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CLINICAL INVESTIGATION

Effect of vitreomacular adhesion on antivascular endothelial growth factor therapy for macular edema secondary to branch retinal vein occlusion

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Abstract
Purpose To investigate the association between vitreomacular adhesion (VMA) and the visual and anatomic outcomes of antivascular endothelial growth factor therapy for macular edema due to branch retinal vein occlusion (BRVO).
Methods This study included 107 eyes of 107 patients with BRVO who underwent intravitreal injection of 1.25 mg bevacizumab. The presence of VMA was determined with spectral-domain optical coherence tomography (SD-OCT). All eyes underwent best-corrected visual acuity (BCVA) and central retinal thickness (CRT) measurements using SD-OCT immediately before the injection and at 3, 6, 9, and 12 months after the injection. The main outcome measures were changes in BCVA and CRT from baseline.
Results The VMA(+) and VMA(−) groups consisted of 47 and 60 eyes, respectively, and patients' age differed significantly between the groups ($P < 0.001$). In both groups, BCVA and CRT improved after the injection. The VMA(+) group showed better improvement in BCVA than did the VMA(−) group ($P = 0.0150$), and the presence of VMA was associated with a greater decrease in CRT after adjusting for age ($P = 0.0019$).
Conclusions Presence of VMA may be associated with superior visual and anatomic outcome for intravitreal bevacizumab in the treatment of macular edema due to BRVO.

Keywords Branch retinal vein occlusion · Macular edema · Bevacizumab · Antivascular endothelial growth factor therapy · Vitreomacular adhesion

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Introduction

Branch retinal vein occlusion (BRVO) is the second most common vascular disorder of the retina after diabetic retinopathy [1]. Its prevalence has been shown to vary from 0.7 to 1.6 % [2, 3]. Secondary macular edema is one of the main reasons for loss of visual acuity in BRVO [4, 5]. Macular grid laser photocoagulation used to be the only established treatment modality for macular edema due to BRVO. However, the visual acuity improvement was limited, leading to the search for other new therapeutic options [6–8]. Various studies have demonstrated the effectiveness of antivascular endothelial growth factor (anti-VEGF) therapy on macular edema secondary to BRVO [9–11]. Among the anti-VEGF agents, offlabel use of bevacizumab, a full-length humanized monoclonal antibody, has long attracted attention and has been reported to be associated with promising short-term anatomic and functional improvement. A recently published randomized control study, the double-masked, multicenter, randomized, phase III, parallel group ranibizumab for the treatment of macular edema after branch retinal vein occlusion (BRAVO) study, supported the role of anti-VEGF therapy for macular edema due to BRVO [12–15].

Recent studies suggested a role of vitreomacular adhesion (VMA) in various VEGF-mediated retinal diseases, such as diabetic maculopathy, age-related macular

degeneration, and BRVO. Interestingly, a recent clinical study described the association between VMA and visual outcome in intravitreal anti-VEGF treatment for exudative age-related macular degeneration (AMD) and suggested that VMA is a morphologic characteristic of resistance to anti-VEGF therapy [16]. Several reports have identified pretreatment factors associated with improvement in the visual and anatomic outcomes [17, 18]. An association between VMA and the visual and anatomic outcomes after anti-VEGF therapy, however, has not been examined in macular edema secondary to BRVO. The purpose of the present study was to investigate the association between VMA and the visual and anatomic outcomes of anti-VEGF therapy for macular edema due to BRVO.

Materials and methods

This study was a retrospective observational case series conducted at the University of Tokyo School of Medicine. Institutional review board approval was obtained from the University of Tokyo. The database of consecutive patients with macular edema secondary to BRVO who underwent intravitreal anti-VEGF injections at the University of Tokyo Hospital from January 2007 to June 2010 was retrospectively reviewed. Inclusion criteria were the administration of intravitreal bevacizumab injections within 3 months of the onset of a venous occlusive event and a follow-up period of at least 12 months. Exclusion criteria included the presence of other ocular abnormalities that had the potential to affect visual acuity adversely and/or previous treatment for BRVO.

