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Research article

Relationship between retinal volume changes and the prognosis of BRVO-ME treated with ranibizumab

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ABSTRACT

Background: This study aimed to evaluate the efficacy of ranibizumab for the treatment of macular edema secondary to branch retinal vein occlusion (BRVO-ME), changes in retinal volume and central retinal thickness (CRT) before and after therapy, and the connection between visual prognosis and changes in retinal volume.
Methods: The 120 patients(121 eyes) of BRVO-ME were recruited from July 2020 to October 2022 at the Affiliated Hospital of Weifang Medical University. The clinical data of patients were retrospectively examined for changes in best-corrected visual acuity (BCVA), retinal volume, and CRT at 1 day, 1 week, 1 month, 3 months, 6 months and 1year after treatment.
Findings: Visual acuity improved gradually and became steady approximately 1 months after treatment, whereas retinal volume decreased gradually in both the outer and full layers and stabilized around 6 month after treatment. The decline in retinal volume and CRT was more visible in the deeper layers than in the inner levels. A higher correlation was observed between retinal volume and BCVA than between CRT and BCVA. BCVA after one year of treatment had a high correlation with baseline outer retinal volume.
Interpretation: Treatment of BRVO-ME with ranibizumab is highly effective, and the recovery of visual function was depends more on early treatment. The outer retina is the major site of edema. Changes in retinal volume may serve as a better predictor of visual prognosis than changes in CRT. Baseline ourter retinal volume is correlated with long-term visual prognosis.

1. Introduction

Branch retinal vein occlusion (BRVO) is the second most common retinal vascular disease, and its main symptom is vision loss, which is mainly caused by impaired venous blood return. Branch retinal vein occlusion causes venous thrombosis, retinal blood return blockage, decreased fresh blood supply, insufficient oxygen supply for retinal tissue metabolism, increased vascular endothelial growth factor (VEGF) release, elevated capillary vascular permeability, further aggravating macular edema, and vision loss. Further development can result in the formation of new capillaries, causing several complications [1–4].

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When anti-VEGF medications are used to treat macular edema secondary to BRVO, the retinal bulge in the macula expands and flattens with time. Ranibizumab is a first-line anti-VEGF agent that binds to VEGF receptors and attenuates vascular leakage.

However, central retinal thickness (CRT) only responds to the degree of edema in the central macular recess, and its clinical significance is more constrained, whereas retinal volume can respond to larger-scale retinal edema changes in the macula. Previously, we gained more clinical experience with optical coherence tomography angiography (OCTA) in a comparative study of CRT before and after treatment. For example, Daisuke Nagasato's study noted that foveal thickness fluctuation was significantly associated with visual acuity [5], and Ding X noted that Intravitreal injections of conbercept can improve BCVA and CRT [6]. The aim of this study was to compare the clinical relevance of retinal volumes with CRT during treatment follow-up in order to evaluate the clinical efficacy of ranibizumab in the treatment of macular edema secondary to BRVO by examining retinal volumes in the macular region in the range of 5×5 mm.

2. Materials and methods

In this retrospective study, patients diagnosed as having BRVO associated with macular edema were recruited and enrolled at the Affiliated Hospital of Weifang Medical University, Weifang, Shandong, China. The study protocol adhered to the Helsinki Declaration and was approved by the Clinical Research Ethics Committee of the Affiliated Hospital of Weifang Medical University, approval number [wyfy-2023-ky-140].

2.1. Patients

In a retrospective analysis of the clinical data of 121 eyes diagnosed with BRVO from July 2020 to October 2022 at the Eye Center of the Affiliated Hospital of Weifang Medical University, all patients with single eye onset were treated with an intravitreal injection of 0.5 mg of ranibizumab in accordance with the principle of 3+PRN. The age of the patients ranged from 29 to 82 years old, 53 eyes in 53 cases of males and 68 eyes in 68 cases of females. The intraocular pressure was 10~21mmgh, the number of razumab injection was 3~10 times, the refractive error of spherical lens was −6.00~+4.50D, the refractive error of column lens was −3.25~+0.00D, and the axial interval was 0–175°. The baseline data of the patients are in Table 1 and include gender, eye type, age, IOP, number of injections, and refractive status. A follow-up was conducted on day 1, week 1, month 1, month 3, month 6 and 1 year following treatment. BCVA, log MAR BCVA, intraocular pressure, slit lamp microscopy, indirect fundoscopy after a dilated pupil, and the retinal volume and CRT parameters of the inner, outer, and full retina were measured before and after treatment on all enrolled patients. Fig. 1 shows the pre-treatment FFA, fundus photography, Optos, and OCT pictures of one case in the ischaemic group and one case in the non-ischemic group. For all procedures, patient consent was obtained, and the pertinent informed consent forms were signed.

2.2. Inclusion and exclusion criteria

Fundoscopy, fundus photography, fluorescein fundus angiography (FFA), and OCTA with dilated pupils were used to confirm the diagnosis of BRVO. The inclusion criteria are as follows: (1) The affected eye(s) were diagnosed with macular edema secondary to BRVO through examinations including OCTA, Fluorescein Fundus Angiography (FFA), fundus photography, and other clinical data. The clinical data were complete. (2) The OCTA examination image was clear, and the edema in the macular area of the retina was thickened and raised. (3) No intravitreal injection or laser photocoagulation therapy was administered to the retina, and all were first-time recipients of treatment. (4) Age >18 years. (5) Patients with macular edema subsiding after 3 consecutive anti-VEGF treatments. (6)First treatment less than 3 months from onset of disease. The exclusionary criteria are as follows: (1) Less than a one-year follow-up period qualifies as an exclusion. (2) patients with high intraocular pressure, glaucoma, cataracts, severe vitreous hemorrhage, optic neuritis, pathologic myopia, diabetic retinopathy, systemic cardiovascular, cerebral vascular diseases and other diseases. (3) patients with contraindications to surgery. (4) patients with macular edema other than those caused by BRVO. (5) patients with low vision or low corrected visual acuity. (6) Those with poor fixation, poor fundus peeping, and refractive media clouding in the afflicted eye. (7)

Table 1
Clinical characteristics of all patients with branch retinal vein occlusion.

