RETINAL DISORDERS

Predicting recurrences of macular edema due to branch retinal vein occlusion during anti-vascular endothelial growth factor therapy

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Abstract

Purpose To determine the predictive factors for recurrent macular edema due to branch retinal vein occlusion (BRVO) during intravitreal ranibizumab (IVR) monotherapy.

Methods Clinical records were retrospectively reviewed for 65 patients (mean age 66.5 years, 65 eyes) who were diagnosed with macular edema due to BRVO and treated with IVR monotherapy for 12 months at the Medical Retina Division, Department of Ophthalmology, Keio University Hospital between October 2013 and August 2017. Best-corrected visual acuity (BCVA), fundus findings, and sectional optical coherence tomography (OCT) images were analyzed.

Results Overall BCVA and central retinal thickness (CRT) improved (all $p < 0.01$). BCVA at 12 months was significantly worse in patients with recurrent macular edema (40 eyes [61.5%]) ($p < 0.01$) than in those without, while CRT decreased and was comparable in both groups at 12 months. Logistic regression analyses showed association of recurrence with disorganization of the retinal inner layer (DRIL) temporal to the fovea at baseline (odds ratio = 7.74; 95% confidence interval 1.62–37.08, $p = 0.01$), after adjusting for age, gender, and initial CRT.

Conclusion Recurrent macular edema due to BRVO affects visual outcome and is associated with initial DRIL temporal to the fovea, evaluated using OCT sectional images before treatments. DRIL may facilitate determination of follow-up schedules in clinical practice.

Introduction

Branch retinal vein occlusion (BRVO) is a common retinal disease [1–3] that causes sudden impairment of visual function. In several clinical studies, anti-vascular endothelial growth factor (VEGF) therapy has been used to rapidly reduce macular edema [4–9]. This condition can be naturally resolved over a period of 2 years in approximately 80% of patients [10],

although the visual outcomes may not be as good as those in treated eyes considering the neurodegeneration that occurs due to prolonged edema. Macular edema decreases as early as 1 week after the initial treatment, and best-corrected visual acuity (BCVA) improves in response to this anatomical recovery [4–8]. However, recurrent macular edema may occur, which should be treated as soon as possible to protect the retinal neural elements and obtain better visual outcome.

Clinicians have used a pro re nata (PRN) regimen for anti-VEGF treatment of macular edema due to BRVO [11–13]. Thus, recurrences of macular edema must be detected early to ensure that appropriate additional treatments are delivered. Monthly follow-up visits may be helpful in this regard; however, it is not practical to implement this schedule in all patients with BRVO. Instead, it would be useful to determine which patients should receive frequent follow-up or be treated with a treat and extend regimen to avoid recurrent macular edema. Researchers must therefore develop methods to predict recurrence of macular edema due to BRVO.

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Previous studies have shown that decreased macular vessel density, as determined with optical coherence tomography angiography (OCTA) [11] and fluorescein angiography (FA) [14], is related to recurrence after anti-VEGF treatment. However, before treatment, it may be difficult to perform OCTA and FA because massive retinal hemorrhage and/or edema in patients with fresh BRVO can cause segmentation error and fluorescence blockade, respectively.

In contrast, sectional images of the retina can easily be obtained using OCT. In this regard, previous reports have focused on findings from the external limiting membrane (ELM), ellipsoid zone (EZ), and interdigitation zone (IZ) as predictors of visual outcome after macular edema due to BRVO [15–18]. However, the predictive factors for recurrences have remained unclear.

Because BRVO lesions originate in the inner retinal layers, it may be useful to measure the impact of inner retinal condition with sectional OCT images. A recent report stated that disorganization of the retinal inner layer (DRIL) may influence improvement of visual acuity in patients with central retinal vein occlusion (CRVO) or BRVO after 6 intravitreal injections of bevacizumab delivered monthly [19]. Conversely, 2 additional reports have shown that DRIL is not related to visual outcome in BRVO [20, 21]. However, these prior studies did not assess recurrence. DRIL was originally reported as a biomarker for use in predicting the prognosis of diabetic macular edema in terms of visual acuity [22, 23] and was later reported to be related to abnormal blood flow [24, 25]. Recurrence of macular edema can theoretically occur in relation to the vulnerability of the blood vessels. Thus, we hypothesized that factors related to abnormal blood flow may predict the risk of recurrent macular edema.