Each patient received an intravitreal injection of 1.25 mg bevacizumab, and further injections were given when a recurrence of edema occurred with a concomitant decrease in visual acuity or if the absorption of fluid was not complete 1 month after the injection. Ophthalmic examination, including best-corrected visual acuity (BCVA) and spectral domain optical coherence tomography (SD-OCT; 3D-OCT 1000; Topcon Corporation, Tokyo, Japan), were performed at baseline and at each visit, which was scheduled at an interval of 4–6 weeks. BCVA was measured by a standard Japanese decimal visual acuity chart, and the values were converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis. The presence of VMA was defined as attachment of the posterior hyaloid line, depicted as a thin, continuous reflective layer above the inner limiting membrane, to the inner retinal surface of the macula detected on SD-OCT (Fig. 1), as described in previous studies [16, 19–21]. If the posterior hyaloid line could not be detected on any section of the entire scan set, the eye was graded as VMA(−). Cases with a hyperreflective area

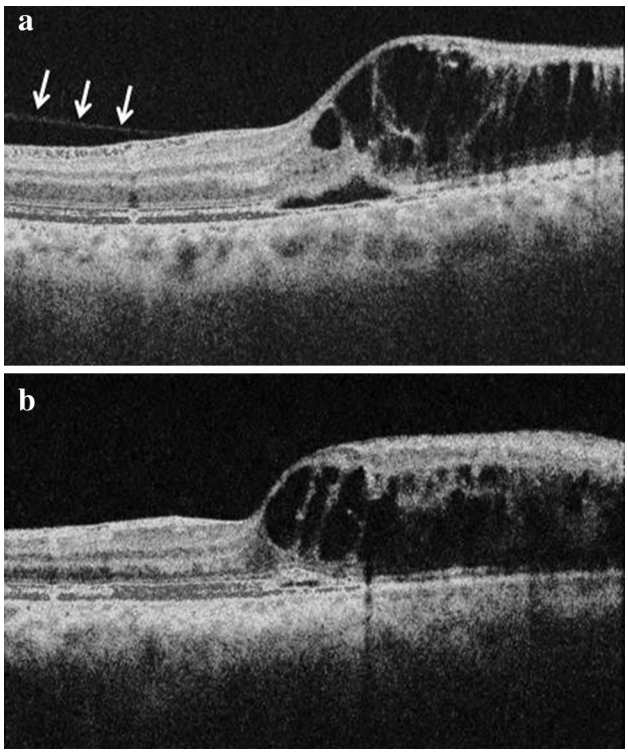

Fig. 1 Optical coherence tomographic (OCT) images with and without vitreomacular adhesion (VMA). **a** Macular edema secondary to branch retinal vein occlusion (BRVO) detected with VMA. The *white arrows* indicate the posterior vitreous cortex. **b** Macular edema secondary to BRVO without VMA. Posterior vitreous detachment was clearly observed in this eye

on the inner surface of the retina, but without VMA, were classified as VMA(−). Cases were judged by 2 independent investigators in a masked fashion. In most cases, the investigators made the same judgment. For the 16 cases in which the judgment differed, we used the judgment determined by the senior investigator. In addition, the central retinal thickness (CRT) was measured with SD-OCT using a built-in software system. The length from the retinal pigment epithelium to the internal limiting lamina was defined as the CRT.

The main outcome measures were changes in BCVA and CRT. Data from the baseline and the follow-up examinations at 3, 6, 9, and 12 months after the injection were used for the analysis.

The results were expressed as mean ± SD. The *t* test was used to compare the patients' baseline age, total number of injections, and baseline BCVA and the CRT of the 2 groups. The Chi square test was used to investigate the differences in sex between the 2 groups. Analysis of covariance (ANCOVA) was used to investigate the differences in the BCVA and CRT of the 2 groups. All statistical analyses were performed using Dr. SPSS II for Windows software (SPSS, Tokyo, Japan). Confounding

factors that produced significant differences between the groups were analyzed as covariate factors in ANCOVA.

We also investigated the pretreatment factors associated with the changes in BCVA and CRT at month 12. Patients' age, VMA, duration of macular edema, and total number of injections were included as the independent variables for multiple regression analysis.

Results

From January 2007 to June 2010, intravitreal bevacizumab therapy was performed in 140 eyes of 139 patients with BRVO. Among those eyes, 20 eyes of 19 patients were lost to follow-up within the first 12 months. Thirteen eyes had low reflectivity strength on OCT imaging before the treatment, which precluded reliable assessment of the OCT image (Q factor <70). Thus, 107 eyes of 107 patients aged between 39 and 87 years (mean age 64.0 years) were selected for analysis.