Variables	Patients of BRVO-ME
Age	57.64 ± 10.82
Gender(male/female)	53/68
Eye(Left/Right)	56/65
IOP(mmHg)	14.84 ± 3.32
Number of injections	3.50 ± 0.96
Number of injections (=3)	82
Number of injections (=4)	25
Number of injections (=5)	10
Number of injections (> 5)	4
refractive status	
SC(D)	0.31 ± 1.64
CC(D)	−0.51 ± 0.68
AX(°)	0~175(44.71 ± 53.43)

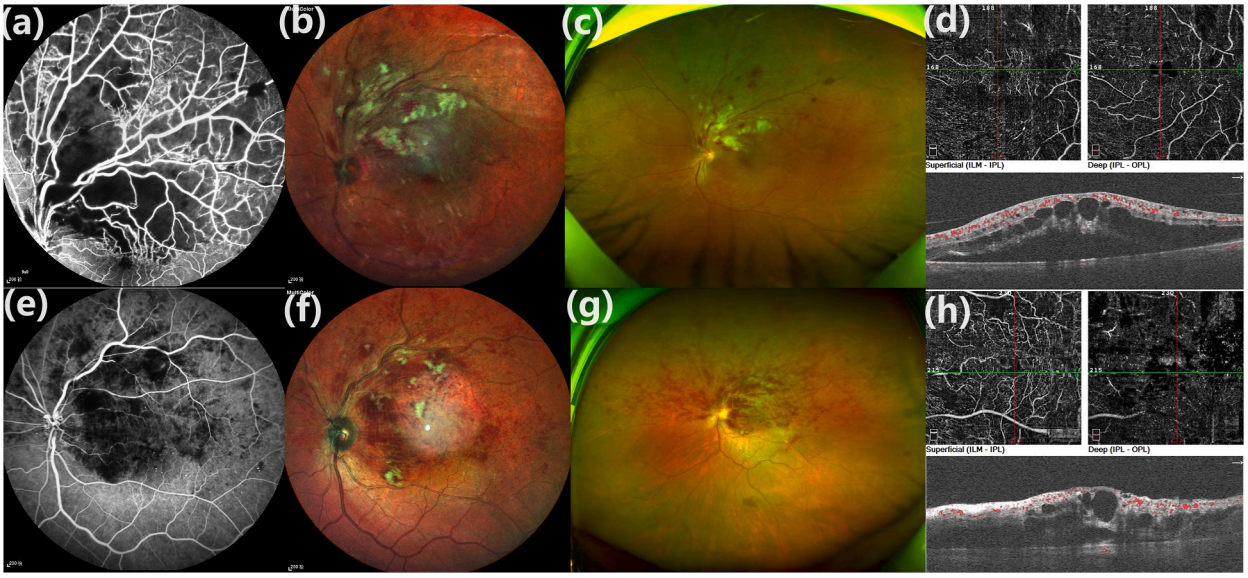

Fig. 1. FFA, fundus photography, optos, and OCT images of 1 case in the ischaemic group and 1 case in the non-ischemic group before treatment. Note: Ischaemic type group: (a), (b), (c), (d); non-ischemic type group: (e), (f), (g), (h).

Prior history of vitreous cavity injection, retinal laser photocoagulation, or possibly ocular vitreous surgery. (8) Inability to undergo an eye exam and surgery. (9) Poor patient compliance and failure to observe and follow up at the appropriate intervals.

2.3. Treatment and examination

The disease was described to the patient and his family after the diagnosis, and they were asked to sign an informed consent form. The conjunctival sac was rinsed with saline three days before the procedure, the eye surface was anesthetized three times, and the towels were routinely disinfected. The preparation was done in accordance with internal eye surgery. During surgery, 0.05 ml of ranibizumab injection was obtained, the needle was inserted perpendicular to the ciliary body flat at 3.5 mm from the corneal limbus, and the drug was injected into the vitreous cavity, followed by immediate pressure with a sterile dry face swab until no significant bleeding was observed. After the procedure, tobramycin-dexamethasone ophthalmic ointment was applied, and the eye was wrapped with sterile gauze until the next day. Topical gatifloxacin eye drops were applied four times per day for 5–7 days after the procedure.

The treatment regimen for 3+PRN was on-demand treatment with anti-VEGF drugs once a month for 3 consecutive months after the initial treatment. After 3 consecutive injections of anti-VEGF drugs, patients were followed up monthly with additional injections if signs of macular edema recurrence remained. Signs of macular edema recurrence included thickening of the macular bulge, macular cystoid edema, and CRT >300 μm on OCTA.

OCTA (OPTOVUE, USA, SD-OCT, wavelength 840um, scanning speed 70,000 A/scan per second) was carried out by choosing the volume and CRT scanning modes(Retinal Map mode) to automatically generate the inner retina (including the inner limiting

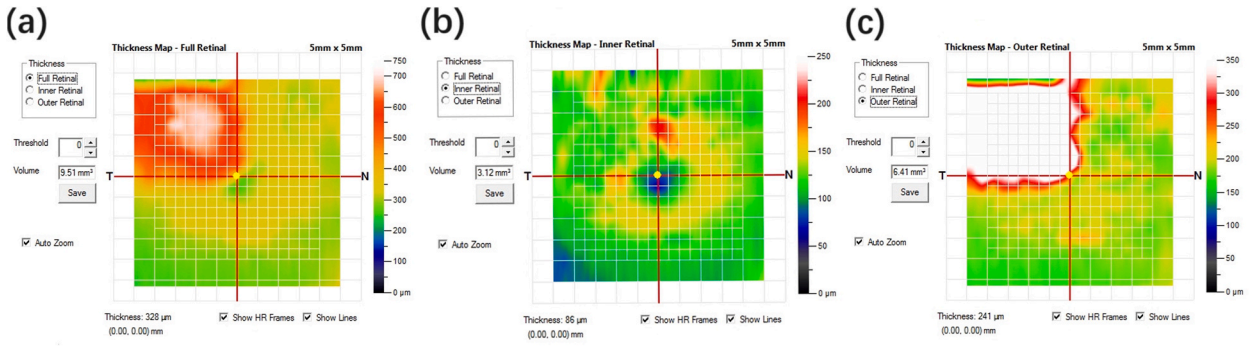

Fig. 2. Retinal volume map of the macular area in OCTA of 5 mm × 5 mm in size. Note: (a) full retinal layer of the macula, with a severe area of red and white macular edema visible over the temporal region; (b) inner retinal layer of the macula, with no obvious area of edema visible over the temporal region; (c) outer retinal layer of the macula, with a large area of red and white edema visible over the temporal region. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

membrane, retina neural fiber layer, retina ganglion cell layer, and inner plexiform layer), the outer retina (including the inner nuclear layer, outer plexiform layer, outer nuclear layer, outer limiting membrane, rod and cone layer, and retinal pigment epithelium), and the full retina (including the inner and outer retina). Retinal volume data were collected in a 5 × 5 mm area centered on the macula, and CRT was collected in a 1-mm area of the central macular retinopathy. All of the above examinations were performed by the same skilled, professional, and certified doctor. Signal strength of OCTA test ≥7. Fig. 2 shows retinal volume maps of the inner, outer, and full macular areas of 5 mm × 5 mm size in OCTA. The inner, outer, and full retinal volumes were measured automatically by the OCTA instrument without the use of additional measurement tools. Fig. 3 shows the OCT image and retinal volume image of the patient at

