

## Results of a Treat-and-Extend Regimen of Intravitreal Ranibizumab Injection for Macular Edema due to Branch Retinal Vein Occlusion

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To investigate the effectiveness of a treat-and-extend regimen (TAE) of intravitreal ranibizumab injections (IVR) for macular edema (ME) due to branch retinal vein occlusion (BRVO). We retrospectively examined 35 eyes of 35 patients with ME due to BRVO who underwent TAE for 1 year. Patients whose treatment interval extended to 12 weeks were switched to a pro re nata regimen (PRN; TAE to PRN group), while TAE was continued for patients whose treatment interval was less than 12 weeks (continued TAE group). Changes in best-corrected visual acuity (BCVA), central retinal thickness (CRT), and predictive factors for inclusion in the TAE to PRN group were analyzed. BCVA and CRT both improved significantly at 1 year compared with baseline ( $p < 0.001$ ). Sixteen eyes (45.7%) were included in the TAE to PRN group, while 19 eyes (54.3%) were included in the continued TAE group. BCVA in the TAE to PRN group was significantly better than that in the continued TAE group at 1 year ( $p = 0.047$ ). BCVA at baseline and macular BRVO were significant predictive factors for inclusion in the TAE to PRN group. TAE was effective for improving BCVA and CRT. The TAE to PRN group showed significantly better prognosis.

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

In several large-scale clinical trials, anti-vascular endothelial growth factor (VEGF) therapy has been shown to be an effective and safe treatment for macular edema (ME) due to branch retinal vein occlusion (BRVO). Thus, anti-VEGF therapy is currently the first-line treatment for ME due to BRVO [1-6]. However, one major problem with this therapy is that a suitable injection protocol has not yet been established [7]. One reason for this problem is that the required frequency of anti-VEGF injections differs greatly among individual BRVO cases. While spontaneous remission

is reported to occur in 18-41% of cases of ME due to BRVO [8,9], a reported 50% of eyes still require anti-VEGF injections for ME after 4 years [8]. Many large-scale studies have used a protocol of monthly injections of anti-VEGF agents for 6 months followed by pro re nata (PRN) injections. However, monthly injections may result in overtreatment for patients who do not require frequent injections of anti-VEGF agents, while a PRN regimen may result in undertreatment for patients who do require more frequent injections. Moreover, both a monthly fixed regimen and a monthly PRN regimen can cause a significant health care burden,

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and frequent anti-VEGF injections may lead to the progression of geographic atrophy in age-related macular degeneration [7, 10]. Therefore, individualized rather than uniform regimens could minimize the number of anti-VEGF injections and clinic visits and thus reduce patient burden.

A treat-and-extend regimen (TAE) is an individualized regimen that aims to decrease the number of injections and visits to the clinic by determining an optimal treatment interval [11-13]. A TAE regimen entails adjustment of the treatment interval according to the occurrence/nonoccurrence of relapse in order to ascertain the maximum treatment interval during which there has been no relapse for every individual. TAE is a regimen primarily used in anti-VEGF therapy for age-related macular degeneration, but it is also thought to be effective in anti-VEGF therapy for treating ME due to BRVO [14]. However, to the best of our knowledge, there has been only one report on the use of anti-VEGF therapy for treating ME due to BRVO using a TAE regimen [14]. Therefore, more knowledge is needed regarding the efficacy of this treatment method.

In the present study, we retrospectively examined 35 eyes of 35 patients with treatment-naïve ME due to BRVO who underwent TAE for 1 year. We investigated the efficacy of TAE with respect to best-corrected visual acuity (BCVA; logarithm of the minimal angle of resolution [logMAR]), central retinal thickness (CRT), and the number of intravitreal ranibizumab injections for treating ME due to BRVO.

## Patients and Methods

**Study design and patients.** We retrospectively reviewed the medical records of 35 eyes of 35 consecutive patients with treatment-naïve ME due to BRVO. The patients were treated with intravitreal injections of ranibizumab (0.5 mg; Lucentis, Genentech/Novartis) using a TAE regimen, described below, for at least one year at Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences from October 2013 to November 2014. 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.