The VMA(+) group comprised 47 eyes, and the VMA(−) group, 60 eyes. As expected, older age was associated with a decreasing prevalence of VMA (odds ratio 0.897/years). The baseline patient characteristics are shown in Table 1. The mean age was 58.6 years in the VMA(+) group and 68.1 years in the VMA(−) group ($P < 0.001$, t test). The baseline BCVA was 0.48 ± 0.38 logMAR in the VMA(+) group and 0.46 ± 0.29 logMAR in the VMA(−) group, with no statistical difference between the groups ($P = 0.721$, t test). The baseline CRT was 547 ± 196 μm in the VMA(+) group and 530 ± 193 μm in the VMA(−) group, with no statistical difference between the groups ($P = 0.670$, t test). On average, patients received 2.17 injections over 12 months in the VMA(+) group and 2.37 injections in the VMA(−) group ($P = 0.451$, t test).

Table 1 Baseline patient characteristics

	VMA(+) ($n = 47$)	VMA(−) ($n = 60$)	P value
Age ± SD (years)	58.6 ± 9.55	68.1 ± 9.05	<0.001[a]
Sex (M/F)	20/27	21/39	0.430[b]
Ischemic/nonischemic	13/34	20/40	0.887[b]
Baseline BCVA ± SD, logMAR	0.48 ± 0.38	0.46 ± 0.29	0.721[a]
Baseline CRT ± SD, μm	547 ± 196	530 ± 193	0.670[a]
Total number of injections ± SD	2.17 ± 1.32	2.37 ± 1.34	0.451[a]

VMA vitreomacular adhesion, *BCVA* best-corrected visual acuity, *logMAR* logarithm of the minimum angle of resolution, *CRT* central retinal thickness, *SD* standard deviation

[a] t test, [b] Chi square test

The BCVA at 3, 6, 9, and 12 months were 0.20 ± 0.28, 0.11 ± 0.20, 0.10 ± 0.19, and 0.086 ± 0.18 logMAR in the VMA(+) group and 0.21 ± 0.21, 0.18 ± 0.24, 0.20 ± 0.24, and 0.21 ± 0.24 logMAR in the VMA(−) group, respectively. The mean changes in BCVA from baseline after the treatment are shown in Fig. 2. The mean BCVA significantly improved in both groups [VMA(+) group: $P < 0.001$ and VMA(−) group: $P < 0.001$; repeated-measures ANOVA). After adjusting for age, the mean BCVA was significantly lower over time in the VMA(−) group than in the VMA(+) group ($P = 0.0150$, repeated measures ANCOVA with age as the covariate).

The CRT at 3, 6, 9, and 12 months were (in μm) 237 ± 128, 203 ± 97, 210 ± 132, and 195 ± 111 in the VMA(+) group and 261 ± 159, 266 ± 148, 298 ± 167, and 272 ± 167 in the VMA(−) group, respectively. The mean CRT significantly decreased in both groups [VMA(+) group: $P < 0.001$ and VMA(−) group: $P < 0.001$; repeated-measures ANOVA; Fig. 3]. After adjusting for age, the mean CRT was significantly thinner over time in the VMA(+) group than in the VMA(−) group. ($P = 0.0019$, repeated-measures ANCOVA with age as the covariate).

We also investigated the changes in BCVA and CRT at each time point. In both groups, the BCVA and CRT improved at month 3 and were maintained at months 6, 9, and 12. At month 3, the BCVA of the 2 groups did not differ significantly ($P = 0.076$, ANCOVA with age as the covariate). At 6, 9, and 12 months, improvement in BCVA was maintained in both groups; however, the change in BCVA was better in the VMA(+) group than in the VMA(−) group ($P = 0.0096$, 0.0105, and 0.0116, respectively; ANCOVA with age as the covariate). Similarly, at months 3, 6, 9 and 12, the CRT was significantly thinner in