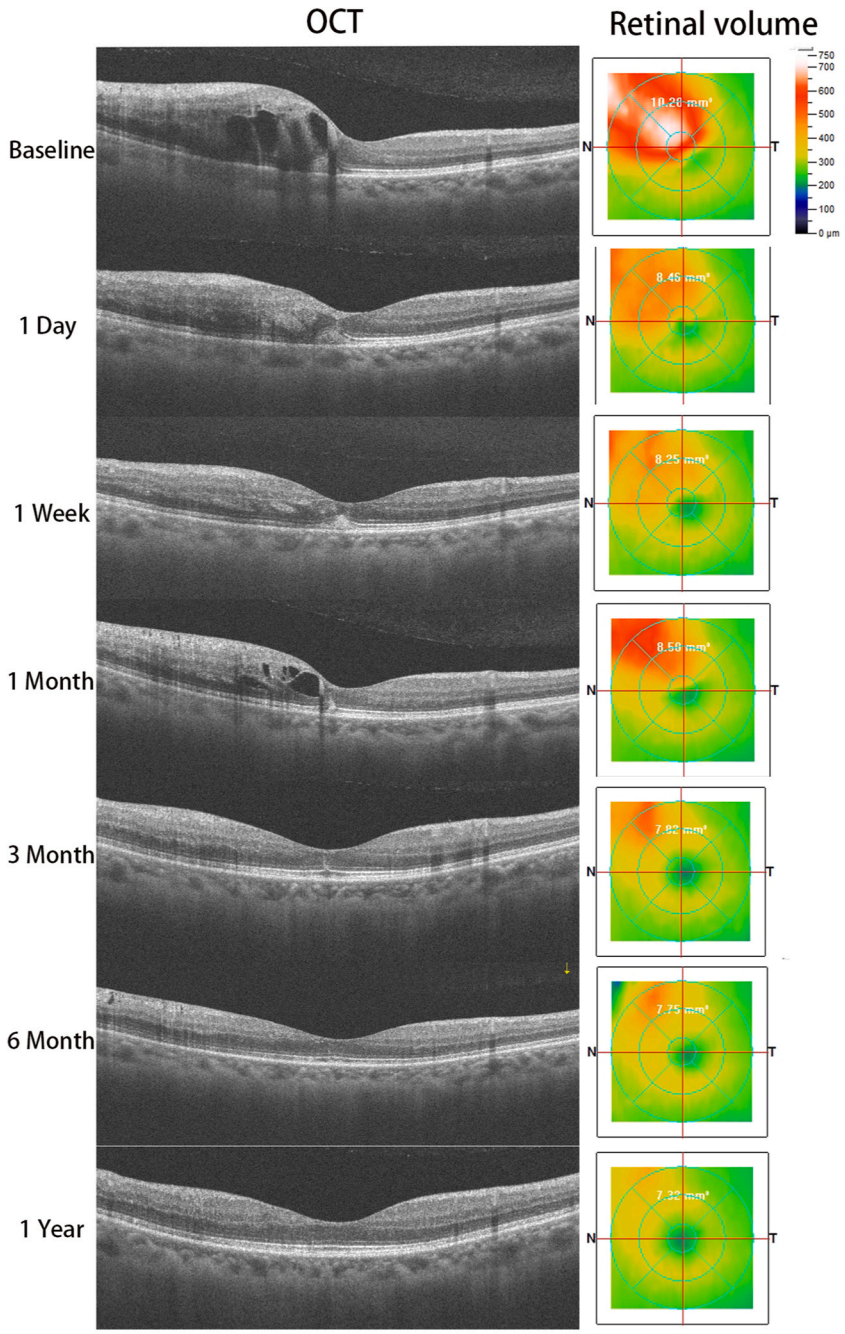

Fig. 3. Changes in full retinal volume before and after therapy based on OCTA imaging. A 5mm × 5 mm OCTA scan of the full retinal volume (right). Transverse OCT images of the macula (left). The top right color-coded maps can be used to evaluate changes in retinal volume and thickness, as well as the degree of edema. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

treatment follow-up.

2.4. Statistical analysis

The study's data were statistically analyzed using the statistical program SPSS 23.0. Measurements were expressed as mean ± standard deviation (x ± s), and repeated measures ANOVA was used for comparison before and after treatment. Spearman's correlation analysis was used to correlate the two sets of parameters (visual acuity and volume, visual acuity and CRT, etc.). Statistics were considered significant at $P < 0.05$.

3. Results

According to the repeated measures ANOVA results, the fluctuation of the decline in LOG MAR BCVA at 1 day, 1 week, and 1 month after treatment was statistically significant ($P < 0.05$), followed by a slow decline with less fluctuation. The decrease in retinal volume at 1 day, 1 week, 1 month, and 6 months after treatment fluctuated statistically significantly ($P < 0.05$), followed by a slow decrease in volume with smaller fluctuations.The decrease in CRT at 1 day, 1 week, and 1 month after treatment fluctuated statistically significantly ($P < 0.05$), followed by a slow decrease in CRT with smaller fluctuations. (Table 2, Figs. 4–6).

Table 3 indicated that the correlation between volume and CRT of the full retina or outer retina and best corrected visual acuity was statistically significant ($P < 0.05$) before treatment, 1 day after treatment, and 1 week after treatment (comparison of their sizes: $0.394 > 0.330$, $0.409 > 0.289$, $0.311 > 0.222$, $0.316 > 0.204$, $0.193 > 0.185$, and $0.242 > 0.181$). Therefore, the correlation between retinal volume and BCVA was greater than the correlation between CRT and BCVA. Both the correlation coefficients for the full and outer retinal volumes were larger than 0.8, indicating that they were highly associated.