In the present study, we first analyzed the influence of recurrent macular edema on visual acuity to determine the impact of recurrence predictors, then, we analyzed factors that may be predictive of recurrence by using retinal sections obtained with OCT at baseline (prior to treatment). Information regarding these predictive factors may be useful for clinicians in managing macular edema due to BRVO.

Materials and methods

This retrospective study was based on a detailed medical chart review; it followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Keio University School of Medicine. All patients provided informed consent for the use of their data for research purposes.

Study participants

In total, 117 consecutive eyes of 117 patients were diagnosed with BRVO. From these, we included in the present study 65 eyes of 65 patients with BRVO-induced macular edema who had received intravitreal ranibizumab (IVR) monotherapy at the Medical Retina Division Clinic of the Department of Ophthalmology, Keio University Hospital (Tokyo, Japan) between October 2013 and August 2017. All patients had attended our clinic for at least 12 months, during which no treatment other than IVR was administered. Patients were excluded if they had a history of any anti-VEGF treatment (10 patients) or photocoagulation (12 patients), regardless of both with or without corticosteroid use within 6 months prior to the initial IVR injection. Those who received corticosteroid and/or photocoagulation therapy (12 patients), who had been sent back to the local clinicians (2 patients), as well as those who gave up or denied IVR upon recurrence for patient-specific reasons (7 patients), and who defaulted visits were lost to follow-up (9 patients) within 12 months after the first IVR treatment were also excluded.

Ophthalmologic examinations

At each follow-up visit, all patients underwent BCVA measurement using refraction tests, slit-lamp examinations, and binocular indirect ophthalmoscopy—ophthalmoscopy was performed after pupil dilation with 0.5% tropicamide. BCVA improvement or worsening was defined as a change of > 0.2 in LogMAR.

FA

FA was performed and fundus photographs were obtained using a Topcon TRC 50DX retinal camera (Topcon Corporation, Tokyo, Japan) to diagnose BRVO and macular edema and to evaluate foveal hemorrhage and distance from disc to occlusive lesion.

OCT

OCT images were recorded at every follow-up visit using a Heidelberg Spectralis OCT system (Heidelberg Engineering GmbH, Dossenheim, Germany). The images were used to evaluate the central retinal thickness (CRT), central choroidal thickness (CCT), DRIL, subretinal fluid build-up, macular edema, and disruptions of ELM and EZ. CRT was defined as the distance between the internal limiting membrane and the putative retinal pigment epithelium at the fovea. CCT was defined as the distance from the hyper-reflective line corresponding to Bruch's membrane beneath the retinal pigment epithelium and the inner surface of the sclera at the foveal center. DRIL was identified when the boundaries between the ganglion cell layer and inner plexiform layer complex, inner nuclear layer, and outer plexiform layer (OPL) could not be distinguished, as described in a previous report [25]. DRIL within 500 μm of the fovea in nasal, temporal, superior, and inferior directions was defined in

Fig. 1 Disorganization of the retinal inner layer (DRIL) in optical coherence tomography (OCT) images in a representative eye. DRIL was analyzed within 500 μm of the fovea in both the vertical and horizontal directions (**a**). OCT images (**b**, horizontal section; **c**, vertical section) of a left eye with macular edema due to branch retinal vein occlusion at baseline. DRIL was observed temporal to the fovea within 500 μm of the fovea (bi-arrows). However, it was not observed on other sides of the fovea
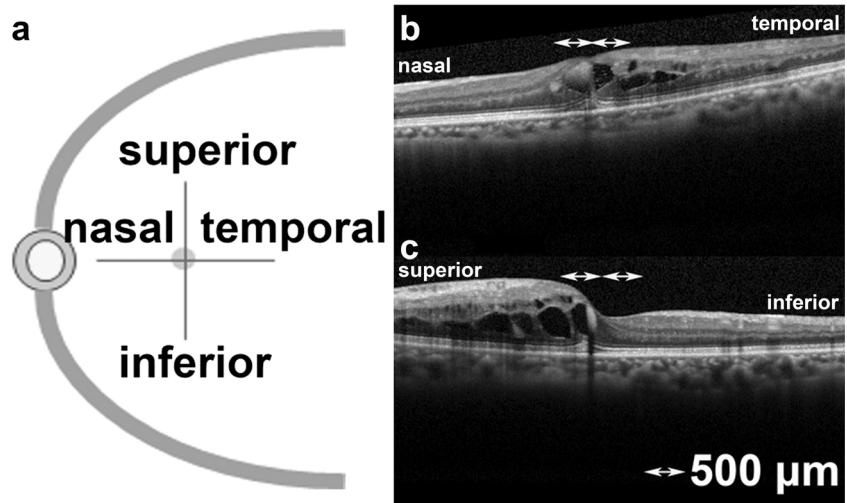
respective horizontal and vertical OCT images (Fig. 1a–c). Measurements were performed using the caliper function of the OCT device, with manual adjustment. Image analyses were performed by 2 retina specialists (MS and YO) in a blinded manner; if the results differed between the 2 specialists, a 3rd specialist (NN) was asked to perform analysis and results were determined by consensus.