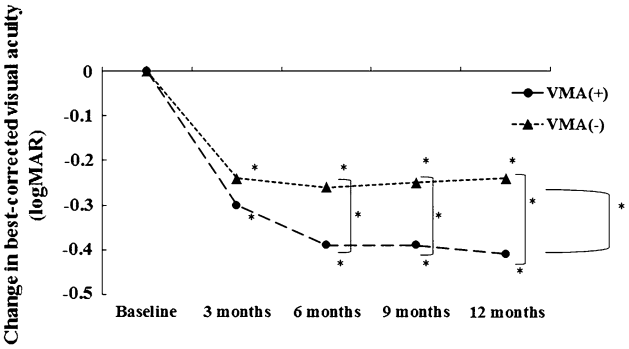

Fig. 2 Mean change in best-corrected visual acuity (BCVA) after antivascular endothelial growth factor therapy. The mean BCVA significantly improved in both groups ($P < 0.001$ and $P < 0.001$). The mean BCVA became significantly lower over time in the VMA(−) group than in the VMA(+) group ($P = 0.0150$). At 6, 9, and 12 months, the mean change in BCVA was better in the VMA(+) group than in the VMA(−) group ($P = 0.0096$, 0.0105, and 0.0116, respectively) (*$P < 0.05$)

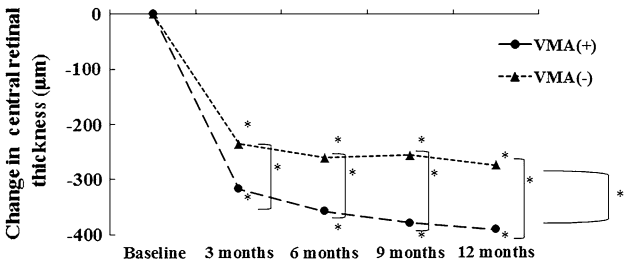

Fig. 3 Mean change in central retinal thickness (CRT) after antivascular endothelial growth factor therapy. The mean CRT significantly improved in both groups ($P < 0.001$ and $P < 0.001$). The mean CRT became significantly lower over time in the VMA(−) group than in the VMA(+) group ($P = 0.0019$). At 3, 6, 9, and 12 months, the CRT was significantly thinner in the VMA(+) group than in the VMA(−) group ($P = 0.0129$, 0.0012, 0.0027, and 0.0062, respectively) (*$P < 0.05$)

the VMA(+) group than in the VMA(−) group ($P = 0.0129$, 0.0012, 0.0027, and 0.0062, respectively; ANCOVA with age as the covariate).

Four eyes in the VMA(+) group developed posterior vitreous detachment (PVD) during the 12 months. One of those eyes was from a 62-year-old female patient. PVD in this eye had formed by 2 months after the first injection. Immediately before and after the PVD formation, the BCVA were both 0.70 logMAR units, and the CRT were 541 and 199 μm, respectively. The second eye was from a 59-year-old female patient, and the PVD had developed by 6 months after the initial treatment. The BCVA immediately before and after the PVD formation were both 0.70 logMAR units, and the CRT were 123 and 196 μm, respectively. The third eye was from a 77-year-old female patient, and we confirmed development of PVD at 7 months after the first injection. The BCVA immediately before and after the PVD formation were both 0.40 logMAR units, and the CRT were 500 and 200 μm, respectively. The fourth eye was from a 59-year-old female patient. The BCVA immediately before and after the PVD formation were both 0.30 logMAR units, and the CRT were 139 and 140 μm, respectively.

Lastly, the pretreatment factors were investigated for their possible association with the changes in BCVA and CRT at month 12 (Tables 2, 3). In these analyses, only the presence of VMA was positively related with change in BCVA ($P = 0.0105$); it was negatively related with change in CRT ($P = 0.0052$).

Table 2 Factors associated with changes in BCVA at 12 months

	Independent variables				
	Age (years)	VMA	Duration of macular edema	Total number of injections	Ischemic
Standardized partial Regression coefficient (*P*)	0.0800 (0.519)	0.322 (0.0105)	−0.144 (0.233)	0.0260 (0.817)	0.1048 (0.368)

VMA vitreomacular adhesion, *BCVA* best-corrected visual acuity

Table 3 Factors associated with changes in CRT at 12 months

	Independent variables				
	Age (years)	VMA	Duration of macular edema	Total number of injections	Ischemic
Standardized partial Regression coefficient (*P*)	−0.221 (0.0952)	−0.371 (0.0052)	−0.0233 (0.859)	0.0300 (0.799)	−0.139 (0.253)