**Ophthalmological examination.** All patients underwent comprehensive ophthalmologic examinations at all visits, including measurement of best-corrected visual acuity (BCVA) with refraction using the 5-m Landolt C acuity chart and indirect and contact lens slit lamp biomicroscopy. Patients' BCVAs were recorded as decimal values and converted to logarithm of the minimal angle of resolution (logMAR) units for statistical analysis. Diagnoses of ME due to BRVO were based on the results of fundus examinations, fluorescein angiography (TRC50DX; Topcon Medical Systems, Tokyo, Japan), and spectral-domain optical coherence tomography (SD OCT; Cirrus; Carl Zeiss Meditec, Jena, Germany; DRI OCT-1 Atlantis; Topcon Medical Systems). We defined ME as central retinal thickness (CRT) greater than 300  $\mu\text{m}$ , as determined by OCT. Patients with a history of thromboembolic events were excluded from this study.

**Treat-and-extend regimen.** Intravitreal injections of ranibizumab were administered to all patients, with slight modifications to the TAE as described in the report of Rush *et al.* [14]. Briefly, the patients were examined and injected with ranibizumab every 4 weeks until no sign of active disease was found. If there was no sign of active disease, a new injection was given, and the period to the next treatment was extended by 4 weeks at a time to a maximum interval of 12 weeks. If an examination revealed any sign of recurrence, the interval was shortened by 2 weeks at a time until the disease was considered to be inactive. Patients whose treatment interval was extended to 12 weeks were subsequently switched from TAE to a PRN regimen and were classified as belonging to the "TAE to PRN group". After switching to PRN, the first treatment interval was set to 12 weeks, and the subsequent treatment interval was set to 4 weeks. In contrast, the TAE regimen was continued for patients whose treatment interval was less than 12 weeks, and these patients were classified as belonging to the "continued TAE group".

Patients who demonstrated a non-perfusion area of at least 10 optic discs area (DA) at baseline following fluorescein angiography underwent retinal photocoagulation.

**Outcome measures.** The main outcome measures were the number of intravitreal injections of ranibizumab and clinic visits during one year as well as changes in BCVA and CRT. We also assessed several

prognostic variables for their ability to predict inclusion in the TAE to PRN group. These variables included age, sex, time from onset of BRVO to initial injection, BCVA, CRT, major or macular BRVO [15,16], presence of a non-perfusion area over 10 optic DA, presence of serous retinal detachment, and history of hypertension.

**Statistical analysis.** Best-corrected visual acuity at baseline and at 1 year were compared using a paired *t*-test. Both BCVA and CRT were compared at baseline, one month, 6 months, and 1 year using a one-way ANOVA with a Bonferroni correction. Predictive variables for inclusion in the TAE to PRN group were analyzed by multiple logistic regression analysis. *P* values less than 0.05 were considered significant. All statistical analyses were performed using SPSS version 22.0 for Windows (IBM, Armonk, NY, USA). Data are presented as the mean ± standard deviation.

### Results

Thirty-five eyes of 35 Japanese patients were included in this study. Baseline characteristics of these patients are shown in Table 1. Fig.1 shows the breakdown of therapeutic processes of all patients during the one year study period.

Nineteen eyes (54.3%) were of patients whose treatment interval was less than 12 weeks, and their TAE regimen was continued. These patients were classified as the continued TAE group. In contrast, 16 eyes (45.7%) were of patients whose treatment interval was extended to 12 weeks, and these were subsequently switched to a PRN regimen. These patients were classified as the TAE to PRN group. Of the 16 eyes in the

TAE to PRN group, 12 eyes (75.0%) did not demonstrate relapsed ME during the PRN period, and further treatment was unnecessary. The remaining 4 eyes (25.0%) did demonstrate relapsed ME during the PRN period and required further treatment.

As shown in Fig.2, mean BCVA (logMAR) had improved significantly at 1, 6 and 12 months ( $0.21 \pm 0.21$ ,  $0.16 \pm 0.22$ , and  $0.09 \pm 0.22$ , respectively) when compared with baseline ( $0.41 \pm 0.33$ , all  $p < 0.001$ , one-way ANOVA with a Bonferroni correction), and BCVA at 1 year was significantly better in the TAE to PRN group compared to that in the continued TAE group ( $0.01 \pm 0.11$  and  $0.16 \pm 0.26$ , respectively;  $p = 0.047$ , unpaired *t*-test; Table 2).

