

Intravitreal PRN ranibizumab treatment for macular edema due to branch retinal vein occlusion

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Background/aim: To evaluate the effect of intravitreal pro re nata (PRN) ranibizumab treatment from the start on the best-corrected visual acuity (BCVA) and the central retinal thickness (CRT) in macular edema (ME) due to branch retinal vein occlusion (BRVO).

Materials and methods: Patients with ME secondary to BRVO, who were treated on a PRN basis after a single intravitreal ranibizumab injection, were retrospectively evaluated. The main outcome measures were changes in BCVA and CRT as measured by optical coherence tomography.

Results: The number of injections over 6 months was 2.43 ± 1.16 . The mean BCVA of the patients was 0.84 ± 0.10 logMAR at baseline and 0.41 ± 0.06 at the 6th month ($P < 0.001$). Mean BCVA of the ischemic BRVO group was 1.06 ± 0.68 logMAR at baseline and 0.44 ± 0.30 logMAR at the 6th month ($P < 0.05$). Similarly, the mean BCVA of the nonischemic BRVO group was 0.77 ± 0.53 logMAR at baseline and 0.41 ± 0.36 logMAR at the 6th month ($P < 0.05$). Between groups, there was no significant difference in mean BCVA at any examination.

Conclusion: Intravitreal ranibizumab is a safe and effective treatment option for ME due to ischemic and nonischemic BRVO using PRN from the start.

Key words: Branch retinal vein occlusion, macular edema, ranibizumab

1. Introduction

Retinal vein occlusion is one of the most common types of retinal vascular diseases (1). Branch retinal vein occlusion (BRVO) is the most common cause (80%) of all retinal vein occlusions, which causes retinal edema that can seriously reduce visual acuity in the case of foveal involvement (2). Management of macular edema (ME) in BRVO has long been a challenge for clinicians. The Branch Vein Occlusion Study Group suggested that grid laser should be used as the standard treatment in suitable patients with ME, which has been proven as the only beneficial treatment for years (3). Recent years witnessed new treatment modalities for ME secondary to BRVO that were evaluated in randomized clinical trials. These are intravitreal triamcinolone injection (4), intravitreal dexamethasone implantation (5), and intravitreal vascular endothelial growth factor (VEGF) inhibitors (6,7). One of these anti-VEGF agents is ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland), which is a humanized monoclonal antibody fragment (Fab) that binds all forms of active VEGF-A.

Previous reports indicated that single-dose intravitreal anti-VEGF injection was associated with transient improvement in BRVO (8–11). Moreover, the BRAVO trial showed the effectiveness of repeated intraocular injections of ranibizumab in terms of improvement in best-corrected visual acuity (BCVA) and central retinal thickness (CRT) in BRVOs (6). In this study, patients with BRVO received monthly intraocular ranibizumab injections for 6 months. Although previous studies (12–14) reported the efficacy of different dosing regimens in BRVO, an established therapeutic algorithm has not been reported yet. In addition, these studies did not address the issue of the ischemic or nonischemic nature of the retinal perfusion. Moreover, despite promising results with different dose regimens for bevacizumab injections, clinical trials for intravitreal ranibizumab injections in BRVO are very limited (15–21). We aimed to assess the efficacy of pro re nata (PRN) intravitreal ranibizumab injection from the start in the treatment of ME in patients with ischemic or nonischemic BRVO.

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2. Materials and methods

In this retrospective study, we enrolled patients with ME due to either ischemic or nonischemic BRVO who were treated with PRN ranibizumab. Patients treated with the PRN regime from the start and having at least a 6-month follow-up were included. Patients previously receiving treatment for retinal vein occlusions such as intravitreal triamcinolone injection, intravitreal bevacizumab injection, or laser photocoagulation and those with conditions preventing any improvement in visual acuity (e.g., macular ischemia, macular degeneration, epiretinal membrane) were excluded from the study. Patients who underwent cataract extraction or other ocular procedures during the follow-up period were also excluded. Naive cases with a less than 2-month time interval between the first BRVO diagnosis and the first injection were included. The local ethics committee approved the study.

Fluorescein angiography (FA) was performed at the first visit in order to identify the morphological peculiarities of the BRVO and assess the status of retinal perfusion. In the case of severe intraretinal hemorrhage that did not allow clear identification of the retinal perfusion, fundus FA was performed after the adequate resolution of retinal hemorrhage. Extent of capillary nonperfusion and dropouts of the retinal capillary bed were determined on FA images. According to FA images, patients were classified into two main groups: ischemic BRVO and nonischemic BRVO. Ischemic BRVO diagnosis was made if the nonperfused area was greater than the 5-disk area. When the nonperfused area was smaller than the 5-disk area, patients were classified as nonischemic (22).