VMA vitreomacular adhesion, *CRT* central retinal thickness

Discussion

Anti-VEGF therapy is now an established treatment for macular edema due to BRVO [9–11]. According to previous studies that investigated the predictive factors for visual improvement with intravitreal bevacizumab therapy for macular edema due to BRVO, younger patient age, shorter duration of BRVO, and worse baseline BCVA have been found to correlate with greater improvement in visual acuity [17]. All patients in the current study received intravitreal bevacizumab injection within 3 months of the onset of BRVO. Some investigators recommend intravitreal bevacizumab injection for cases in which macular edema has persisted for at least for 3 months. But another report suggested that shorter duration of macular edema before the treatment resulted in a greater increase in visual improvement and that treatment within less than 3 months resulted in a better visual outcome [17]. In addition, better pretreatment visual acuity was associated with better posttreatment visual acuity [18]. One study demonstrated that eyes with ischemic macular edema had worse visual acuity after treatment [17]. Although these analyses demonstrated the pretreatment factors associated with visual improvement, as far as we are aware and based on a Medline search, the present study is the first to evaluate the effect of VMA on anti-VEGF therapy for macular edema secondary to BRVO.

The present study has demonstrated that the presence of VMA is associated with better improvement in visual acuity and greater reduction of CRT with anti-VEGF therapy for macular edema secondary to BRVO. These results indicate that eyes with VMA are more responsive to anti-VEGF therapy than are eyes without VMA. A recent

report [16] suggested a negative association between VMA and visual outcome in the treatment of exudative AMD with anti-VEGF. In that study, the visual prognosis after anti-VEGF treatment for exudative AMD eyes was worse in eyes with VMA. Thus, the results of the current study contradict the findings for exudative AMD, and the finding that the presence of VMA was significantly associated with good anatomic and visual outcome among our group of subjects was unexpected. The discrepancies between the previous study and the current results may be reconciled by considering the different effects of VMA on AMD and BRVO, which are summarized as follows.

First, it is possible that the extent of macular edema due to BRVO is less affected by VMA than is exudative change in AMD. Macular edema in BRVO has an acute onset, whereas the exudative change in wet AMD is chronic. According to previous studies, hyaloid adhesion to the macula is likely to be present in eyes with exudative AMD [20–23]. Posterior vitreous detachment may be protective against exudative AMD [17, 24]. Several investigators assume that the presence of the posterior vitreous cortex attached to the macula may cause hypoxia and trap pro-angiogenic cytokines such as VEGF within the macula, resulting in CNV [25–28]. Indeed, several investigations suggest that some patients with wet AMD may benefit from the release of VMA by means of vitrectomy or perhaps pharmacologic vitreolysis [29–31]. Accumulating evidence strongly supports an association between VMA and exudative AMD. In contrast, clinical studies suggest that the presence of VMA results in poor visual outcomes in RVO, but the evidence is only anecdotal. In the current study, BCVA and CRT before treatment did not differ regardless of the presence or absence of VMA. This finding fails to support the notion that the presence of VMA influences the severity of macular edema due to BRVO, at least, at baseline. In contrast, our previous investigation suggested that the presence of VMA influences the severity of wet AMD at baseline [32].

Secondly, it is generally accepted that the condition and state of the vitreous is related to the clearance of intravitreally injected drugs [33–35]. The state of the vitreous affects the diffusion of the intravitreally injected molecules, and thus their half-life. In general, clearance increases when the vitreous is replaced with water [33], and it has been argued that the loss of the gel structure of the vitreous body as a consequence of vitrectomy or age-related liquefaction has important effects on the distribution of small molecules in the eye [34–36]. Thus far, the pharmacokinetics of eyes with normal viscous vitreous gel and of eyes with age-related liquefied vitreous has not been compared in humans. But a recent laboratory study clearly demonstrated that the distribution of fluorescein isothiocyanate–dextran (average molecular weight: 150 kDa, approximately the same molecular weight as that of bevacizumab) in liquefied vitreous is greater than that in normal viscous vitreous in rabbits, suggesting faster clearance in liquefied vitreous [37]. Indeed, it has been demonstrated that vitrectomized eyes are poorly responsive to intravitreal bevacizumab therapy [38, 39]. It is rational to consider that sufficient therapeutic levels cannot be sustained in vitrectomized eyes owing to the rapid clearance of bevacizumab. This may hold true for intravitreally injected bevacizumab in eyes with age-related liquefaction of the vitreous gel.