Intravitreal ranibizumab monotherapy and follow-up

During the induction phase of the treatment, ranibizumab (0.5 mg, 0.05 mL) was injected intravitreally via the pars plana under sterile conditions. This injection was then repeated as needed (PRN) if follow-up OCT showed macular edema. The need for retreatment was determined by retinal specialists (MS, NN, HS, and YO). Follow-ups were conducted every 1 month after therapy initiation until the macular edema disappeared with the PRN regimen of anti-VEGF therapy. When no macular edema was detected for more than 2 months, the follow-up interval was extended to 2 months.

Statistical analyses

Data are expressed as mean ± standard deviation. Commercially available software (IBM SPSS Statistics, version 24.0; IBM Japan, Tokyo, Japan) was used for all statistical analyses. The Wilcoxon signed-rank test, Mann–Whitney U test, chi-squared test, and logistic regression analyses were used. All p values < 0.05 were considered to be statistically significant.

Results

Sixty-five eyes of 65 patients (male, 33 eyes [50.8%]; mean age, 66.5 years; Table 1) were included. The mean number of injections was 1.9 ± 1.1 (range 1–5) for the initial resolution of

macular edema and 3.5 ± 1.8 (range 1–7) over the 12-month follow-up period. Eleven eyes (16.9%) required no additional injections during the 12-month follow-up period after the initial injection. Recurrence of macular edema after remission

Table 1 Baseline characteristics

Age (years old)	66.5 ± 10.3
Male (eyes (%))	33 (50.8%)
Best-corrected visual acuity (BCVA; LogMAR)	0.28 ± 0.32
Central retinal thickness (CRT; μm)	492.9 ± 190.3
Central choroidal thickness (CCT; μm)	216.0 ± 83.9
Distance from disc to occlusive lesion (μm)	2948.5 ± 1648.9
Presence of the finding at baseline	
Disruption of external limiting membrane (ELM; eyes (%))	20 (30.8%)
Disruption of ellipsoid zone (EZ; eyes (%))	13 (20.0%)
Major BRVO (eyes (%))	43 (66.2%)
Artery on vein (eyes (%))	57 (87.7%)
Foveal hemorrhage (eyes (%))	17 (26.2%)
Subretinal fluid (eyes (%))	34 (52.3%)
Disorganization of the retinal inner layer; DRIL (eyes (%))	53 (81.5%)
Nasal to the fovea	36 (55.4%)
Superior to the fovea	38 (58.5%)
Inferior to the fovea	37 (56.9%)
Temporal to the fovea	38 (58.5%)
Systemic complication	
Hypertension (eyes (%))	31 (47.7%)
Diabetes (eyes (%))	5 (10.9%)
Hyperlipidemia	5 (7.7%)

Data are mean ± standard deviation

BCVA best-corrected visual acuity, *CRT* central retinal thickness, *CCT* central choroidal thickness, *BRVO* branch retinal vein occlusion, *DRIL* disorganization of the retinal inner layer

was observed in 40 eyes (61.5%) during the 12-month follow-up period (Table 2).