Table 4 indicated that BCVA after 1 year of treatment correlates with baseline outer retinal layer volume. The outer retina at baseline and 1 day after treatment correlated with visual prognosis at 1 year.

4. Discussion

A common retinal vascular disorder with a prevalence of 1.6 % is retinal branch vein occlusion. The main cause of visual impairment in this disease is decreased venous blood return within the retinal circulation following branch vein thrombosis in the retina, increased retinal capillary pressure and permeability, dilated and tortuous obstructing veins, leakage of blood outside the retinal vessels under high-pressure and high-permeability conditions, and a lack of fresh blood perfusion within the retinal capillaries [7–10]. The decrease in circulating blood promotes hypoxia in retinal tissues and triggers VEGF synthesis, thus increasing retinal capillary permeability and resulting in a vicious cycle that eventually produces macular edema and neovascularization [11,12]. As a result, the fundus presents as retinal blockage, tortuous dilatation of branching veins, flame-like hemorrhage accompanied by vascular travel, and cystoid edema in the macula. Currently, intravitreal injection of ranibizumab, a small-molecule antibody fragment, has been used in China for the treatment of macular edema and improving or lessening visual impairment in patients [13]. It can quickly bind to the capillary VEGF receptor area after easily crossing the retinal barrier, thus reducing the permeability of the diseased vessels and the gradual absorption of perivascular tissue fluid [14].

The retina is the site of visual imaging, and macular edema can cause irreversible vision loss. Retinal function can be assessed via retinal anatomy with OCTA [15]. Changes in CRT were significantly related to log MAR BCVA and central recess receptor function [5], but this study did not follow up for multiple post-treatment time points to examine the correlation with BCVA; larger changes in macular central recess thickness were associated with a worse visual prognosis [16], this result is different from our study, which found a correlation between baseline full and outer volume and visual acuity after 1 year of treatment, and the reason for the different results is that the metrics and purpose of the study were different, and the results of this study can be complemented with those of Chen AX; and the volume of the retinal macula decreases following anti-VEGF treatment in patients with macular edema secondary to BRVO compared with pre-treatment [17]. This study is consistent with our findings, however, we stratified the retinal volumes in more detail, correlating each layer of retinal volume with BCVA at multiple time points during the 1-year post-treatment follow-up period, and found patterns of change in retinal volume. Therefore, the limited studies have been done on retinal volume, and the trends of retinal

Table 2
Retinal volume and CRT follow-up results.

	Baseline	1 day	1 week	1 month	3 month	6 month	1 year
LogMAR(BCVA)	0.65 ± 0.37	**0.59 ± 0.35**	**0.49 ± 0.32**	**0.42 ± 0.36**	0.31 ± 0.28	0.29 ± 0.28	0.28 ± 0.27
IRV(mm3)	2.39 ± 0.38	2.35 ± 0.42	2.30 ± 0.42	2.28 ± 0.41	2.25 ± 0.14	**2.14 ± 0.24**	2.25 ± 0.42
ORV(mm3)	6.06 ± 1.57	**5.09 ± 1.28**	**4.39 ± 0.82**	**4.14 ± 0.94**	4.09 ± 0.72	**3.84 ± 0.79**	3.84 ± 0.57
FRV(mm3)	8.45 ± 1.56	**7.43 ± 1.48**	**6.69 ± 1.05**	**6.34 ± 1.08**	6.34 ± 0.8	**5.98 ± 1.06**	6.07 ± 0.97
ICRT(mm)	0.13 ± 0.05	0.13 ± 0.05	0.12 ± 0.07	**0.08 ± 0.03**	0.08 ± 0.02	**0.07 ± 0.02**	0.07 ± 0.03
OCRT(mm)	0.39 ± 0.2	**0.29 ± 0.13**	**0.24 ± 0.09**	0.21 ± 0.10	0.20 ± 0.07	0.19 ± 0.08	0.21 ± 0.11
FCRT(mm)	0.52 ± 0.2	**0.42 ± 0.15**	**0.36 ± 0.13**	**0.29 ± 0.11**	0.27 ± 0.08	0.26 ± 0.09	0.28 ± 0.03

NOTE: IRV: Inner retinal volume; ORV: Outer retinal volume; FRV: Full retinal volume; ICRT: Inner central retinal thickness; OCRT: Outer central retinal thickness; FCRT: Full central retinal thickness. P-valuesindicate repeated measures ANOVA results for fluctuations in changes in outcomes between two adjacent follow-up visits. Black indicates $P < 0.05$, $P < 0.05$ is considered significant.

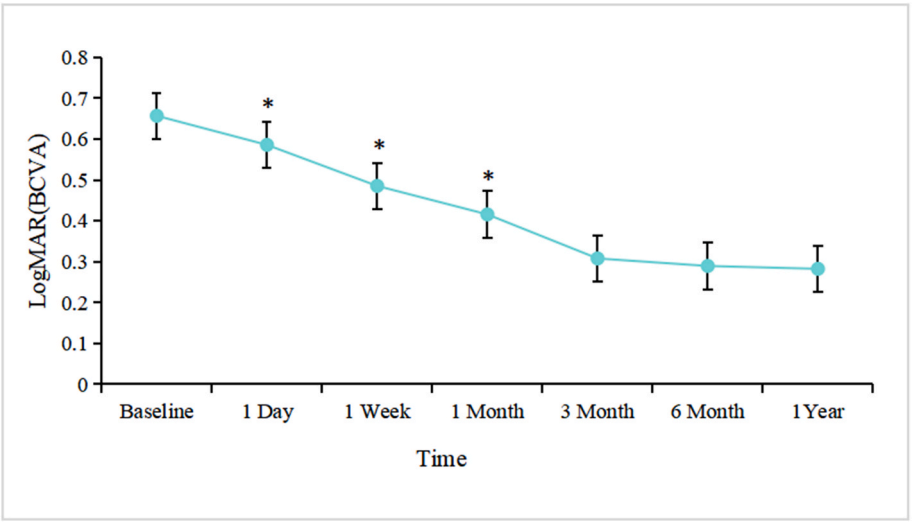

Fig. 4. Mean best-corrected visual acuity (logMAR) at baseline, 1 day, 1 week, 1 month, 3 months, and 6 months after combined intravitreal ranibizumab injections in patients with BRVO-ME (n = 121). * indicates repeated measures ANOVA $P < 0.05$.