Intravitreal ranibizumab was initiated in the patients with an initial Snellen visual acuity of less than 20/40 and fluid accumulation within the macula secondary to BRVO. Patients with initial Snellen visual acuity better than 20/40 were followed for spontaneous resolution and were not included. Patients were examined monthly and were treated again if the CRT was ≤ 300 μm or if there was persistent ME surrounding the macula that may have led to visual impairment according to the treating physician's evaluation. Intravitreal injection was not performed in the case of visual impairment without ME. Ranibizumab was administered intravitreally to all patients at a dose of 0.5 mg/0.05 mL under sterile operating room conditions.

Patients were examined monthly for 6 months. Each patient had an ophthalmic examination including the best-corrected Snellen visual acuity (BCVA), biomicroscopic examination, funduscopic examination, intraocular pressure (IOP) measurement, and measurement of the CRT using spectral-domain optical coherence tomography (OCT) (Optovue; Fremont, CA, USA) at baseline prior to injection of ranibizumab and at each follow-up visit. CRT was calculated as the distance between the inner

limiting membrane and the retinal pigment epithelium–choriocapillaris interface of radial lines through the foveal area (23). The calipers were set by hand because automated measurement protocols are more prone to errors (24). To minimize observer variations, one experienced physician obtained all scans. BCVA measurements were converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analysis.

The main outcomes of this study were functional changes, mean gain in BCVA, and percentage of cases having a gain of three or more lines in BCVA. Beside anatomical alterations, changes in CRT measured by OCT and mean number of ranibizumab injections were also evaluated as secondary outcomes.

2.1. Statistical analysis

All data were statistically analyzed using SPSS 16 for Mac OS X (SPSS Inc., Chicago, IL, USA). Mean \pm standard deviation (SD), median, and minimum and maximum values are used to describe the quantitative variables. Frequency and percentages are given for the nominal data. Normality assumption was checked by Shapiro–Wilk test and it was found that the data did not show normal distribution. In order to test the time-based changes in both BCVA and CRT, the Wilcoxon test was used. Comparisons between ischemic and nonischemic groups were performed by Mann–Whitney U test. Frequency and incidence data were compared using the chi-square test. $P < 0.05$ was considered to be statistically significant.

3. Results

A total of 30 eyes of 30 patients with ME secondary to BRVO were analyzed. The mean age of patients was 58.30 years (SD 9.91; min: 38, max: 85), and 30% of patients were male. Patient characteristics are shown in the Table.

The mean baseline visual acuity was 0.84 logMAR (SD 0.10; min: 0.30, max: 1.30). In our study group, there was a progressive improvement in visual acuity during the follow-up period. Moreover, this improvement was significant when compared to baseline visual acuity at all visits ($P < 0.001$). The mean logMAR visual acuity at the 6th month of follow-up was 0.41 (SD 0.06; min: 0.30, max: 1.00).

The mean BCVA of the ischemic BRVO group was 1.06 (SD 0.68; min: 0.30, max: 1.30) logMAR at baseline and 0.44 (SD 0.30; min: 0.30, max: 1.00) logMAR at the 6th month ($P < 0.05$). Mean BCVA of the nonischemic BRVO group was 0.77 (SD 0.53 min: 0.30, max: 1.30) logMAR at baseline and 0.41 (SD 0.36; min: 0.30, max: 1.00) logMAR at the 6th month ($P < 0.05$). Between groups, there was no significant difference in mean BCVA at any examination time point ($P > 0.05$) (Figure 1).

In our study group, 3 or more Snellen lines were gained by 37% of the patients. None of the patients lost ≤ 3

Table. Baseline characteristics of the study subgroups.

	Ischemic group (n = 7)	Nonischemic group (n = 23)	P-value
Male, n (%)	3 (42.8 %)	12 (52.1 %)	0.50
Age, mean	61.42 ± 5.65	60.73 ± 11.02	0.88
Baseline visual acuity, log MAR	1.06 ± 0.68	0.77 ± 0.53	0.33
Mean BCVA at month 6, log MAR	0.44 ± 0.30	0.41 ± 0.36	0.83
Mean CRT at baseline, µm	602.14 ± 250.85	616.43 ± 254.10	0.90
Mean CRT at month 6, µm	259.29 ± 109.33	254.04 ± 103.55	0.73

BCVA: Best-corrected visual acuity; CRT: central retinal thickness.

lines. At the 6th month, 3 of 7 eyes (43%) in the ischemic group and 8 of 23 eyes (35%) in the nonischemic group had visual improvement of ≤3 Snellen lines. There was not a statistically significant difference between groups regarding visual acuity changes in Snellen lines ($P > 0.05$). The changes in Snellen lines in both groups are illustrated in Figure 2.