Overall, the mean BCVA (Fig. 2a) and CRT (Fig. 2b) were improved at 3, 6, and 12 months, compared with the baseline values ($p < 0.01$ for all); this improvement was observed regardless of the presence of recurrent macular edema after initial resolution of macular edema (Fig. 2a, b, $p < 0.01$ for all). BCVA improved or was maintained in 62 eyes (95.4%) after 12 months (data not shown).

Interestingly, when the mean values between the groups with and without recurrence were compared, mean BCVA at each time point after treatment, including at the 12-month follow-up, was worse in patients who had recurrent macular edema (Fig. 2a, $p < 0.01$ for all), whereas the initial mean BCVA was nearly identical in both groups (Fig. 2a, Table 2, $p = 0.396$). Mean CRT was different between the groups at baseline (Table 2, $p < 0.001$) and at the 3-month follow-up (Fig. 2b, $p < 0.01$); however, the values became comparable at the 6-month follow-up, with additional injections as needed (Fig. 2b).

Differences in the initial conditions of the eyes with and without recurrence are shown in Table 2. In eyes with recurrence, the mean age of the patients was older (68.8 ± 10.0 years

vs. 62.7 ± 9.6 years; $p = 0.01$); the mean CRT was greater (563.3 ± 194.3 μm vs. 380.2 ± 117.2 μm; $p < 0.001$); and the incidences of DRIL nasal (73% vs. 28%; $p < 0.001$), inferior (73% vs. 32%; $p = 0.001$), and temporal to (80% vs. 24%; $p < 0.001$) the fovea were higher, relative to those in eyes without recurrence. The incidences of disruptions of ELM and EZ did not differ between eyes with and without recurrence. The total number of injections required during the 12-month follow-up period was significantly greater in eyes with recurrence (Table 2, 4.4 ± 1.6 vs. 2.0 ± 1.1 injections, respectively; $p < 0.001$). The mean duration to the first recurrence after the first remission was 4.4 ± 5.8 months (data not shown). The incidence of DRIL temporal to the fovea was also higher at the time of first macular edema remission and at the 12-month follow-up in eyes with recurrence (Supplementary Table 1).

Next, the risk of recurrence was analyzed using logistic regression analysis (Table 3). Crude analysis showed that increased age ($p = 0.01$); increased CRT ($p = 0.001$); and eyes with DRIL nasal ($p = 0.002$), inferior ($p = 0.004$), and temporal ($p < 0.001$) to the fovea initially exhibited increased risk for recurrence of macular edema. Moreover, after adjustment for age, gender, and initial CRT at baseline, eyes with DRIL

Table 2 Differences between eyes with or without recurrent macular edema

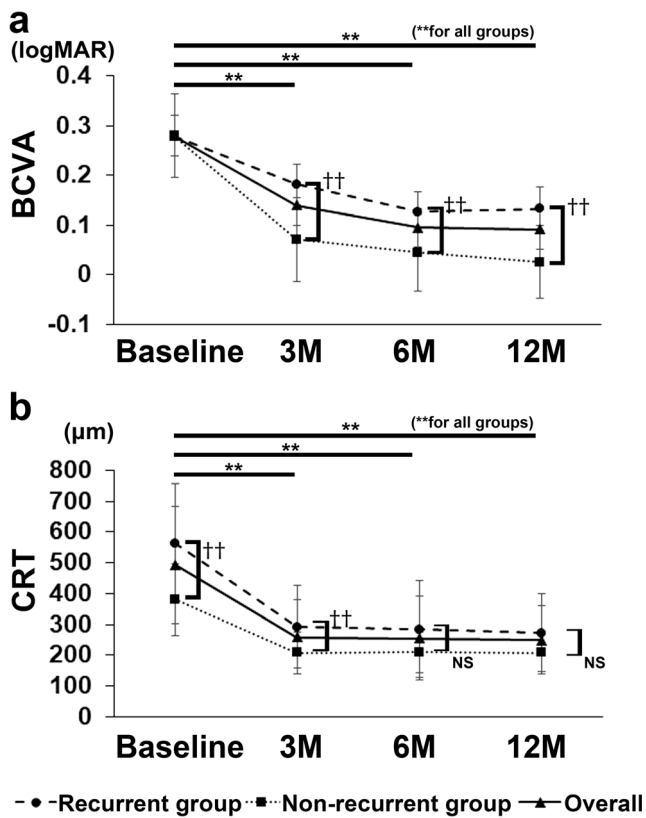|	Recurrences		p value
	+	−	
Eyes (%)	40 [61.5%]	25 [38.5%]	
Mean value at baseline			
Age (years old)	68.8 ± 10.0	62.7 ± 9.6	0.010[*]
Male (eyes [%])	17 [42.5%]	16 [64.0%]	0.092
BCVA (LogMAR)	0.28 ± 0.25	0.28 ± 0.42	0.396
CRT (μm)	563.3 ± 194.3	380.2 ± 117.2	< 0.001[**]
CCT (μm)	219.3 ± 82.3	210.9 ± 87.7	0.517
Distance from disc to occlusive lesion (μm)	2909.2 ± 1652.3	3011.5 ± 1675.3	0.746
Presence of the finding at baseline			
Disruption of ELM, eyes (%)	11 [27.5%]	9 [36.0%]	0.470
Disruption of EZ, eyes (%)	8 [20.0%]	5 [20.0%]	1.000
Major BRVO (eyes (%))	27 [67.5%]	17 [68.0%]	0.967
Artery on vein	35 [87.5%]	22 [88%]	0.952
DRIL at baseline (eyes (%))			
Nasal to the fovea	29 [72.5%]	7 [28.0%]	< 0.001[**]
Superior to the fovea	27 [67.5%]	11 [44.0%]	0.061
Inferior to the fovea	29 [72.5%]	8 [32.0%]	0.001[**]
Temporal to the fovea	32 [80.0%]	6 [24.0%]	< 0.001[**]
Mean injection number	4.4 ± 1.6	2.0 ± 1.0	< 0.001[**]