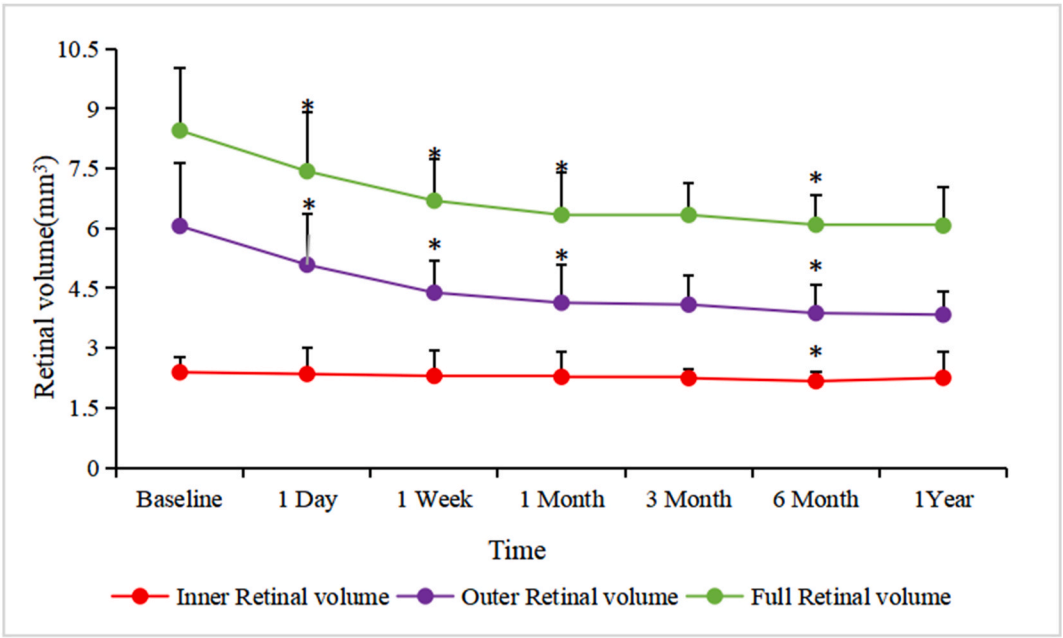

Fig. 5. Mean retinal volume (mm3) at baseline, 1 day, 1 week, 1 month, 3 months, and 6 months after combined intravitreal ranibizumab injections in patients with BRVO-ME (n = 121). * indicates repeated measures ANOVA $P < 0.05$.

volume and CRT changes are unknown. CRT was one of the key indicators of visual prognosis in patients with macular edema secondary to BRVO. What's more, in the present study, with the advancement of OCTA technology, the volume of the retinal macula in the 5 × 5 mm area could more accurately reflect the severity of macular edema. The more retinal volume, the more severe the visual function impairment; the more retinal volume, the more severe the edema [18]. Retinal volume is a three-dimensional index, whereas CRT is a one-dimensional index. Considering that retinal volume responds to visual function with high accuracy and authenticity, it is more useful for predicting postoperative visual acuity in BRVO patients and is helpful for treatment and follow-up in the clinic.

The findings of the statistical analyses were clinically significant and revealed a progressive improvement in the patients' visual acuity during the follow-up period of BRVO treatment with ranibizumab. The anatomical and physiological structure of the retina recovered most quickly within 6 month after treatment, and the retinal edema improved insignificantly thereafter. Moreover, the change in BCVA was different from the change in retinal volume; the BCVA of the patients could only reach its maximum recovery and remain stable at 1 months after treatment, indicating a gradual recovery of the functional role of the retina within 1 months of

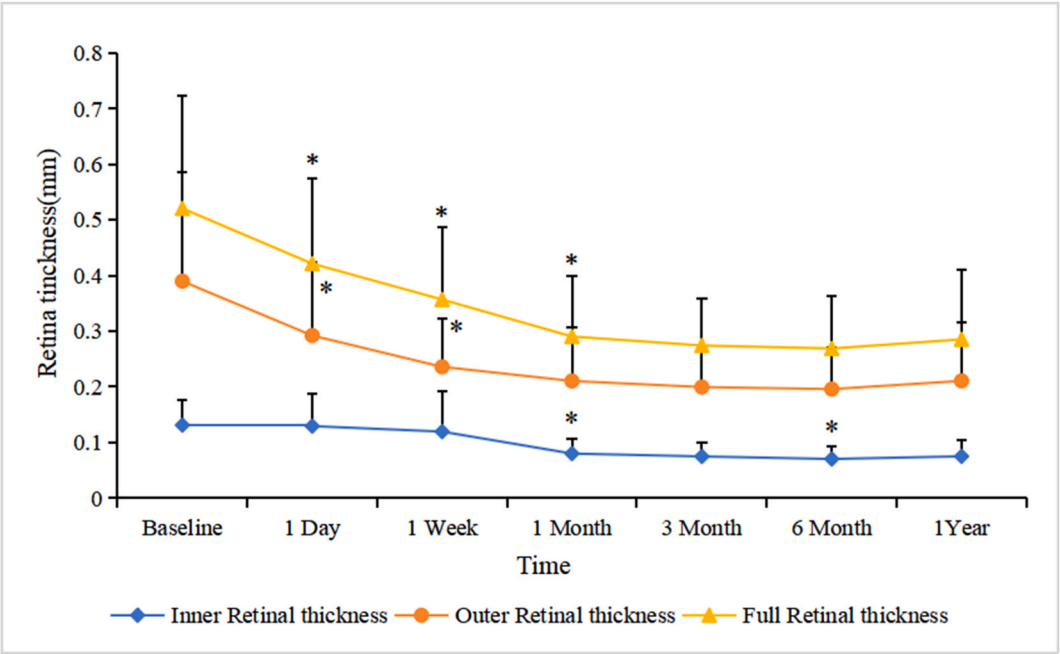

Fig. 6. Mean retinal thickness (mm) at baseline, 1 day, 1 week, 1 month, 3 months, and 6 months after combined intravitreal ranibizumab injections in patients with BRVO-ME (n = 121). * indicates repeated measures ANOVA P < 0.05.