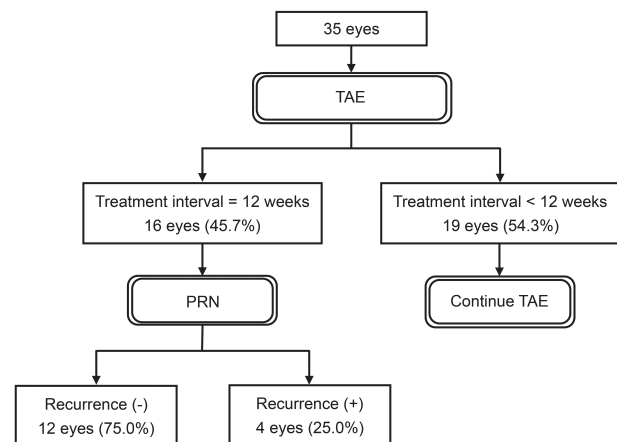
As shown in Fig.3, mean CRT decreased significantly at 1, 6, and 12 months ( $269.4 \pm 50.1 \mu\text{m}$ ,  $289.1 \pm 85.2 \mu\text{m}$ , and  $271.3 \pm 67.7 \mu\text{m}$ , respectively) when compared with baseline ( $445.1 \pm 113.2 \mu\text{m}$ , all  $p < 0.001$ , one-way ANOVA with Bonferroni test). No significant difference was observed in CRT between the TAE to PRN group and the continued TAE group at 1 year ( $273.9 \pm 85.2$  and  $269.0 \pm 51.0$ , respectively;  $p = 0.833$ , unpaired *t*-test; Table 2).

Among all patients, the mean number of injections and the mean number of clinic visits in 1 year were  $6.0 \pm 2.1$  and  $6.8 \pm 1.6$ , respectively (Table 2). In the TAE to PRN group, the mean number of injections and the mean number of clinic visits in 1 year were  $4.2 \pm 0.4$  and  $6.1 \pm 0.8$ , respectively. These numbers were both significantly lower than in the continued TAE group,

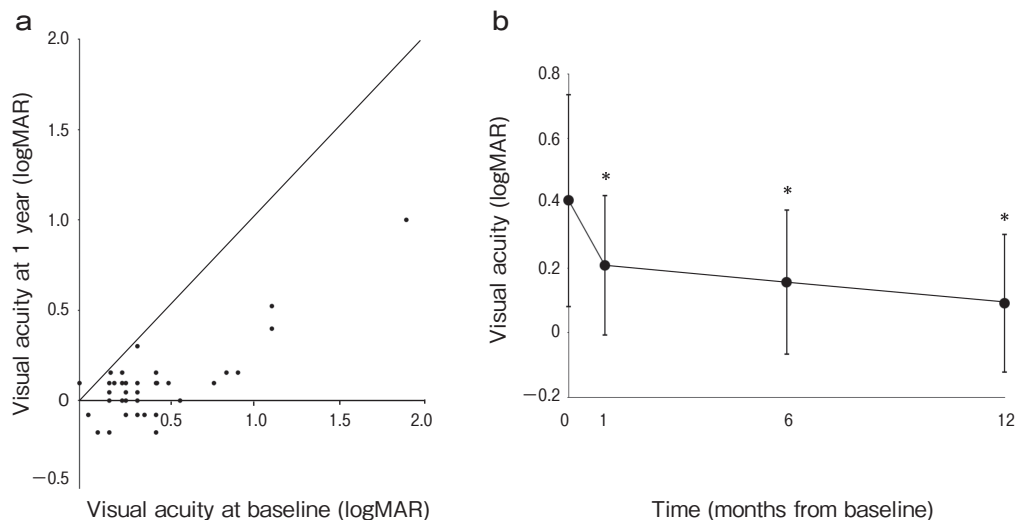
**Table 1** Baseline patient characteristics

Cases	35
Age (years)	71.2 ± 11.5
Sex (male/female)	15/20
Time period from onset of BRVO to initial injection (months)	1.9 ± 1.6
Major BRVO/Macular BRVO	22/13
NPA ≥ 10DA (eyes (%))	14 (40.0)
SRD (eyes (%))	15 (42.9)
Hypertension (eyes (%))	22 (62.9)

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** Breakdown of therapeutic processes of all patients during the one-year study period. TAE, treat-and-extend; ME, macular edema; PRN, pro re nata.