Data are mean ± standard deviation. Mann–Whitney U test and chi-squared test

BCVA best-corrected visual acuity, *CRT* central retinal thickness, *CCT* central choroidal thickness, *ELM* external limiting membrane, *EZ* ellipsoid zone, *BRVO* branch retinal vein occlusion, *DRIL* disorganization of the retinal inner layer

[*] $p < 0.05$

[**] $p < 0.01$

Table 3 Risk factors for recurrent macula edema within 12 months

	Crude			Multivariate, adjusted		
	p value	OR	95% CI	p value	OR	95% CI
Age	0.010[*]	1.08	1.02–1.14	-	-	-
Gender	0.057	2.72	0.97–7.60	-	-	-
Value at baseline						
BCVA	0.921	1.08	0.23–5.13	0.11	0.14	0.01–1.58
CRT	0.001[**]	1.01	1.00–1.01	-	-	-
CCT	0.428	1.00	0.10–1.01	0.61	1.00	0.10–1.01
Distance from disc to occlusive lesion (μm)	0.549	1.00	1.00–1.00	0.37	1.00	0.10–1.00
Presence of the finding at baseline						
Disruption of ELM	0.471	0.674	0.23–1.97	0.807	1.17	0.32–4.26
Disruption of EZ	1.000	1.000	0.29–3.49	0.459	1.860.	0.36–9.55
Major BRVO	0.967	0.98	0.34–2.85	0.626	73	0.20–2.64
Artery on vein	0.878	0.89	0.19–4.08	0.123	0.22	0.03–1.51
Foveal hemorrhage	0.209	0.49	0.16–1.50	0.110	0.31	0.07–1.31
Subretinal fluid	0.418	1.51	0.56–4.09	0.716	0.79	0.22–2.87
DRIL						
Nasal to the fovea	0.002[**]	5.73	1.93–16.97	0.183	2.46	0.65–9.27
Superior to the fovea	0.103	2.33	0.84–6.46	0.251	2.25	0.56–9.00
Inferior to the fovea	0.004[**]	4.81	1.65–13.98	0.345	1.89	0.51–7.05
Temporal to the fovea	< 0.001[**]	10.52	3.28–33.69	0.010[*]	7.74	1.62–37.08

Logistic regression analyses. In the multivariable analysis, potential risk factors were adjusted respectively for age, gender, and initial CRT

BCVA best-corrected visual acuity, CRT central retinal thickness, CCT central choroidal thickness, ELM external limiting membrane, EZ ellipsoid zone, BRVO branch retinal vein occlusion, DRIL disorganization of the retinal inner layers