Mean baseline macular thickness was 613.10 µm (SD 45.47; min: 275, max: 1390). In the study group, the final measured mean macular thickness was 255.27 µm (SD 18.80 µm; min: 216, max: 293). At all visits, there was a statistically significant decrease in macular thickness compared to baseline ($P < 0.001$).

In the ischemic BRVO group, CRT improved from 602.14 µm (SD 250.86; min: 393, max: 1110) at baseline to 259.29 µm (SD 109.33; min: 165, max: 470) at the final visit. In the nonischemic BRVO group, CRT improved from

616.43 µm (SD 254.10; min: 275, max: 1390) at baseline to 254.04 µm (SD 103.56; min: 142, max: 510) at the final visit. Each group showed a statistically significant reduction in CRT from baseline during all monthly visits ($P < 0.05$). During the follow-up, the mean CRT between the groups was not statistically significant ($P > 0.05$, Figure 3).

During the follow-up period, recurrence of ME occurred in 24 of 30 patients (80%), and 6 (20%) cases had a complete ME resolution after a single injection. The mean time interval between first injection and ME recurrence was 1.16 months (SD: 0.87). ME recurrence was detected 1 month after the first injection in 13 (43%) patients, 2 months after the first injection in 8 (27%) patients, and 3 months after the first injection in 2 (7%) patients. At the end of the follow-up period, 8 (27%) patients had a CRT greater than 250 µm in the final OCT scan.

The frequency of complete ME resolution at the 6th month was not significantly different between groups (73% [17 of 23] eyes in the nonischemic group versus 71% [5 of 7] eyes in the ischemic group, $P > 0.05$).

During the follow-up period, an average of 2.43 injections (SD 1.16; min: 1, max: 5) were administered.

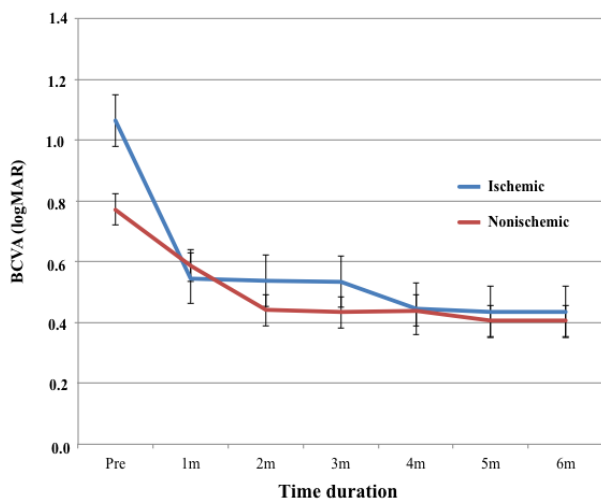


Figure 1. Mean baseline BCVA changes during follow-up in both groups. The difference between the groups was not statistically significant ($P > 0.05$). BCVA: Best-corrected visual acuity; X-axis, time (months); Y-axis, mean BCVA (logMAR).

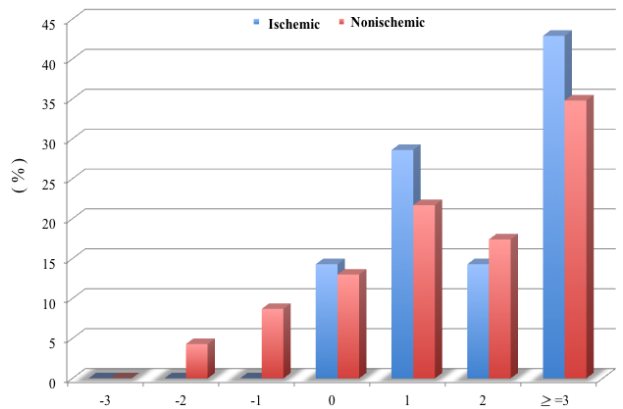


Figure 2. Visual acuity change in Snellen lines in both groups (chi-square test, $P > 0.05$).