The current study demonstrated that BCVA and CRT after the injection at 3 months did not differ significantly; however, eyes with VMA did show better visual outcomes at 6, 9, and 12 months. This may support the notion that the injected drugs that amass in the vitreous body last longer in eyes with VMA, and thus, the visual prognosis after anti-VEGF therapy might not differ significantly in the short-term. Alternatively, eyes with VMA may have a benign natural course. The patients of the current study were recruited from real-world medical practice and not treated with a stringent treatment regimen. If more intensive treatment had been performed in the VMA(−) group, the BCVA and CRT might have been better.

In multiple regression analyses, only the presence of VMA was positively related with changes in BCVA; it was negatively related with changes in CRT. These results indicate that VMA was strongly correlated with the visual and anatomic improvements. Age was also not significantly correlated with changes in BCVA and CRT at 12 months. Various past studies demonstrated that younger patients had better prognosis with anti-VEGF therapy for macular edema secondary to BRVO [18]. Although further studies are needed, the good treatment efficacy for younger patients in previous reports may be partly attributable to the higher prevalence of VMA in younger patients than in older patients.

The current study has several limitations. Firstly, in diagnosing the presence of VMA, we used only spectral OCT. Ultrasound examination is the generally accepted approach to detect PVD, and OCT is not the best tool to evaluate complete PVD. However, the current analysis did not attach high priority to determining complete PVD or partial vitreous adhesion, but instead focused on the status of the posterior vitreous attachment to the macula. In addition, with careful observation by two investigators, we judged whether the posterior vitreous cortex adhered to the posterior pole in a 3D hair scan. Similar to the current report, recent reports examined the state of the vitreoretinal interface and vitreomacular traction with OCT, and these investigators also assumed that OCT is the best clinical instrument to detect VMA [16, 36]. However, wide vitreous attachment over the entire posterior pole may be difficult to find even with careful observation. Secondly, the

total number of injections in both groups was low when compared with the number in previous studies. It has been demonstrated that 33 % of patients with macular edema secondary to BRVO treated with single intravitreal bevacizumab injection had no recurrence and that 58 % of patients needed two injections [40]. Another study demonstrated that 48.6 % patients showed a resolution of macular edema without recurrence after receiving a single injection [41]. The number of injections in the current study is relatively low when compared with these previous studies. In real-world medical practice, it is hard to adhere rigidly to stringent predetermined criteria. Thirdly, we could not provide the systemic factors associated with BRVO in each patient enrolled in this study, e.g., hypertension and coagulation abnormality. The cause of BRVO is important and may exert influence on the visual and anatomic prognosis, but was not included in our routine examination. It will be an important issue for future research. Fourthly, a study suggested removing the posterior hyaloid or PVD formation as treatment for BRVO [42, 43], but the current results contradict that previous hypothesis. It is possible that the natural evolution in patients with BRVO with VMA may be better than that without VMA. In the current study, four eyes in the VMA(+) group developed PVD during the 12-month follow-up. Each case seemed to have good visual and anatomic recovery after the release from VMA. However, the number of such cases is too small to reach a meaningful conclusion. A detailed, prospective study is required to assess the contribution of the vitreous body to intravitreal injection therapy. Finally, the number of patients enrolled in the 2 study groups was unequal and relatively low to detect statistically significant differences in changes in BCVA and CRT between the groups.

In conclusion, the presence of VMA is highly associated with the visual prognosis and seems to be associated with anatomic improvement after anti-VEGF therapy for macular edema secondary to BRVO. The current study did not find that VMA is associated with inferior visual and anatomic outcome after intravitreal bevacizumab. In fact, the presence of VMA may be associated with superior visual and anatomic outcome for intravitreal bevacizumab in the treatment of macular edema due to BRVO.

Conflicts of interest R. Terao, None; K. Yuda, None; K. Kure, None; T. Inoue, None; H. Ohtsu, None; Y. Yanagi, None.