**Fig. 2** Change in visual acuity during the study period. **(a)** Visual acuity at baseline and at 1 year. Scatterplot showing a comparison of best-corrected visual acuity at baseline and at 1 year in 35 eyes that underwent intravitreal injections of ranibizumab using a treat-and-extend regimen. logMAR, logarithm of the minimal angle of resolution. **(b)** Course of visual acuity. Graph showing the best-corrected visual acuity measured at baseline, 1 month, 6 months and 1 year. Visual acuity was significantly improved at each time point compared to baseline. Error bars represent the standard deviation. logMAR, logarithm of the minimal angle of resolution. (\*) indicates  $p < 0.01$ .

**Table 2** Comparison of results at 1 year between the TAE to PRN group and the continued TAE group

	Total (n = 35)	TAE to PRN (n = 16)	Continued TAE (n = 19)	P value
BCVA at 1 year (logMAR)	0.09 ± 0.22	0.01 ± 0.11	0.16 ± 0.26	0.047
CRT at 1 year (μm)	271.3 ± 67.7	273.9 ± 85.2	269.0 ± 51.0	0.833
Mean number of injections	6.0 ± 2.1	4.2 ± 0.4	7.5 ± 1.8	< 0.001
Mean number of visits	6.8 ± 1.6	6.1 ± 0.8	7.5 ± 1.8	0.006

Data are presented as the mean ± standard deviation.

PRN, pro re nata; TAE, treat-and-extend regimen; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimal angle of resolution; CRT, central retinal thickness.

for which the mean number of injections and the mean number of clinic visits in 1 year were both  $7.5 \pm 1.8$  ( $p < 0.001$  and  $p = 0.006$ , respectively; unpaired *t*-test).

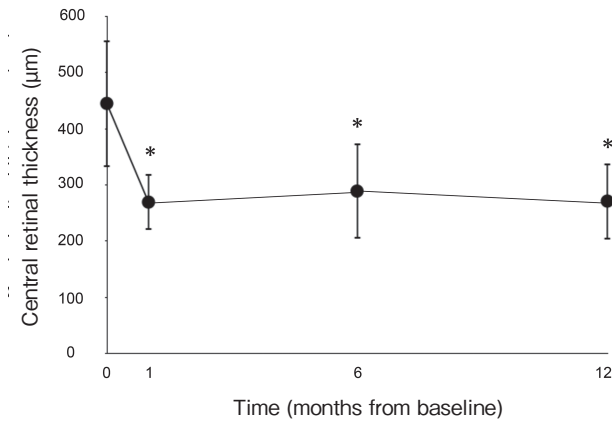
For the 4 eyes that demonstrated relapsed ME during the PRN period in the TAE to PRN group, the mean number of injections and the mean number of visits during the PRN period were 1.0 and 3.5, respectively. The mean number of injections and the mean number of visits among these 4 patients during the whole 1 year study period were 5.0 and 7.5, respectively.

For the 19 eyes in the continued TAE group, the distribution of treatment intervals at 1 year is shown in Fig. 4. These treatment intervals ranged from 4 weeks to 11 weeks, and the mean treatment interval was  $8.1 \pm 2.0$  weeks. The treatment interval was 8 weeks or more for 12 eyes (63.2%).

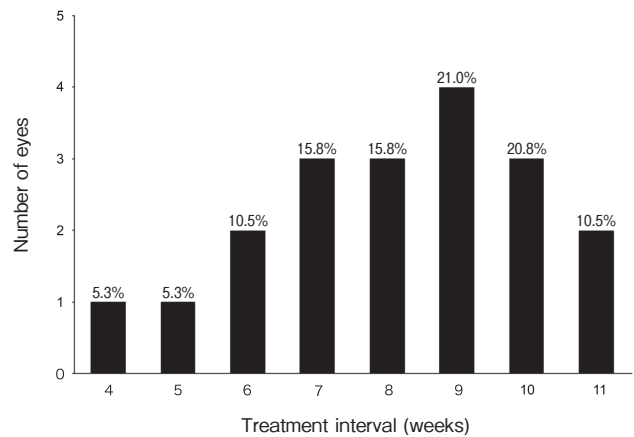
The TAE to PRN group and the continued TAE group demonstrated significant differences in age, BCVA at baseline, and retinal vein occlusion site (major branch retinal vein versus macular branch retinal vein; Table 3). Multiple logistic regression analysis revealed that BCVA at baseline and macular BRVO were significant predictive factors for switching to PRN ( $p < 0.026$  and  $p < 0.025$ , respectively; Table 4).

