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CLINICAL INVESTIGATION

Predictive factors for recurrence of macular edema after successful intravitreal bevacizumab therapy in branch retinal vein occlusion

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Abstract
Purpose Our aim was to investigate predictive factors associated with efficacy and recurrence after intravitreal bevacizumab (IVB) therapy for macular edema (ME) in patients with branch retinal vein occlusion (BRVO).
Methods Fifty-two eyes of 52 patients who underwent IVB as a primary treatment against ME associated with BRVO were included retrospectively. Based on the postoperative central retinal thickness (CRT), the patients were classified into two groups: an effective group in which the CRT decreased to ≤250 μm within postoperative 3 months and an ineffective group in which the CRT remained >250 μm throughout the first 3 months. The effective group was then divided into two subgroups: a recurrent group in which ME had once resolved but recurred afterward, and a nonrecurrent group in which the resolution of ME was maintained throughout the follow-up period without additional injections. Preoperative factors such as age, gender, estimated elapsed time from disease onset to IVB, visual acuity, and CRT were compared between groups.
Results There was no significant difference between effective ($n = 37$) and ineffective ($n = 15$) groups in all preoperative factors. Between recurrent ($n = 26$) and nonrecurrent ($n = 11$) groups, elapsed time was significantly different (29.7 ± 29.5 vs. 15.7 ± 8.9 weeks, respectively; $P = 0.036$), and there were no significant differences in the remaining factors.
Conclusions Early IVB treatment against BRVO may suppress ME recurrence.

Keywords Branch retinal vein occlusion · Macular edema · Bevacizumab · Recurrence

Introduction

Branch retinal vein occlusion (BRVO) is a common vascular retinal disorder [1]. Loss of vision due to BRVO is usually caused by macular edema (ME) [2]. Various treatments have been used, such as anti-vascular endothelial growth factor (VEGF) therapy [3–5], intravitreal administration of steroids [6, 7], laser treatment [8], and surgical procedures [9, 10]. Recently, anti-VEGF therapy has become widely used for treating ME associated with BRVO [3]. However, treatment success is often temporary or ineffective despite multiple intravitreal injections. To our knowledge, only a few studies deal with ME recurrence associated with BRVO after anti-VEGF therapy [11, 12], and the predictive factors are still unclear. The purpose of this study was to investigate predictive factors of IVB therapy for recurrent ME associated with BRVO.

Methods

All procedures conformed to the tenets of the Declaration of Helsinki, and the study design was approved by the Institutional Review Board of Kobe City Medical Center

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General Hospital. The review board waived the need for written informed consent because the study design consisted of a retrospective chart review. We retrospectively examined consecutive nonrandomized patients who underwent 1.25 mg of intravitreal injection of bevacizumab (IVB) from 2009 to 2013 as a primary treatment for ME associated with BRVO and who were followed monthly for at least 5 months. Eyes that had undergone pars plana vitrectomy prior to IVB for BRVO were excluded. Eyes with previous scatter photocoagulation (PC) were included, but those with previous grid-pattern PC were excluded. Best-corrected visual acuity (BCVA) was measured using the Landolt ring and converted to the logarithm of the minimal angle of resolution (logMAR). Fluorescein angiography was performed, and eyes with retinal nonperfusion over five disc areas were diagnosed as having ischemic BRVO. Optical coherence tomography (OCT) was performed to measure central retinal thickness (CRT) using 3D OCT-1000 (Topcon, Tokyo, Japan) or Spectralis Heidelberg retina angiograph plus OCT (Heidelberg Engineering, Dossenheim, Germany); 3D OCT-1000 images were obtained using TrueMap^{TM} (Version 2.12, Topcon, Japan) software. Spectralis OCT images were obtained using Spectralis Family Acquisition Module (Version 4.0.2.0, Heidelberg, Germany) and Heidelberg Eye Explorer (Version 1.6.1.0, Heidelberg, Germany) software. Horizontal and vertical scans of the macula were recorded for diseased eyes. Measurements were performed under pupillary dilation. The eye-tracking system of the device was used to assure that scans were performed in the correct position.