References

1. Orth DH, Patz A. Retinal branch vein occlusion. Surv Ophthalmol. 1978;22:357–76.
2. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. Trans Am Ophthalmol Soc. 2000;98:133–41.
3. Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in Australia. The Blue Mountains Eye Study. Arch Ophthalmol. 1996;114:1243–7.
4. The Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. Am J Ophthalmol. 1984;98:271–82.
5. Glacet-Bernard A, Coscas G, Chabanel A, Zourdani A, Lelong F, Samama MM. Prognostic factors for retinal vein occlusion: prospective study of 175 cases. Ophthalmology. 1996;103:551–60.
6. Kawaji T, Hirata A, Awai N, Takano A, Inomata Y, Fukushima M, et al. Trans-tenon retrobulbar triamcinolone injection for macular edema associated with branch retinal vein occlusion remaining after vitrectomy. Am J Ophthalmol. 2005;140:540–2.
7. Murakami T, Tsujikawa A, Ohta M, Miyamoto K, Kita M, Watanabe D, et al. Photoreceptor status after resolved macular edema in branch retinal vein occlusion treated with tissue plasminogen activator. Am J Ophthalmol. 2007;143:171–3.
8. Parodi MB, Bandello F. Branch retinal vein occlusion: classification and treatment. Ophthalmologica. 2009;223:298–305.
9. Rabena MD, Pieramici DJ, Castellarin AA, Nasir MA, Avery RL. Intravitreal bevacizumab (avastin) in the treatment of macular edema secondary to branch retinal vein occlusion. Retina. 2007;27:419–25.
10. Costa RA, Jorge R, Calucci D, Melo LA, Cardillo JA, Scott IU. Intravitreal bevacizumab (avastin) for central and hemicentral retinal vein occlusions: IBeVO study. Retina. 2007;27:141–9.
11. Kriechbaum K, Michels S, Prager F, Georgopoulos M, Funk M, Geitzenauer W, et al. Intravitreal Avastin for macular oedema secondary to retinal vein occlusion: a prospective study. Br J Ophthalmol. 2008;92:518–22.
12. Rouvas A, Petrou P, Ntouraki A, Douvali M, Ladas I, Vergados I. Intravitreal ranibizumab (Lucentis) for branch retinal vein occlusion-induced macular edema: nine-month results of a prospective study. Retina. 2010;30:893–902.
13. Brown DM, Campochiaro PA, Bhisitkul RB, Ho AC, Gray S, Saroj N, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. Ophthalmology. 2011;118:1594–602.
14. Campochiaro PA, Heiser JS, Feiner L, Gray S, Saroj N, Rundle AC, et al. Ranibizumab for macular edema following branch retinal vein occlusion. Ophthalmology. 2010;117:1102–12.
15. Russo V, Barone A, Conte E, Prascina F, Stella A, Noci ND. Bevacizumab compared with macular laser grid photocoagulation for cystoid macular edema in branch retinal vein occlusion. Retina. 2009;29:511–5.
16. Lee SJ, Koh HJ. Effects of vitreomacular adhesion on anti-vascular endothelial growth factor treatment for exudative age-related macular degeneration. Ophthalmology. 2011;118:101–10.
17. 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.
18. Kondo M, Kondo N, Ito Y, Kachi S, Kikuchi M, Yasuma TR, et al. Intravitreal injection of bevacizumab for macular edema secondary to branch retinal vein occlusion: results after 12 months and multiple regression analysis. Retina. 2009;29:1242–8.
19. Krebs I, Brannath W, Glittenberg C, Zeiler F, Sebag J, Binder S, et al. Posterior vitreomacular adhesion: a potential risk factor for exudative age-related macular degeneration. Am J Ophthalmol. 2007;144:741–6.
20. Mojana F, Cheng L, Bartsch DU, Silva GA, Kozak I, Nigam N, et al. The role of abnormal vitreomacular adhesion in age-related macular degeneration: spectral optical coherence tomography and surgical results. Am J Ophthalmol. 2008;146:218–27.