Table 3
Correlation of logMAR(BCVA) with retinal volume and CRT and correlation of full retinal volume with outer retinal volume.

	Follow up time	FRV	FCRT	ORV	OCRT	IRV	ICRT
LogMAR(BCVA)	Baseline	0.394**	0.330**	0.409**	0.289**	−0.058	0.073
	1 day	0.311**	0.222*	0.316**	0.204*	−0.042	0.162
	1 week	0.193*	0.185*	0.242**	0.181*	−0.089	0.163
	1 month	0.038	0.008	0.051	−0.101	−0.09	0.127
	3 month	−0.014	−0.015	0.028	−0.049	0.124	0.041
	6 month	−0.048	0.032	0.042	−0.001	−0.193	0.084
	1 year	0.013	−0.022	0.003	−0.061	−0.065	0.036
FRV	Baseline	1	0.811**	0.970**	0.802**	0.061	0.11
	1 day	1	0.755**	0.915**	0.748**	0.346**	0.513**
	1 week	1	0.658**	0.888**	0.698**	0.477**	0.577**
	1 month	1	0.593**	0.825**	0.478**	0.549**	0.421**
	3 month	1	0.713**	0.962**	0.723**	0.584**	0.637**
	6 month	1	0.660**	0.929**	0.638**	0.595**	0.562**
	1 year	1	0.541**	0.843**	0.493**	0.534**	0.524**

NOTE: IRV: Inner retinal volume; ORV: Outer retinal volume; FRV: Full retinal volume; ICRT: Inner central retinal thickness; OCRT: Outer central retinal thickness; FCRT: Full central retinal thickness. Table shows the Spearman correlation coefficients and p-values (* indicates P < 0.05, ** indicates P < 0.01).

Table 4
Correlation between LOG MAR BCVA(1 Year) and outer retinal volume (at various time points). Table shows the Spearman correlation coefficients.

	ORV	ORV	ORV	ORV	ORV	ORV	ORV
Time	(Baseline)	(1 Day)	(1 Week)	(1 Month)	(3 Month)	(6 Month)	(1 Year)
Spearman index	0.392**	0.254**	0.161	0.057	0.108	0.07	0.078

Note: ORV: Outer retinal volume; p-values (** indicates P < 0.01).

treatment, and the functional role of the retina was slightly restored after the duration of treatment continued to be prolonged (Fig. 4). In conclusion, functional and anatomical recovery of the retina do not occur at the same time, visual recovery occurred mainly during the early treatment period, and there was no significant recovery of vision at 6 months after treatment, although the retinal volume was still decreasing. CRT declined significantly by 1 month of treatment, whereas retinal volume in the 5mm × 5 mm range declined significantly by 6 months of treatment, so it was predominantly the peripheral retinal volume that continued to decline even after 1

month of treatment.

Furthermore, the outer retina was the major location of edema, and the edema diminished the fastest. This was similar to the findings of Moussa et al., who found that reduced vascular density was more pronounced in the deep capillary plexus (DCP) than in the superficial capillary plexus (SCP), suggesting that ischaemic injury in BRVO occurs preferentially in DCP [19]; and Coscas et al., who found that capillary non-perfusion was more common in DCP than in SCP [20]. The reasons for this may be more related to the anatomical differences between the inner and outer retinas. In the inner retina, SCP is directly connected to the small retinal arteries, so even if venous obstruction occurs, its perfusion is less affected. In the outer retina, the DCP was directly connected to the retinal veins, so when venous reflux was blocked, the DCP would be affected in the first instance, and its perfusion would be significantly reduced [21]. Hypoxia in DCP could cause edema in the outer retina, so the outer retina was more severely edematous than the inner retina. In addition, the retinal blood-retina barrier along the venous distribution area was disrupted, various cytokines were released, the canal wall was damaged, and leakage occurred. Fluid leakage in the macula accumulated in the outer plexiform layer of the retina, and cone and rod cell function was greatly disrupted when the retinal vessels were not adequately perfused [22,23]. Ranibizumab improved the patient's vision by reducing macular edema and retinal vascular leakage [24]. As a result, visual acuity can be predicted using the outer retinal volume and the full retinal volume.

Qian T indicated that anti-vegf therapy is significantly better than corticosteroid/laser therapy in improving BCVA [25], that's why it makes sense to study anti-VEGF drugs. However, he did not point out the detailed follow-up changes of retinal thickness and BCVA in patients after treatment with different methods. Therefore, this study provides accurate data and information to determine the comparative follow-up of different treatments on visual acuity and retinal edema in patients with BRVO, and establishes a foundation for further clinical work and research. In addition, the Campochiaro PA study noted that 0.5 mg versus 0.3 mg of ranibizumab was used to treat BRVO patients separately, and a study of CRT and BCVA at 6 months post-treatment in both groups found that 0.5 mg was the most efficacious and most helpful in improving patients' vision [26]. This result is similar to our findings, but Campochiaro PA focused more on the comparison of the drug effect of different drug dosages of ranibizumab, our study used 0.5 mg of ranibizumab treatment with long term follow up of 1 year, and analyzed multiple between points after treatment, and found that visual acuity, CRT, and volume early in the treatment had a large effect on prognostic visual acuity, and also found that the different follow up trends and fluctuations in CRT and volume over time.

Moreover, the correlation between retinal volume and BCVA was greater than the correlation between CRT and BCVA (Table 2). Because there was still a significant decrease in retinal volume after 1 month of treatment and a slow recovery of BCVA, there was also a gradual decrease in the correlation between retinal volume and visual acuity later in treatment.(Figs. 4–6). As a result, studying the link between the volume of the retina and changes in visual acuity is more therapeutically important. In addition, because outer retinal volume had the highest correlation with visual acuity, a comparison of the correlation between BCVA after one year of treatment and outer retinal bodies at each time during follow-up found that baseline outer retinal volume had the highest correlation with BCVA.