Based on postoperative CRT, patients were classified into two groups: an effective group if CRT decreased to $\leq$250 μm within postoperative 3 months, and an ineffective group if CRT remained >250 μm throughout the first 3 months (Fig. 1). The effective group was then divided into two subgroups: a recurrent group if ME was once resolved to $\leq$250 μm but recurred again, and a nonrecurrent group if ME resolution was maintained throughout the follow-up period without additional injections (Fig. 1). We examined any differences between groups in age, gender, estimated elapsed time from disease onset to IVB, baseline BCVA, baseline CRT, and follow-up period after IVB therapy.

SPSS statistics 22 for Windows (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Welch's t test was used to compare continuous variables between the groups. Fisher's exact test was applied for categorical variables. The level of significance was set at $P < 0.05$ for all statistical tests. Continuous data are expressed as mean ± standard deviation (SD).

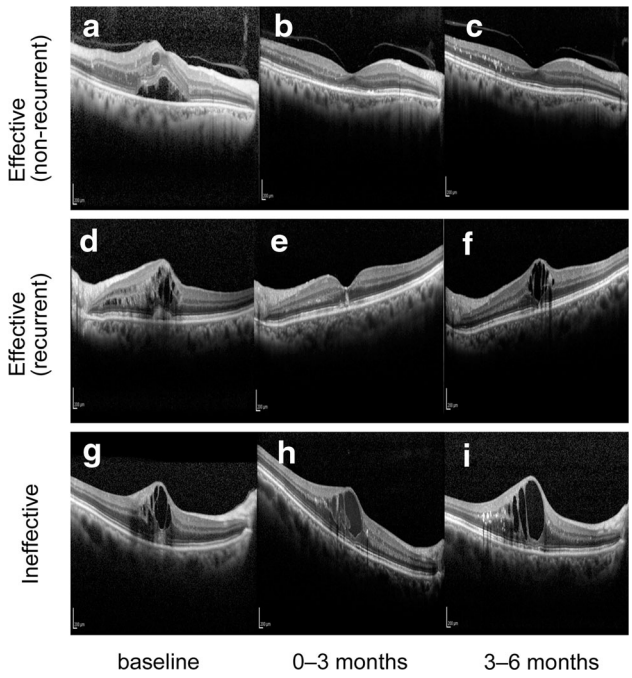

Fig. 1 Optical coherence tomography of representative cases in each group. Effective (nonrecurrent) (**a**–**c**), effective (recurrent) (**d**–**f**), and ineffective (**g**–**i**) groups at baseline (**a**, **d**, **g**), 0–3 months after IVB (**b**, **e**, **h**), and 3–6 months after IVB (**c**, **f**, **i**). *IVB* intravitreal bevacizumab injection

Results

In total, 52 eyes of 52 Japanese patients were evaluated. There were 27 men and 25 women, and average patient age was 68.3 ± 11.4 years. The major branch of the retinal vein was occluded in 28 eyes and the macula branch in 24. Fluorescein angiography showed that 16 eyes were ischemic and 31 were nonischemic; angiography was not performed in five eyes. Five eyes had undergone scatter PC prior to initial IVB. The effective group consisted of 37 eyes (71 %) and the ineffective group of 15 (29 %). Within the effective group, the nonrecurrent subgroup consisted of 11 eyes (30 %) and the recurrent subgroup of 26 (70 %). The first recurrence of ME in the recurrent group occurred within 5 months after primary IVB in all cases. There was no significant difference between effective and ineffective groups in age, gender, occlusion site, retinal ischemia, history of scatter PC prior to IVB, estimated elapsed time from disease onset to IVB, baseline BCVA, baseline CRT, and follow-up period (Table 1). However, elapsed time for the nonrecurrent group was significantly shorter than for the recurrent group (15.7 ± 8.9 vs. 29.7 ± 29.5 weeks, respectively; $P = 0.036$); there was no significant difference in other factors (Table 2). A scatter diagram of the