[*] $p < 0.05$

[**] $p < 0.01$

the inner retinal layer [31, 32]. Another previous report stated that non-perfused areas in the inner layer, which can be detected by FA, correspond to EZ disruption that reflects photoreceptor damage [33]. Thus, abnormal inner retinal blood flow and recurrent macular edema may cause damage to photoreceptors. Analysis of a hyper-reflective band involving the inner retinal layer in OCT images, known as paracentral acute middle maculopathy (PAMM), showed that ischemic lesions in vascular occlusive diseases of the retina develop at the venular pole of the deep capillary plexus [34] and may then progress laterally and anteriorly into the inner retina at the level of the superficial capillary plexus. This ischemic mechanism also supports our abovementioned hypothesis that inner retinal findings involve photoreceptor disorder.

Importantly, recurrence was associated with the presence of DRIL temporal to the fovea, but not with the disruption of either ELM or EZ. Given that DRIL is related to flow abnormality in the deep plexus [24], the areas affected by DRIL may have experienced persistent hypoxia, leading to excessive VEGF expression and thus recurrent macular edema. Alternatively, hypoxia may have interrupted the recovery of vessels that were

influenced at the time of occlusion due to insufficient nutrient and oxygen supply to the affected vascular cells. This interpretation of our results is consistent with a previous report using FA, which found that 35% of patients showed recurrence 6 months after a single injection of an anti-VEGF drug; the risk was increased if the patients had a non-perfused area in the deep capillary plexus within 1 mm of the fovea [14]. Notably, the previous study using FA had a limitation in the recording of clear images if the eyes had severe hemorrhage causing blockade of the signals [14]. In contrast, the current study did not have this limitation; the inner retinal layers in the sectional OCT images could be evaluated regardless of the extent of hemorrhage and edema before treatment. DRIL, as identified in sectional OCT images, would be of value for predicting recurrent macular edema in daily clinical practice.

DRIL temporal to the fovea was responsible for the recurrence of macular edema. Notably, retinal vessels temporal to the fovea are at a greater distance from the disc, and the presence of microvascular changes on the temporal side may result in a greater area of vascular abnormality. This would increase the risk of extracellular fluid accumulation. Alternatively,

because the capillary densities in the neurofiber layer, ganglion cell layer, inner plexiform layer, and inner nuclear layer are lower on the side temporal to the fovea [35], we speculate that further reductions in blood flow caused by BRVO, as suggested by DRIL, could lower the ability of the retina to absorb extracellular fluid, thereby resulting in edema.

The limitations of the current study are its relatively small sample size and retrospective design; moreover, the need for retreatment was determined by attending doctors, rather than by the reading center. However, recurrent macular edema was recorded in OCT images that were reviewed during the current study, and we confirmed that retreatment was performed properly, based on the criterion, if follow-up OCT showed macular edema.

In summary, visual prognosis was worse in eyes with recurrent macular edema, despite reduction in CRT that indicated sufficient treatment. DRIL temporal to the fovea was a significant risk factor for recurrence. Use of OCT sectional images is valuable for diagnosis of macular edema, as well as for evaluation of DRIL temporal to the fovea at baseline; this can help to predict prognosis and determine follow-up schedules for early retreatment of recurrent edema and/or the treatment protocol in the daily clinic.

Compliance with ethical standards

Conflict of interest MS has received a speaker honorarium from Novartis Pharmaceuticals Japan. TK has received grants from Tsubota Laboratory, Inc., Fuji Xerox Co., Ltd., SEED Co., Ltd., Kowa Company, Santen Pharmaceutical Co. Ltd., and ROHTO Pharmaceutical Co., Ltd.; grants and speaker honorariums from Novartis Pharmaceuticals Japan; and personal fees from Bayer Yakuhin, Ltd.; all of these grants, honorariums, and fees were outside of the scope of the submitted work. KT reports research funding and consultancies from Santen Pharmaceutical Co. Ltd., Otsuka Pharmaceutical Co., Ltd., and Wakamoto Pharmaceutical Co., Ltd.; patents with JINS, Inc., Echo Electricity Co., and Kowa Company; KT is also the CEO of Tsubota Laboratory, Inc.; all of these grants, consultancies, patents, and employment arrangements were outside of the scope of the submitted work. YO received grants and speaker honorariums from Santen Pharmaceutical Co. Ltd., Novartis Pharmaceuticals Japan, Bayer Yakuhin, Ltd., Nitto Medic, Co. Ltd., Wakasa Seikatsu, Co. Ltd.; all of these grants and honorariums were outside of the scope of the submitted work. NN, SM, MK, HS, KW, and HS declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Keio University School of Medicine, Tokyo, Japan, and were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Rogers SL, McIntosh RL, Lim L, Mitchell P, Cheung N, Kowalski JW et al (2010) Natural history of branch retinal vein occlusion: an evidence-based systematic review. Ophthalmology 117(6):1094–1101