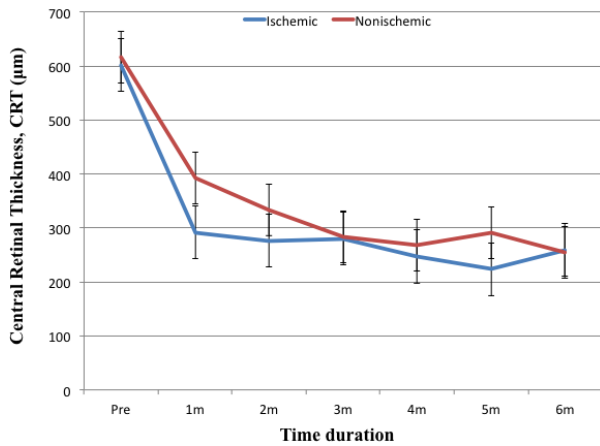


Figure 3. Central retinal thickness change during follow-up in both groups. The difference between groups was not statistically significant ($P > 0.05$). CRT, Central retinal thickness; X-axis, time (months); Y-axis, mean central retinal thickness (µm).

The number of injections over 6 months was 2.2 (SD 1.1; min: 1, max: 5) in the eyes with nonischemic BRVO and 3.1 (SD 1.2; min: 2, max: 5) in those with ischemic BRVO, respectively, showing insignificant difference between the two groups ($P > 0.05$). The frequency of cases in which only one injection was performed over the 6-month period was 26% (6 of 23 eyes) in the nonischemic group and 0% in the ischemic group. Most cases in both the ischemic and the nonischemic group had two injections (43% in ischemic and 48% in nonischemic group, respectively; Figure 4).

In our study, we did not observe any endophthalmitis, retinal detachment, or other complications related to the procedure. We also did not witness any ocular or systemic adverse events related to ranibizumab in the study group. During the follow-up, none of the patients developed any neovascular complications or needed peripheral laser photocoagulation.

4. Discussion

In this retrospective study, we investigated the efficacy of PRN ranibizumab injections from the start for the treatment of ME in cases of both ischemic and nonischemic BRVO. PRN treatment from the start yielded favorable results, both anatomically and functionally. There was a significant improvement in vision, resulting in a gain of 2 or more lines in 53% of the patients and of 3 or more lines in 36.6%. Anatomical results were also impressive, resulting in a substantial decrease in CRT measurements.

ME is a well-known complication related to BRVO, primarily causing a decrease in vision. VEGF has a role in the complex and intriguing pathophysiological mechanisms causing ME via the effects on blood-retinal barrier breakdown and vascular permeability (19). Several

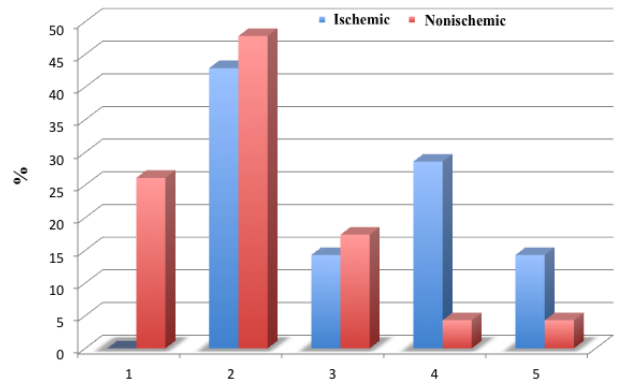


Figure 4. Frequency of injections during the follow-up period in both groups (chi-square test, $P < 0.05$).

clinical studies evaluated the role of anti-VEGF therapy among patients with retinal vascular diseases with ME and found a beneficial effect of this treatment on the progression of ME (6,25–30). A multicenter randomized study, BRAVO, evaluated the role of 6-month ranibizumab therapy in BRVO, which revealed a decrease in CRT and improvement in visual acuity compared to the control group (25). Despite these beneficial effects of anti-VEGF therapy on ME, anti-VEGF therapy has also important disadvantages regarding the short durability of the regimen and transient therapeutic effects requiring reinjections.

In the present study, the mean baseline logMAR visual acuity was 0.84 ± 0.10 and there was a significant increase in visual acuity after the first injection. This increase in visual acuity continued in the following months and there was a statistically significant improvement at all visits compared to the baseline visual acuity. At the 6th month of follow-up, mean logMAR visual acuity reached 0.41 ± 0.06 . In a previous study, Rouvas et al. (20) reported that baseline logMAR visual acuity improved from 0.74 ± 0.28 to 0.48 ± 0.3 . Similarly, Ahn et al. (31) reported an improvement from 0.61 ± 0.35 logMAR to 0.35 ± 0.30 logMAR. Although mean baseline visual acuity was lower in our study than in those two studies, visual acuities at the 6th month were similar in our study. Moreover, different from other studies, we did not apply grid laser rescue treatment in our study.