Table 1 Characteristics of effective and ineffective groups

	Effective	Ineffective	*P* value
Number of eyes	37	15	
Gender (male/female)	19/18	8/7	0.86
Age (years)	68.7 ± 11.6	67.2 ± 11.4	0.68
Occlusion site (major branch/macular branch)	21/16	7/8	0.51
Ischemia (ischemic/nonischemic)	13/21	3/10	0.27
History of PC (%)	4 (10.8 %)	1 (6.7 %)	0.55
Elapsed time (weeks)	25.5 ± 25.9	26.4 ± 25.8	0.91
Baseline logMAR	0.50 ± 0.29	0.45 ± 0.23	0.50
Baseline CRT (μm)	507 ± 145	564 ± 149	0.22
Follow-up (weeks)	72.3 ± 52.7	100.1 ± 59.9	0.13

PC photocoagulation, *logMAR* logarithm of the minimal angle of resolution, *CRT* central retinal thickness

Table 2 Characteristics of nonrecurrent and recurrent groups

	Effective		*P* value
	Non-recurrent	Recurrent	
Number of eyes	11	26	
Gender (male/female)	5/6	14/12	0.46
Age (years)	66.0 ± 10.6	69.9 ± 12.0	0.37
Occlusion site (major branch/macular branch)	6/5	15/11	0.71
Ischemia (ischemic/nonischemic)	3/7	10/14	0.41
History of PC (%)	0 (0 %)	4 (15.4 %)	0.23
Elapsed time (weeks)	15.7 ± 8.9	29.7 ± 29.5	0.036
Baseline logMAR	0.47 ± 0.28	0.51 ± 0.30	0.71
Baseline CRT (μm)	467 ± 133	524 ± 148	0.27
Follow-up (weeks)	64.7 ± 58.0	75.5 ± 51.1	0.60

PC photocoagulation, *logMAR* logarithm of the minimal angle of resolution, *CRT* central retinal thickness

elapsed time in each group is shown in Fig. 2. There were no vision-threatening complications in this study.

Discussion

Several studies suggest macular ischemia [13], baseline BCVA [4], age [4], duration from onset to primary IVB [4, 14], baseline CRT [4], and vitreomacular adhesion [15] as predictive factors for BRVO prognosis. These varying data may have resulted from studies with different designs, such as the number of eyes (38–205), IVB dose (1.25–2.0 mg), follow-up interval (4–12 weeks), final follow-up time (3–12 months), definition of recurrence (CRT >250 μm or >30 % after primary IVB), patient history/risk factors of BRVO (hypertension, hyperlipidemia, diabetes mellitus, thrombophilia, hypercoagulation, systemic and inflammatory diseases, medications, and ocular conditions) [4, 16–18], and exclusion criteria. In the study we report here, we found no significant differences in age, gender, estimated elapsed time from disease onset to IVB, preoperative visual acuity, and preoperative CRT between effective and ineffective groups. However, within the effective group, elapsed time in the nonrecurrent group was significantly shorter than in the recurrent group, suggesting that duration from symptom onset to initial IVB could affect the ME recurrence rate but not the efficacy rate after single IVB injection. To our knowledge, there are only a few studies dealing with ME recurrence associated with BRVO after anti-VEGF therapy. Yasuda et al. report that in 62 IVB-effective eyes with BRVO, 21 (34 %) showed no ME recurrence [12]. This rate was consistent with our results showing that within the effective group, 11 of 37 eyes (30 %) showed no recurrence. Those authors also report that all seven eyes with "rebound" ME had undergone initial IVB treatment within 8 weeks from symptom onset, suggesting that the rebound was more likely to occur when IVB therapy was initiated at a relatively early stage of ME, before edema had reached the maximum degree [12]. They defined ME rebound when the ratio of foveal thickness and recurrence/foveal thickness at baseline became ≥110 % after an initial decrease of foveal thickness [12]. This definition of rebound is quite different from our definition of recurrence; therefore, there is no discrepancy