2. Yasuda M, Kiyohara Y, Arakawa S, Hata Y, Yonemoto K, Doi Y et al (2010) Prevalence and systemic risk factors for retinal vein occlusion in a general Japanese population: the Hisayama study. Invest Ophthalmol Vis Sci. 51(6):3205–3209

3. Mitchell P, Smith W, Chang A (1996) Prevalence and associations of retinal vein occlusion in Australia. The Blue Mountains Eye Study. Arch Ophthalmol. 114(10):1243–1247

4. Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, Saroj N et al (2010) Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology 117(6):1124–1133 e1

5. Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N et al (2011) Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. Ophthalmology 118(10):2041–2049

6. Campochiaro PA, Heier JS, Feiner L, Gray S, Saroj N, Rundle AC et al (2010) Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology 117(6):1102–1112 e1

7. Ehlers JP, Kim SJ, Yeh S, Thorne JE, Mruthyunjaya P, Schoenberger SD et al (2017) Therapies for macular edema associated with branch retinal vein occlusion: a report by the American Academy of Ophthalmology. Ophthalmology 124(9):1412–1423

8. Heier JS, Campochiaro PA, Yau L, Li Z, Saroj N, Rubio RG et al (2012) Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. Ophthalmology 119(4):802–809

9. Clark WL, Boyer DS, Heier JS, Brown DM, Haller JA, Vitti R et al (2016) Intravitreal aflibercept for macular edema following branch retinal vein occlusion: 52-week results of the VIBRANT study. Ophthalmology 123(2):330–336

10. Hayreh SS, Zimmerman MB (2014) Branch retinal vein occlusion: natural history of visual outcome. JAMA Ophthalmol. 132(1):13–22

11. Hasegawa T, Murakawa S, Maruko I, Kogure-Katakura A, Iida T (2018) Correlation between reduction in macular vessel density and frequency of intravitreal ranibizumab for macular oedema in eyes with branch retinal vein occlusion. Br J Ophthalmol. 103(1):72–77

12. Shiono A, Kogo J, Sasaki H, Yomoda R, Jujo T, Tokuda N et al (2018) Optical coherence tomography findings as a predictor of clinical course in patients with branch retinal vein occlusion treated with ranibizumab. PLoS One. 13(6):e0199552

13. Tilgner E, Dalcegio Favretto M, Tuisl M, Wiedemann P, Rehak M (2017) Macular cystic changes as predictive factor for the recurrence of macular oedema in branch retinal vein occlusion. Acta Ophthalmol. 95(7):e592–e5e6

14. Yoo JH, Ahn J, Oh J, Cha J, Kim SW (2017) Risk factors of recurrence of macular oedema associated with branch retinal vein occlusion after intravitreal bevacizumab injection. Br J Ophthalmol. 101(10):1334–1339

15. Kang HM, Chung EJ, Kim YM, Koh HJ (2013) Spectral-domain optical coherence tomography (SD-OCT) patterns and response to intravitreal bevacizumab therapy in macular edema associated with branch retinal vein occlusion. Graefes Arch Clin Exp Ophthalmol. 251(2):501–508

16. Moon BG, Cho AR, Kim YN, Kim JG (2018) Predictors of refractory macular edema after branch retinal vein occlusion following intravitreal bevacizumab. Retina. 38(6):1166–1174

17. Murakami T, Okamoto F, Iida M, Sugiura Y, Okamoto Y, Hiraoka T et al (2016) Relationship between metamorphopsia and foveal microstructure in patients with branch retinal vein occlusion and cystoid macular edema. Graefes Arch Clin Exp Ophthalmol. 254(11):2191–2196