In our study, the proportion of patients who gained 3 or more lines at 6 months was lower than in the BRAVO study (37% vs. 61%, respectively) (25). In the BRAVO study, monthly injections were administered, the results of which were thought to reflect the optimal treatment results under ideal conditions. However, the reported results in daily practice were lower. In a previous study, Brynskov et al. (21) reported that 32% of patients gained 3 or more lines. In that study, the first 3 injections were routinely performed and later injections were scheduled according

to PRN injection criteria. Rouvas et al. (20) performed PRN injection from the beginning and reported that 39% of patients showed a gain of 3 or more lines. Although the percentage of patients gaining 3 or more lines in our study is similar to the results of these aforementioned studies, the risk of treatment delay should be kept in mind.

The rationale behind our study was mainly based on the hypothesis that we could gain a similar effect on visual acuity using fewer injections compared to previous studies that used a regular injection protocol or an as-needed approach. Similar to our study protocol, fewer injections were performed in 2 different studies that used bevacizumab with a mean number of 2.3 and 2.6 injections in 6 months (18,32). In line with those results, the injection frequency was 2.4 in our study with ranibizumab and we found similar improvement in visual acuity and CRT as in those studies. Although Rouvas et al. (20) found good anatomic and visual success in a prospective study with an OCT-guided as-needed treatment regimen using ranibizumab, they performed a mean of 6 injections during a 9-month follow-up. In light of those data, lower injection frequency was found to be associated with similar functional or anatomic benefit in our study.

Specifically, the BRAVO study investigated the efficacy of ranibizumab therapy in BRVO patients; however, that study did not address the issue of the ischemic or nonischemic nature of the retinal perfusion (25). In our analysis, we classified the study population into ischemic and nonischemic groups according to the retinal perfusion in FA. The clinical end point was similar between the groups in terms of mean change from baseline CRT and BCVA at the 6th month. Similarly, Puche et al. (33) did not find a difference between ischemic and nonischemic groups regarding the mean change from baseline CRT and BCVA. However, the ischemic group had a tendency to receive more injections compared to the nonischemic group, which did not reach statistical significance. In addition, eyes in the nonischemic group had a lower mean baseline logMAR BCVA compared to the ischemic group. As the visual acuity outcomes in BRVO were reported to be related to the initial visual acuity at presentation, the ischemic group in our analysis seemed to get more benefit from ranibizumab injections (34).

One of the important drawbacks regarding the design of such studies, including our study, is the initiation of

anti-VEGF therapy irrespective of the duration of patients' diagnosis. The exact history of the disease might not be obtained, mostly due to the socioeconomic status of the patient population, self-reporting issues, or variations in admissions to different healthcare services. Because the exact duration of the disease cannot be obtained in such a retrospective analysis, our study, like several previous studies, was mainly based on the clinical evaluation of the clinician (18,35). Moreover, the possibility of spontaneous resolution during the natural history of the disease should be considered, which might weaken the exact role of anti-VEGF therapy (16). In addition, different from most of the previous studies, we used a stricter follow-up protocol with regular monthly visits (18,21).

There are some limitations regarding our study. First, this study was a retrospective analysis of a single center and did not have a control group. Second, in addition to the low number of patients in the study groups, there was an imbalance regarding distribution of the patients between groups due to the incidence of ischemic BRVO in the real-life clinical setting. This might cause low statistical power. Therefore, further large-scale studies are needed in order to clarify the effect of PRN ranibizumab therapy in ischemic and nonischemic BRVO. Third, fundus FA was performed in the beginning of the study and was not repeated thereafter due to the possible changes in the retinal perfusion during follow-up. Finally, although a PRN from-the-start approach has a lower cost with a high safety profile, fewer injections might have a potential to cause treatment delay. Therefore, stricter follow-up should be considered in such a situation.

In summary, intravitreal ranibizumab injection based on PRN from the start was an effective and safe modality for the treatment of ME secondary to BRVO. Our clinical experience demonstrated that using an as-needed approach was associated with improvement in both BCVA and CRT with fewer ranibizumab injections. Moreover, we observed similar functional and anatomical improvement in both ischemic and nonischemic patients with similar injection rates. Despite an increasing body of evidence for the efficacy of ranibizumab treatment for ME secondary to BRVO as a PRN from-the-start strategy, an optimal treatment regimen has not been determined yet. Further studies are needed to evaluate the optimal treatment regimen for these patients.

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