## Discussion

The present study demonstrates that a TAE regimen of intravitreal ranibizumab injections for treating ME due to BRVO effectively improves visual acuity and reduces CRT. Our results are similar to those of a previous study by Rush *et al.*, in which ME due to BRVO



**Fig. 3** Course of central retinal thickness (CRT). Graph showing CRT at baseline, 1 month, 6 months and 1 year. CRT was significantly improved at each time point compared to baseline. Error bars represent the standard deviation. logMAR, logarithm of the minimal angle of resolution. (\*) indicates  $p < 0.01$ .



**Fig. 4** Treatment intervals within the continued TAE group at 1 year. Individual patients demonstrated a wide distribution of maximum treatment intervals, ranging from 4 to 11 weeks.

**Table 3** Comparison of baseline characteristics between the TAE to PRN group and the continued TAE group

	TAE to PRN (n = 16)	Continued TAE (n = 19)	P value
Age (years)	66.6 ± 12.9	75.1 ± 8.8	0.025
Sex (male/female)	7/9	8/11	0.678
Time period from onset of BRVO to initial injection (months)	2.2 ± 1.9	1.6 ± 1.1	0.346
BCVA at baseline (logMAR)	0.24 ± 0.11	0.55 ± 0.38	0.003
CRT at baseline (μm)	431.1 ± 119.9	457.0 ± 109.1	0.510
Major BRVO/Macular BRVO	6/10	16/3	0.004
NPA ≥ 10DA (eyes (%))	4 (25.0)	10 (52.6)	0.096
SRD (eyes (%))	7 (43.8)	8 (42.1)	0.922
Hypertension (eyes (%))	11 (68.6)	11 (57.9)	0.508

Data are presented as the mean ± 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.

**Table 4** Multiple logistic regression analysis for predictive factors for switching to PRN

Covariate	Odds ratio	P value	95% CI	
			Lower limit	Upper limit
Age	0.901	0.129	0.787	1.031
BCVA (logMAR) at baseline	$3.000 \times 10^{-5}$	0.026	$2.974 \times 10^{-9}$	0.295
Major BRVO	14.414	0.025	1.405	147.879

CI, confidence interval; BCVA, branch retinal vein occlusion; logMAR, logarithm of the minimal angle of resolution.

was treated with intravitreal bevacizumab injections using a TAE regimen [14]. Rush *et al.* reported a mean change in visual acuity (logMAR) of  $-0.30 \pm 0.20$ , with 59.6% of subjects showing an improvement in visual acuity of 0.3 or greater. These results were similar to those reported in the Treatment of Macular Edema fol-

lowing Branch Retinal Vein Occlusion (BRAVO) Study, in which ranibizumab was administered PRN following monthly injections. In the BRAVO study, the mean change in visual acuity (logMAR) was  $-0.37 \pm 0.29$ , with 60.3% of subjects showing an improvement in visual acuity of 0.3 or greater [1]. In the present study,

we observed visual acuity improvement similar to those of Rush *et al.* and the BRAVO study, with a mean change in visual acuity (logMAR) of  $-0.31 \pm 0.20$  and 56.9% of subjects showing an improvement in visual acuity of 0.3 or greater.

The main advantage of a TAE regimen compared to a monthly or a PRN treatment schedule is that the number of injections and the number of clinic visits can be reduced while maintaining the efficacy of the anti-VEGF drugs in improving visual acuity. In the report of Rush *et al.*, the mean number of injections required over 1 year was 8.2, which is very similar to the mean of 8.4 injections presented by the BRAVO study [1, 14]. However, the mean number of required visits to the clinic reported by Rush *et al.* was 8.2, which is much less than the 12 visits reported by the BRAVO study. In the present study, the mean number of injections required during a 1 year period was  $6.0 \pm 2.1$ , and number of clinic visits was  $6.8 \pm 1.6$ . Both of these results are lower than those reported by Rush *et al.* These differences can be explained by the extension of the treatment interval to every 2 weeks in the study by Rush *et al.*, as opposed to every 4 weeks in the present study. Further studies investigating the optimal treatment interval for extension will be needed in order to reduce the burden on both patients and health care providers.