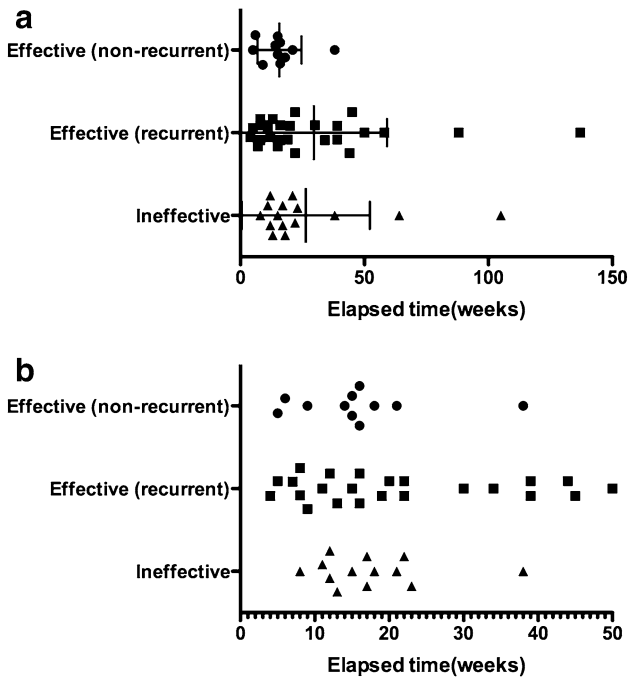

Fig. 2 Scatter diagram showing elapsed time of each patient. **a** Distribution of elapsed times overall. *Error bars* standard deviation. **b** Enlargement of the region of short elapsed time (≤50 weeks)

between their report and our finding that recurrence also occurred when the initial IVB was undergone after 8 weeks from symptom onset (Fig. 2). Hanada et al. report that, in a total of 95 IVB treatment sessions conducted on 37 eyes of 37 patients with BRVO, 25 injections were given, with a follow-up period of ≥6 months without additional treatment [11]. In their study, the probability of retreatment with IVB was ∼70 % after each individual injection, regardless of the number of injections. However, predictive factors for retreatment were not described [11]. Our study showed that early IVB treatment may suppress ME recurrence associated with BRVO. Although it is possible that cases with spontaneous ME resolution may have been masked by early IVB treatment, it is unlikely to be the sole reason for the shorter elapsed time in the nonrecurrent group, because the elapsed times between the effective and ineffective groups were not significantly different. The mechanism of how early IVB treatment suppresses ME recurrence is unclear; however, a previous study reports that anti-VEGF therapy for retinal vein occlusion reduced the occurrence of retinal nonperfusion and could eliminate a positive feedback loop in which retinal ischemia results in high levels of VEGF that promote worsening of retinal ischemia [19]. It is suggested that early anti-VEGF therapy can decrease the level of VEGF in the acute phase of the disease and interrupt the positive feedback loop of VEGF, suppressing ME recurrence. It is also suggested that PC downregulates VEGF expression in the ischemic retina [20, 21]. In eyes previously treated with PC, VEGF levels might not be high but continue to be expressed over a considerable period; or VEGF might not play a major role in prolonged ME. It is possible that ME is more likely to recur after single IVB in these eyes. Indeed, four of 26 eyes in the recurrent group but none of 11 eyes in the nonrecurrent group had undergone scatter PC prior to IVB (Table 2). However, the number of eyes previously treated with PC was too small to evaluate its role in ME recurrence.

An intravitreal anti-VEGF injection has a low probability of vision-threatening complications. It is reported that rhegmatogenous retinal detachment (RD) was found in 0.013–0.02 % and endophthalmitis in 0.02–0.095 % of eyes after anti-VEGF injections [22–28]. Although the complication rate after a single injection was very low, repeated injections could lead to an increase in the risk of complications, such as RD and endophthalmitis.