This study was innovative because it examined the trend and relationship between changes in retinal volume and CRT and BCVA in patients with BRVO following ranibizumab therapy. Furthermore, limited studies have focused on retinal volume, even though earlier studies have revealed the importance of CRT for prognosis and follow-up [27–29]. Compared to the traditional measurement of retinal thickness, this article accurately evaluated the ocular health status by measuring retinal volume. Through the data analysis of 121 patients, this study found that retinal volume is more representative than retinal thickness. Therefore, retinal volume reflected a more complete and accurate condition of retinal edema and could be used as an important indicator of prognostic follow-up. This measurement method had the potential to become an important tool for future ophthalmic diagnosis and treatment. This study has the following limitations: (1) Imaging cannot detect the boundary of macular edema in patients with severe macular edema and significant changes in volume and thickness; the boundary must be manually changed, and subjective factors that influence experimental data cannot be prevented. (2) Without a comparative study based on different sites or different subtypes, only a generalized analysis of the volume change following treatment for the inner, outer, and full layers of the macular area was carried out. (3) The follow-up time is brief, and the number of patients enrolled is small. Therefore, more research is required on changes in macular volume and their clinical implications in patients receiving anti-VEGF for retinal branch vein occlusion.

5. Conclusions

This study show that visual acuity gradually improved and stabilized at 1 month after treatment; the retinal volume gradually decreased and stabilized at 6 months after treatment; the recovery of visual function was depends more on early treatment; the outer retina was the primary site of edema; and retinal volume changes better mirrored the visual prognosis than the CRT changes; baseline ourter retinal volume is correlated with long-term visual prognosis.

Statement of ethics

This study was approved by the Ethics Committee of Affiliated Hospital of Weifang Medical University, with ethics approval reference [wyfy-2023-ky-140].

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Data availability statement

Data included in article/supplementary material/referenced in article.

CRediT authorship contribution statement

Zhen Xing: Investigation, Formal analysis, Data curation, Conceptualization. **Hong Liu:** Methodology, Funding acquisition, Formal analysis, Data curation. **Yan Sun:** Methodology, Investigation, Data curation. **Yu-peng Zhang:** Funding acquisition, Formal analysis, Data curation, Conceptualization. **Xiu-ming Xing:** Methodology, Investigation, Funding acquisition. **Kai-li Yang:** Project administration, Methodology, Investigation. **Jun Zhao:** Writing – original draft, Software. **Shu-na Wang:** Writing – original draft, Visualization, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35406.

References

[1] Y. Sakanishi, K. Tamaki, K. Mashimo, T. Sakuma, N. Ebihara, Relationship between recurrence of macular edema due to branch retinal vein occlusion and changes in choroidal thickness, Ophthalmic Res. 64 (3) (2021) 363–368, https://doi.org/10.1159/000512357.
[2] C.S. Yang, J.H. Liu, Y.C. Chung, Y.B. Chou, K.H. Hung, Combination therapy with intravitreal bevacizumab and macular grid and scatter laser photocoagulation in patients with macular edema secondary to branch retinal vein occlusion, J Ocul Pharmacol Ther 31 (3) (2015) 179–185, https://doi.org/10.1089/jop.2014.0069.
[3] R. Shi, Z. Guo, X. Yang, X. Che, Aggravation of retinal hard exudates after intravitreal anti-vascular endothelial growth factor therapy for cystoid macular edema and the risk factors: a retrospective study, BMC Ophthalmol. 22 (1) (2022) 92, https://doi.org/10.1186/s12886-022-02315-z.
[4] I.U. Scott, P.C. Van Veldhuisen, N.L. Oden, M.S. Ip, B.A. Blodi, M.E. Hartnett, G. Cohen, Baseline predictors of visual acuity and retinal thickness outcomes in patients with retinal vein occlusion: standard Care versus COrticosteroid for REtinal Vein Occlusion Study report 10, Ophthalmology 118 (2) (2011) 345–352, https://doi.org/10.1016/j.ophtha.2010.06.034.
[5] J.T. Kim, Y.S. Chun, J.K. Lee, N.J. Moon, D.Y. Yi, Comparison of vessel density reduction in the deep and superficial capillary plexuses in branch retinal vein occlusion, Ophthalmologica 243 (1) (2020) 66–74, https://doi.org/10.1159/000502385.
[6] X. Ding, Y. Wang, B. Zou, D. Zang, Y. Hao, Effect of conbercept treatment on macular edema and microvascular structure in eyes with retinal vein occlusions, Int. J. Gen. Med. (2022) 7311–7318. https://doi:10.2147/IJGM.S373015.
[7] M.E. Thomley, C.N. Gross, A. Preda-Naumescu, K.S. Chen, T. Swain, Iii JO. Mason, J.N. Crosson, Real-world outcomes in patients with branch retinal vein occlusion- (BRVO-) related macular edema treated with anti-VEGF injections alone versus anti-VEGF injections combined with focal laser, J Ophthalmol 2021 (2021) 6641008, https://doi.org/10.1155/2021/6641008.
[8] Y.J. Choi, D. Jee, J.W. Kwon, Characteristics of major and macular branch retinal vein occlusion, Sci. Rep. 12 (1) (2022) 14103, https://doi.org/10.1038/s41598-022-18414-2.
[9] G. Ryu, D. Park, J. Lim, J. van Hemert, M. Sagong, Macular microvascular changes and their correlation with peripheral nonperfusion in branch retinal vein occlusion, Am. J. Ophthalmol. 225 (2021) 57–68, https://doi.org/10.1016/j.ajo.2020.12.026.
[10] W. Tang, J. Guo, X. Zhuang, T. Zhang, L. Wang, K. Wang, Q. Chang, W. Liu, G. Xu, Wide-field swept-source optical coherence tomography angiography analysis of the periarterial capillary-free zone in branch retinal vein occlusion, Transl Vis Sci Technol 10 (2) (2021) 9, https://doi.org/10.1167/tvst.10.2.9.
[11] J. Ahn, D.D. Hwang, Peripapillary retinal nerve fiber layer thickness in patients with unilateral retinal vein occlusion, Sci. Rep. 11 (1) (2021) 18115, https://doi.org/10.1038/s41598-021-97693-7.
[12] Y. Sakanishi, S. Morita, K. Mashimo, K. Tamaki, N. Ebihara, Subfoveal choroidal thickness and treatment outcomes of intravitreal aflibercept for branch retinal vein occlusion, Life 11 (6) (2021) 572, https://doi.org/10.3390/life11060572.
[13] A. Arrigo, F. Bandello, Retinal vein occlusion: drug targets and therapeutic implications, Expert Opin. Ther. Targets 25 (10) (2021) 847–864, https://doi.org/10.1080/14728222.2021.2005026.
[14] S. Morikawa, F. Okamoto, T. Murakami, Y. Sugiura, T. Hiraoka, T. Oshika, Aniseikonia following intravitreal ranibizumab treatment for branch retinal vein occlusion, Jpn. J. Ophthalmol. 65 (5) (2021) 672–679, https://doi.org/10.1007/s10384-021-00852-6.
[15] D. Nagasato, Y. Muraoka, M. Tanabe, N. Nishigori, R. Osaka, Y. Mitamura, H. Tabuchi, S. Kadomoto, T. Murakami, S. Ooto, K. Suzuma, A. Tsujikawa, Foveal thickness fluctuation in anti-VEGF treatment for branch retinal vein occlusion: a long-term study, Ophthalmol Retina 6 (7) (2022) 567–574, https://doi.org/10.1016/j.oret.2022.02.008.
[16] A.X. Chen, T.E. Greenlee, T.F. Conti, I.N. Briskin, R.P. Singh, Fluctuations in macular thickness in patients with retinal vein occlusion treated with anti-vascular endothelial growth factor agents, Ophthalmol Retina 4 (12) (2020) 1158–1169, https://doi.org/10.1016/j.oret.2020.05.018.
[17] H. Sasajima, M. Zako, Y. Ueta, H. Tate, C. Otaki, K. Murotani, T. Suzuki, H. Ishida, Y. Hashimoto, N. Tachi, Direct photocoagulation for treating microaneurysms with hyperreflective ring in eyes with refractory macular edema associated with branch retinal vein occlusion, J. Clin. Med. 11 (3) (2022) 823, https://doi.org/10.3390/jcm11030823.
[18] H.F. Qin, F.J. Shi, C.Y. Zhang, D.W. Luo, S.Y. Qin, J. Wu, H. Xie, J.T. Zhang, Q.H. Qiu, K. Liu, G.T. Xu, G.X. Xu, J.F. Zhang, Anti-VEGF reduces inflammatory features in macular edema secondary to retinal vein occlusion, Int. J. Ophthalmol. 15 (8) (2022) 1296–1304, https://doi.org/10.18240/ijo.2022.08.11.
[19] M. Moussa, M. Leila, A.S. Bessa, M. Lolah, M. Abou Shousha, H.M. El Hennawi, T.A. Hafez, Grading of macular perfusion in retinal vein occlusion using en-face swept-source optical coherence tomography angiography: a retrospective observational case series, BMC Ophthalmol. 19 (1) (2019) 127, https://doi.org/10.1186/s12886-019-1134-x.
[20] F. Coscas, A. Glacet-Bernard, A. Miere, V. Caillaux, J. Uzzan, M. Lupidi, G. Coscas, E.H. Souied, Optical coherence tomography angiography in retinal vein occlusion: evaluation of superficial and deep capillary plexa, Am. J. Ophthalmol. 161 (2016) 160–171, https://doi.org/10.1016/j.ajo.2015.10.008.