18. Muraoka Y, Tsujikawa A, Takahashi A, Iida Y, Murakami T, Ooto S et al (2015) Foveal damage due to subfoveal hemorrhage associated with branch retinal vein occlusion. PLoS One. 10(12):e0144894

19. Mimouni M, Segev O, Dori D, Geffen N, Flores V, Segal O (2017) Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with macular edema secondary to vein occlusion. Am J Ophthalmol. 182:160–167

20. Nakano E, Ota T, Jingami Y, Nakata I, Hayashi H, Yamashiro K (2018) Disorganization of the retinal inner layers after anti-VEGF treatment for macular edema due to branch retinal vein occlusion. Ophthalmologica 240(4):229–234

21. Babiuch AS, Han M, Conti FF, Wai K, Silva FQ, Singh RP (2019) Association of disorganization of retinal inner layers with visual acuity response to anti-vascular endothelial growth factor therapy for macular edema secondary to retinal vein occlusion. JAMA Ophthalmol. 137(1):38–46

22. Sun JK, Radwan SH, Soliman AZ, Lammer J, Lin MM, Prager SG et al (2015) Neural retinal disorganization as a robust marker of visual acuity in current and resolved diabetic macular edema. Diabetes 64(7):2560–2570

23. Sun JK, Lin MM, Lammer J, Prager S, Sarangi R, Silva PS et al (2014) Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. JAMA Ophthalmol. 132(11):1309–1316

24. Spaide RF (2015) Volume-rendered optical coherence tomography of diabetic retinopathy pilot study. Am J Ophthalmol. 160(6):1200–1210

25. Moein HR, Novais EA, Rebhun CB, Cole ED, Louzada RN, Witkin AJ et al (2017) Optical coherence tomography angiography to detect macular capillary ischemia in patients with inner retinal changes after resolved diabetic macular edema. Retina

26. Brown DM, Campochiaro PA, Bhisitkul RB, Ho AC, Gray S, Saroj N et al (2011) Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. Ophthalmology. 118(8):1594–1602

27. Miwa Y, Muraoka Y, Osaka R, Ooto S, Murakami T, Suzuma K et al (2017) Ranibizumab for macular edema after branch retinal vein occlusion: one initial injection versus three monthly injections. Retina. 37(4):702–709

28. Suzuki M, Ozawa Y, Kubota S, Hirasawa M, Miyake S, Noda K et al (2011) Neuroprotective response after photodynamic therapy: role of vascular endothelial growth factor. J Neuroinflammation. 8: 176

29. Saint-Geniez M, Maharaj AS, Walshe TE, Tucker BA, Sekiyama E, Kurihara T et al (2008) Endogenous VEGF is required for visual function: evidence for a survival role on muller cells and photoreceptors. PLoS One. 3(11):e3554

30. Noma H, Mimura T, Eguchi S (2013) Association of inflammatory factors with macular edema in branch retinal vein occlusion. JAMA Ophthalmol. 131(2):160–165

31. Coscas F, Glacet-Bernard A, Miere A, Caillaux V, Uzzan J, Lupidi M et al (2016) Optical coherence tomography angiography in retinal vein occlusion: evaluation of superficial and deep capillary plexa. Am J Ophthalmol. 161(160-71):e1–e2

32. Kang JW, Yoo R, Jo YH, Kim HC (2017) Correlation of microvascular structures on optical coherence tomography angiography with visual acuity in retinal vein occlusion. Retina 37(9):1700–1709

33. Kanakis MG, Giannouli K, Andreanos K, Papaconstantinou D, Koutsandrea C, Ladas I et al (2017) Capillary nonperfusion and photoreceptor loss in branch retinal vein occlusion: spatial correlation and morphologic characteristics. Retina 37(9):1710–1722

34. Bakhoum MF, Freund KB, Dolz-Marco R, Leong BCS, Baumal CR, Duker JS et al (2018) Paracentral acute middle maculopathy and the ischemic cascade associated with retinal vascular occlusion. Am J Ophthalmol. 195:143–153

35. Campbell JP, Zhang M, Hwang TS, Bailey ST, Wilson DJ, Jia Y et al (2017) Detailed vascular anatomy of the human retina by projection-resolved optical coherence tomography angiography. Sci Rep. 7:42201