The main limitations of this study were the retrospective design, the small number of patients, and short follow-up period. Also, the nonperfusion area must be evaluated, because it is related with VEGF and the prognosis of visual acuity [29]. To investigate predictive factors for BRVO prognosis more thoroughly in the future, a randomized prospective study, including an anatomical and physiological analysis, is recommended.

In conclusion, early IVB treatment against BRVO may suppress ME recurrence and reduce the number of IVB injections, minimizing both the risk of vision-threatening complications and the economic burden to the patient.

Conflicts of interest R. Yamada, None; A. Nishida, None; M. Shimozono, None; T. Kameda, None; N. Miyamoto, None; M. Mandai, None; Y. Kurimoto, None.

References

1. Jaulim A, Ahmed B, Khanam T, Chatziralli IP. Branch retinal vein occlusion: epidemiology, pathogenesis, risk factors, clinical features, diagnosis, and complications. An update of the literature. Retina. 2013;33:901–10.
2. Recupero SM, Perdicchi A, Scuderi GL, Amodeo S, Medori EM, Leonardi A. Visual acuity in central and branch vein retinal occlusion in the presence of macular edema: 1 year of follow-up. Ann Ophthalmol (Skokie). 2006;38:107–10.
3. Heier JS, Campochiaro PA, Yau L, Li Z, Saroj N, Rubio RG, et al. Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. Ophthalmology. 2012;119:802–9.
4. Jaissle GB, Szurman P, Feltgen N, Spitzer B, Pielen A, Rehak M, et al. Predictive factors for functional improvement after intravitreal bevacizumab therapy for macular edema due to branch retinal vein occlusion. Graefes Arch Clin Exp Ophthalmol. 2011;249:183–92.
5. Prager F, Michels S, Kriechbaum K, Georgopoulos M, Funk M, Geitzenauer W, et al. Intravitreal bevacizumab (avastin) for macular oedema secondary to retinal vein occlusion: 12-month