[21] X. Chen, E. Rahimy, R.C. Sergott, R.P. Nunes, E.C. Souza, N. Choudhry, N.E. Cutler, S.K. Houston, M.R. Munk, A.A. Fawzi, S. Mehta, J.P. Hubschman, A.C. Ho, D. Sarraf, Spectrum of retinal vascular diseases associated with paracentral acute middle maculopathy, Am J Ophthalmol. Jul 160 (1) (2015) 26–34, https://doi.org/10.1016/j.ajo.2015.04.004.

[22] L. Chen, M. Yuan, L. Sun, Y. Wang, Y. Chen, Evaluation of microvascular network with optical coherence tomography angiography (OCTA) in branch retinal vein occlusion (BRVO), BMC Ophthalmol. 20 (1) (2020) 154, https://doi.org/10.1186/s12886-020-01405-0.

[23] J.H. Jang, Y.C. Kim, J.P. Shin, Correlation between macular edema recurrence and macular capillary network destruction in branch retinal vein occlusion, BMC Ophthalmol. 20 (1) (2020) 341, https://doi.org/10.1186/s12886-020-01611-w.

[24] C.A. Rodríguez-Fernández, A. Campo-Gesto, A. López-López, M. Gayoso-Rey, Real-world evidence for treat-and-extend regimen of ranibizumab therapy for macular oedema secondary to branch retinal vein occlusion, Pharmaceuticals 15 (1) (2022) 59, https://doi.org/10.3390/ph15010059.

[25] T. Qian, M. Zhao, X. Xu, Comparison between anti-VEGF therapy and corticosteroid or laser therapy for macular oedema secondary to retinal vein occlusion: a meta-analysis, J Clin Pharm Ther. 42 (5) (2017) 519–529. https://doi:10.1111/jcpt.12551.

[26] P.A. Campochiaro, J.S. Heier, L. Feiner, S. Gray, N. Saroj, A.C. Rundle, W.Y. Murahashi, R.G. Rubio, Investigators Bravo, Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study, Ophthalmology 117 (6) (2010) 1102–1112.e1. https://doi:10.1016/j.ophtha.2010.02.021.

[27] J.Y. Bai, W.Y. Wang, Z.Z. Dou, B.C. Geng, X.Y. Xu, Y.Z. Zhu, S.Y. Zhao, M. Liu, S.Y. Jia, W.J. Luo, Efficacy of intravitreal conbercept injection on short- and long-term macular edema in branch retinal vein occlusion, Int. J. Ophthalmol. 15 (3) (2022) 489–494, https://doi.org/10.18240/ijo.2022.03.18.

[28] S.Z. Gu, O. Nanegrungsunk, S.B. Bressler, W. Du, F. Amer, H. Moini, N.M. Bressler, Correlation between change in central subfield thickness and change in visual acuity in macular edema due to retinal vein occlusion: post hoc analysis of COPERNICUS, GALILEO, and VIBRANT, Graefes Arch. Clin. Exp. Ophthalmol. 260 (12) (2022) 3799–3807, https://doi.org/10.1007/s00417-022-05697-4.

[29] U. Limon, B.I. Sezgin Akçay, Add-on effect of simultaneous intravitreal dexamethasone to intravitreal bevacizumab in patients with macular edema secondary to branch retinal vein occlusion, J Ocul Pharmacol Ther 38 (2) (2022) 183–188, https://doi.org/10.1089/jop.2021.0100.