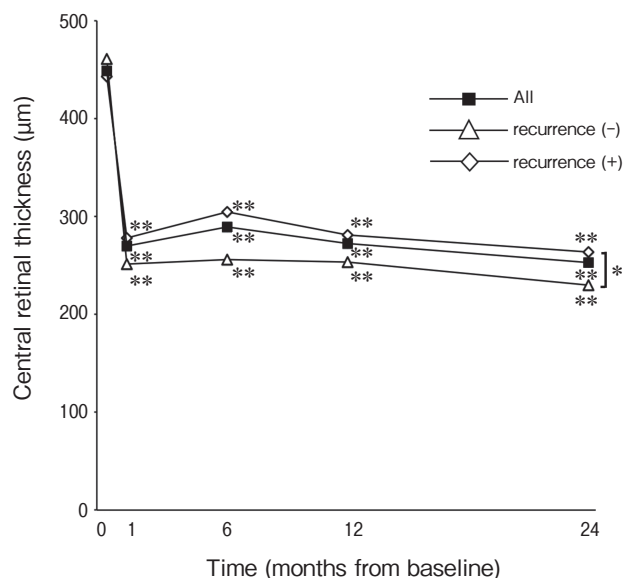


Fig. 4 Course of central retinal thickness (CRT). The mean CRT at baseline, 1 month, 6 months, 1 year, and 2 years in the total patient group, the recurrence(+) group, and the recurrence(-) group. In each group, the CRT was significantly improved at each time point compared to baseline. * $p < 0.05$. ** $p < 0.01$.

decreased significantly, from $460.9 \pm 128.4 \mu\text{m}$ at baseline to $253.4 \pm 52.9 \mu\text{m}$ and $229.7 \pm 18.4 \mu\text{m}$ at 1 year and 2 years, respectively (both $p < 0.001$, Fig. 4). For the recurrence(+) group, the mean CRT decreased significantly from $443.0 \pm 111.4 \mu\text{m}$ at baseline to $280.9 \pm 76.7 \mu\text{m}$ and $258.2 \pm 37.4 \mu\text{m}$ at 1 year and 2 years, respectively (both $p < 0.001$, Fig. 4). No significant difference was observed in the CRT between the recurrence(-) and recurrence(+) groups at baseline, 1 month, 6 months, or 1 year (Table 2, Fig. 4). However, at 2 years the mean CRT was significantly thicker in the recurrence(+) group compared to the recurrence(-) group ($p = 0.03$, Fig. 4).

In the total patient group, the mean number of injections was 6.0 ± 2.2 for the first year and 3.2 ± 2.9 for the second year. In the recurrence(-) group, the mean number of injections was 4.0 ± 0.0 for the first year and 0.0 ± 0.0 for the second year. For the recurrence(+) group, the mean number of injections was 6.9 ± 2.1 for the first year and 4.6 ± 2.4 for the second year.

Our comparison of the recurrence(-) and (+) groups by univariate analyses revealed significant differences in visual acuity ($p = 0.004$), age ($p = 0.014$), and occlusion of a major vein ($p = 0.018$, Table 2).

Discussion

A TAE regimen allows the interval of anti-VEGF drug injections to reflect the rate of ME recurrence in an individualized manner. Herein we investigated the 2-year results of intravitreal ranibizumab injections using a TAE regimen for ME due to BRVO, and we noted that the recurrence frequency of ME after treatment varied among patients. There was no recurrence of ME after the initial treatment in 31.3% of all of the 32 patients, whereas 34.4% of the patients showed ME recurrence and required injection intervals of < 12 weeks at 2 years after the initial treatment.

The RETAIN study used a treatment protocol that included switching from monthly ranibizumab injections to PRN injections, and the RETAIN authors reported that 48% of their patients had a recurrence of their ME within 6 months of the initial treatment [4]. Guichard *et al.* administered ranibizumab injections using a TAE regimen for ME due to retinal vein occlusion, and they reported that at 2 years after the initial treatment, the treatment interval was ≥ 12 weeks in 42% of all cases and < 10 weeks in 58% of the cases [14]. The diversity of ME recurrence reported in these studies is consistent with our present findings. It is apparent that because a monthly administration can be overtreatment for patients who are less likely to have an ME relapse whereas PRN administration can be undertreatment for patients with frequent recurrences of ME [16,17], a TAE regimen has the potential to be an effective, individualized alternative for the treatment of ME due to BRVO.

As shown in Table 2, our results indicate that patients are less likely to experience a recurrence of ME if they have better visual acuity, are younger, or have macular BRVO. These results are consistent with those of a previous report by our group in which we investigated the 1-year results of a TAE regimen for ME due to BRVO [15]. Of note, ME due to macular BRVO has been reported to be more likely to show spontaneous remission compared to ME due to major BRVO [18]. In addition, macular BRVO has been reported to require fewer injections than major BRVO, suggesting that macular BRVO is more reactive to anti-VEGF treatment [19,20]. Together these results indicate that major BRVO involves more widespread retinal ischemia than macular BRVO, resulting in a greater production of VEGF and inflammatory cytokines (such as monocyte

chemoattractant protein-1 [MCP-1] and interleukin [IL]-6) from the ischemic retina [19, 20].

The present study has important limitations, including its retrospective design and small sample size. To establish the optimal ranibizumab treatment protocol for ME due to BRVO, randomized and prospective clinical studies with more patients are necessary. Importantly, our TAE regimen may result in overtreatment for patients who do not require any treatment because of spontaneous ME remission. The enlargement of the foveal avascular zone area and the presence of collateral circulation in BRVO cases are factors related to the progression of visual acuity and macular morphology [21, 22]. Further studies must investigate the relationship between these factors and treatment results of ME cases due to BRVO. In conclusion, our 2-year results suggest that a TAE regimen may be especially effective for patients with lower visual acuity, older age, and a major BRVO.

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