results of a prospective clinical trial. Br J Ophthalmol. 2009;93:452–6.
6. Haller JA, Bandello F, Belfort R Jr, Blumenkranz MS, Gillies M, Heier J, et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. Ophthalmology. 2011;118:2453–60.
7. Scott IU, Vanveldhuisen PC, Oden NL, Ip MS, Domalpally A, Doft BH, et al. Baseline characteristics and response to treatment of participants with hemiretinal compared with branch retinal or central retinal vein occlusion in the standard care vs corticosteroid for retinal vein occlusion (SCORE) study: SCORE study report 14. Arch Ophthalmol. 2012;130:1517–24.
8. The Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. Am J Ophthalmol. 1984;98:271–82.
9. Charbonnel J, Glacet-Bernard A, Korobelnik JF, Nyouma-Moune E, Pournaras CJ, Colin J, et al. Management of branch retinal vein occlusion with vitrectomy and arteriovenous adventitial sheathotomy, the possible role of surgical posterior vitreous detachment. Graefes Arch Clin Exp Ophthalmol. 2004;242:223–8.
10. Tachi N, Hashimoto Y, Ogino N. Vitrectomy for macular edema combined with retinal vein occlusion. Doc Ophthalmol. 1999;97:465–9.
11. Hanada N, Iijima H, Sakurada Y, Imasawa M. Recurrence of macular edema associated with branch retinal vein occlusion after intravitreal bevacizumab. Jpn J Ophthalmol. 2012;56:165–74.
12. Yasuda S, Kondo M, Kachi S, Ito Y, Terui T, Ueno S, et al. Rebound of macular edema after intravitreal bevacizumab therapy in eyes with macular edema secondary to branch retinal vein occlusion. Retina. 2011;31:1075–82.
13. Chung EJ, Hong YT, Lee SC, Kwon OW, Koh HJ. Prognostic factors for visual outcome after intravitreal bevacizumab for macular edema due to branch retinal vein occlusion. Graefes Arch Clin Exp Ophthalmol. 2008;246:1241–7.
14. Yoon YH, Kim HK, Yoon HS, Kang SW, Kim JG, Park KH, et al. Improved visual outcome with early treatment in macular edema secondary to retinal vein occlusions: 6-month results of a Korean RVO study. Jpn J Ophthalmol. 2014;58:146–54.
15. Terao R, Yuda K, Kure K, Inoue T, Ohtsu H, Yanagi Y. Effect of vitreomacular adhesion on antivascular endothelial growth factor therapy for macular edema secondary to branch retinal vein occlusion. Jpn J Ophthalmol. 2014;58:139–45.
16. Klein R, Moss SE, Meuer SM, Klein BE. The 15-year cumulative incidence of retinal vein occlusion: the beaver dam eye study. Arch Ophthalmol. 2008;126:513–8.
17. Lim LL, Cheung N, Wang JJ, Islam FM, Mitchell P, Saw SM, et al. Prevalence and risk factors of retinal vein occlusion in an Asian population. Br J Ophthalmol. 2008;92:1316–9.
18. Rehak J, Rehak M. Branch retinal vein occlusion: pathogenesis, visual prognosis, and treatment modalities. Curr Eye Res. 2008;33:111–31.
19. Campochiaro PA, Bhisitkul RB, Shapiro H, Rubio RG. Vascular endothelial growth factor promotes progressive retinal nonperfusion in patients with retinal vein occlusion. Ophthalmology. 2013;120:795–802.
20. Manaviat MR, Rashidi M, Afkhami-Ardekani M, Mohiti-Ardekani J, Bandala-Sanchez M. Effect of pan retinal photocoagulation on the serum levels of vascular endothelial growth factor in diabetic patients. Int Ophthalmol. 2011;31:271–5.
21. Mohamed TA. Mohamed Sel D. Effect of pan-retinal laser photocoagulation on plasma VEGF, endothelin-1 and nitric oxide in PDR. International. J ophthalmol. 2010;3:19–22.
22. Inoue M, Kobayakawa S, Sotozono C, Komori H, Tanaka K, Suda Y, et al. Evaluation of the incidence of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor. Ophthalmologica. 2011;226:145–50.
23. Lyall DA, Tey A, Foot B, Roxburgh ST, Virdi M, Robertson C, et al. Post-intravitreal anti-VEGF endophthalmitis in the United Kingdom: incidence, features, risk factors, and outcomes. Eye (Lond). 2012;26:1517–26.
24. McCannel CA. Meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents: causative organisms and possible prevention strategies. Retina. 2011;31:654–61.
25. Meyer CH, Michels S, Rodrigues EB, Hager A, Mennel S, Schmidt JC, et al. Incidence of rhegmatogenous retinal detachments after intravitreal antivascular endothelial factor injections. Acta Ophthalmol. 2011;89:70–5.
26. Moshfeghi AA, Rosenfeld PJ, Flynn HW Jr, Schwartz SG, Davis JL, Murray TG, et al. Endophthalmitis after intravitreal vascular endothelial growth factor antagonists: a six-year experience at a university referral center. Retina. 2011;31:662–8.
27. Shah CP, Garg SJ, Vander JF, Brown GC, Kaiser RS, Haller JA. Outcomes and risk factors associated with endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. Ophthalmology. 2011;118:2028–34.
28. Wu L, Martinez-Castellanos MA, Quiroz-Mercado H, Arevalo JF, Berrocal MH, Farah ME, et al. Twelve-month safety of intravitreal injections of bevacizumab (avastin): results of the Pan-American Collaborative Retina Study Group (PACORES). Graefes Arch Clin Exp Ophthalmol. 2008;246:81–7.
29. Sophie R, Hafiz G, Scott AW, Zimmer-Galler I, Nguyen QD, Ying H, et al. Long-term outcomes in ranibizumab-treated patients with retinal vein occlusion; the role of progression of retinal nonperfusion. Am J Ophthalmol. 2013;156:693–705.