In the present study, patients whose treatment interval was extended to 12 weeks were subsequently switched to a PRN regimen (the TAE to PRN group), while the TAE regimen was continued for patients whose treatment interval was less than 12 weeks (the continued TAE group) [14]. The final best corrected visual acuity in the TAE to PRN group was significantly better than that of the continued TAE group ( $0.01 \pm 0.11$  and  $0.16 \pm 0.26$ , respectively,  $p=0.047$ ; Table 2), while the number of ranibizumab injections in 1 year was significantly lower in the TAE to PRN group compared to the continued TAE group ( $4.2 \pm 0.4$  times,  $7.5 \pm 1.8$  times, respectively,  $p<0.001$ ; Table 2). Indeed, for all 16 patients in the TAE to PRN group, edema improved with only a single administration of ranibizumab and there was no subsequent relapse before starting a PRN regimen. Additionally, there was no relapse in 12 of the 16 eyes (75%) after switching to PRN. In the 4 eyes (25%) for which relapse was observed after switching to PRN, the mean number of injections during the PRN duration was only 1. These results indicate that nearly half of the patients with ME due to BRVO (45.7%)

respond favorably to anti-VEGF therapy and do not require frequent anti-VEGF drugs. Monthly injections or a continued TAE regimen for these patients may thus have resulted in overtreatment.

Interestingly, at 1 year the patients in the continued TAE group demonstrated diverse maximum treatment intervals, ranging from 4 weeks to 11 weeks (Fig. 4). In the BRAVO study and the Study Evaluating Dosing Regimens for Treatment with Intravitreal Ranibizumab Injections in Subjects with Macular Edema following Retinal Vein Occlusion (SHORE study), all patients underwent a PRN regimen following a 6 month period of monthly treatments [1, 17]. However, the diversity of treatment intervals observed in the present study indicates that monthly injections of anti-VEGF drugs for patients with little need for them may result in overtreatment. For example, Hikichi *et al.* have reported that 26% of cases exhibited improvement after only one injection over 2 years [18]. In such cases, monthly injections would result in overtreatment. On the other hand, a PRN regimen for patients with a more significant need for anti-VEGF drugs may result in undertreatment. For example, Farinha *et al.* have reported that PRN treatment improves visual acuity in the short term: they observed 13.2 letters of improvement in ETDRS visual acuity after 6 months compared to the baseline [19]. In the long term, however, the improved visual acuity could not be maintained. Two years after treatment, the improvement of visual acuity decreased to 6.0 letters compared to the baseline. Therefore, continuation of a TAE regimen may be most effective for patients whose treatment interval is less than 12 weeks.

Following multiple logistic regression analysis, visual acuity at baseline and the retinal vein occlusion site were both found to be associated with inclusion in the TAE to PRN group. In particular, macular BRVO was significantly associated with inclusion in the TAE to PRN group (odds ratio=14.414,  $p=0.025$ ; Table 4). The natural history of macular BRVO is separate from that of major BRVO, and amelioration of ME has been reported to be achieved earlier in macular BRVO than in major BRVO [15]. Moreover, a PRN regimen of anti-VEGF drugs has been shown to lead to a lower number of anti-VEGF injections in macular BRVO compared to major BRVO [20, 21]. As reported by Noma *et al.*, the extent of macular ischemia is greater in major BRVO compared to macular BRVO, resulting in increased levels of VEGF and other growth factors as

well as inflammatory cytokines, such as MCP-1 and IL-6. Consequently, ME is more likely to develop in major BRVO [21].

The present study has important limitations, including its retrospective design, small sample size, and relatively short study period. However, the results of this study demonstrate that a TAE regimen of ranibizumab injections is effective for improving visual acuity as well as for reducing the number of necessary injections in the treatment of ME due to BRVO. In addition, we report that treatment prognosis and frequency varied greatly depending on whether or not the treatment interval could be extended to 12 weeks. These results indicate that uniform treatment regimens for BRVO, such as monthly or PRN injections, may result in either overtreatment or undertreatment. Further, when determining a TAE anti-VEGF therapy, a combination of TAE with a PRN regimen is effective for patients who responded well during the TAE period. However, since our procedure involves a minimum of four injections, the combination of TAE with a PRN regimen may result in overtreatment in cases in which the disease does not reoccur after one injection [18]. Further randomized and controlled clinical studies involving a larger number of patients are needed to confirm our results.

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