21. Robison CD, Krebs I, Binder S, Barbazetto IA, Kotsolis AI, Yannuzzi LA, et al. Vitreomacular adhesion in active and end-stage age-related macular degeneration. Am J Ophthalmol. 2009;148:79–82.
22. Weber-Krause B, Eckardt U. Incidence of posterior vitreous detachment in eyes with and without age-related macular degeneration: an ultrasonic study (in German). Ophthalmologe. 1996;93:660–5.
23. Lee SJ, Lee CS, Koh HJ. Posterior vitreomacular adhesion and risk of exudative age-related macular degeneration: paired eye study. Am J Ophthalmol. 2009;147:621–6.
24. Simpson AR, Petrarca R, Jackson TL. Vitreomacular adhesion and neovascular age-related macular degeneration. Surv Opthalmol. 2012;57:498–509.
25. Adamis AP, Shima DT. The role of vascular endothelial growth factor in ocular health and disease. Retina. 2005;25:111–8.
26. Anderson DH, Mullins RF, Hageman GS, Johnson LV. A role for local inflammation in the formation of drusen in the aging eye. Am J Ophthalmol. 2002;134:411–31.
27. Donoso LA, Kim D, Frost A, Callahan A, Hageman G. The role of inflammation in the pathogenesis of age-related macular degeneration. Surv Ophthalmol. 2006;51:137–52.
28. Zarbin MA. Current concepts in the pathogenesis of age-related macular degeneration. Arch Ophthalmol. 2004;122:598–614.
29. Simpson AR, Petrarca R, Jackson TL. Vitreomacular adhesion and neovascular age-related macular degeneration. Surv Ophthalmol. 2012;57:498–509.
30. de Smet MD, Gandorfer A, Stalmans P, Veckeneer M, Feron E, Pakola S, et al. Microplasmin intravitreal administration in patients with vitreomacular traction scheduled for vitrectomy: the MIVI I trial. Ophthalmology. 2009;116:1349–55.
31. Stalmans P, Benz MS, Gandorfer A, Kampik A, Girach A, Pakola S, et al. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes. N Engl J Med. 2012;367:606–15.
32. Nomura Y, Ueta T, Iriyama A, Inoue Y, Obata R, Tamaki Y, et al. Vitreomacular interface in typical exudative age-related macular degeneration and polypoidal choroidal vasculopathy. Ophthalmology. 2012;118:853–9.
33. Doft BH, Weiskopf J, Nilsson-Ehle I, Wingard LB. Amphotericin clearance in vitrectomized versus nonvitrectomized eyes. Ophthalmology. 1985;92:1601–5.
34. Stefánsson E, Novack RL, Hatchell DL. Vitrectomy prevents retinal hypoxia in branch retinal vein occlusion. Invest Ophthalmol Vis Sci. 1990;31:284–9.
35. Chin H, Park TS, Moon YS, Oh JH. Difference in clearance of intravitreal triamcinolone acetonide between vitrectomized and nonvitrectomized eyes. Retina. 2005;25:556–60.
36. Barton KA, Shui YB, Petrash M, Beebe DC. Comment on: the Stokes-Einstein equation and the physiological effects of vitreous surgery. Acta Ophthalmol Scand. 2007;85:339–40.
37. Tan LE, Orilla W, Hugbes PM, Tsai S, Burke JA, Wilson CG. Effects of vitreous liquefaction on the intravitreal distribution of sodium fluorescein, fluorescein dextran, and fluorescent microparticles. Invest Ophthalmol Vis Sci. 2011;52:1111–8.
38. Kondo M, Ito Y, Terasaki H. Intravitreal bevacizumab (Avastin) for persistent macular edema in vitrectomized eyes: limited effect and early recurrence. Retinal Cases Brief Rep. 2007;1:195–7.
39. Yanyali A, Aytug B, Horozoglu F, Nohutcu AF. Bevacizumab (Avastin) for diabetic macular edema in previously vitrectomized eyes. Am J Ophthalmol. 2007;144:124–6.
40. 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.
41. Yunoki T, Miyakoshi A, Nakamura T, Fujita K, Fuchizawa C, Hayashi A. Treatment of macular edema due to branch retinal vein occlusion with single or multiple intravitreal injections of bevacizumab. Jpn J Ophthalmol. 2012;56:156–64.
42. Tachi N, Hashimoto Y, Ogino N. Vitrectomy for macular edema combined with retinal vein occlusion. Doc Ophthalmol. 1999;97:465–9.
43. Sakuma T, Mizota A, Inoue J, Tanaka M. Intravitreal injection of autologous plasmin enzyme for macular edema associated with branch retinal vein occlusion. Am J Ophthalmol. 2010;150:876–82.