

# Relationship between Recurrence of Macular Edema Due to Branch Retinal Vein Occlusion and Changes in Choroidal Thickness

Yoshihito Sakanishi Kazunori Tamaki Keitaro Mashimo Toshiro Sakuma  
Nobuyuki Ebihara

Department of Ophthalmology, Juntendo University Urayasu Hospital, Urayasu City, Japan

## Keywords

Branch retinal vein occlusion · Choroid · Macular edema

## Abstract

**Introduction:** The role of vascular endothelial growth factor in macular edema (ME) due to branch retinal vein occlusion (BRVO) by enhancing vascular permeability has been well studied. ME due to BRVO often recurs; however, there has been no report on the relationship between this recurrence and choroidal thickness (CT), considering the high vascularity of the choroid. This study was designed to investigate this relationship. **Methods:** In this retrospective consecutive case series, patients with recurrence of ME within 6 months of receiving intravitreal aflibercept injection treatment for naive ME due to BRVO at Juntendo University Urayasu Hospital were included. Retinal thickness (RT) and CT were measured in the fovea and on the occlusion, non-occlusion, nasal, and temporal sides at baseline, after the first intravitreal aflibercept administration, and before and after recurrence. We also examined the change for each side before and after reinjection. **Results:** This study included 11 patients and 11 eyes. The subfoveal CT and RT at baseline were  $261.9 \pm 93.4 \mu\text{m}$  and  $691.5 \pm 254.4 \mu\text{m}$ , respectively, which significantly decreased to  $208.5 \pm 70.3 \mu\text{m}$  and  $188.6 \pm 33.8 \mu\text{m}$ , respectively, at 1 month after the first injection ( $p = 0.001$  and  $p < 0.01$ , respectively). These values also significantly decreased

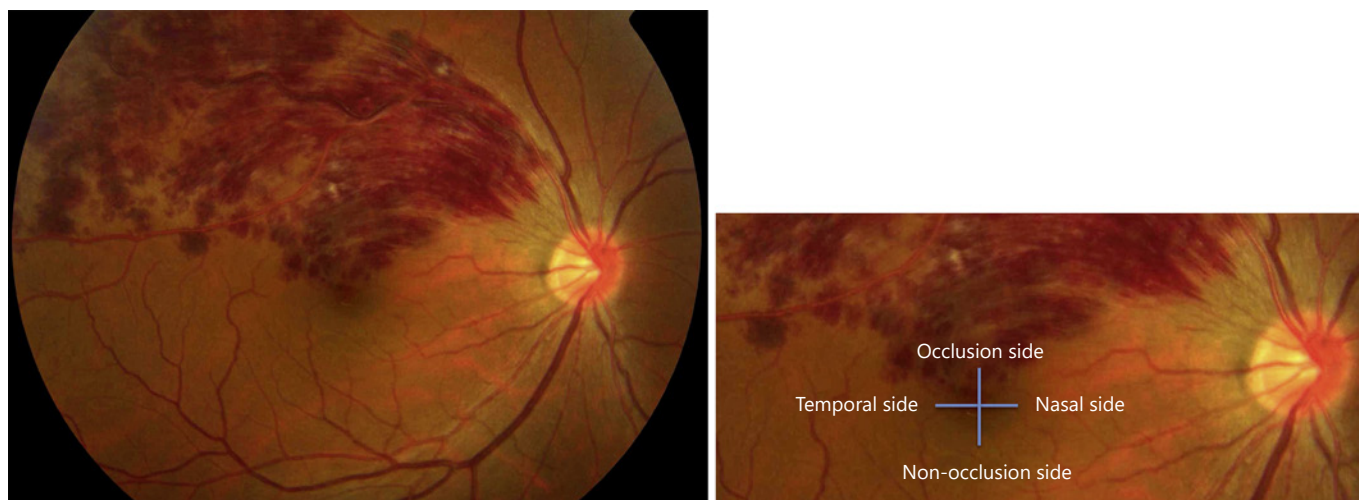
at all the other sites after treatment. There were 14 recurrences within the 6 months following intravitreal aflibercept injection; RT significantly changed at all sites before and after recurrence and reinjection. CT significantly changed at the subfovea and on the occlusion and non-occlusion sides; however, there was no significant change on the nasal and temporal sides. **Conclusion:** In patients with BRVO, the CT around the macula after initial treatment was significantly reduced; however, at the time of ME recurrence and reinjection, there were site-dependent differences in the changes observed in the CT. These findings suggest that the pathologies of ME at initial occurrence and at the time of recurrence are different.

© 2020 The Author(s).

Published by S. Karger AG, Basel

## Introduction

Retinal vein occlusion (RVO) is a disease involving vascular occlusion due to turbulence in venous blood and is classified as central, hemi-central, and branch RVO. Branch retinal vein occlusion (BRVO) is a major retinal vascular disease and is caused by venous thrombosis at the arteriovenous crossing points [1–3]. BRVO causes macular edema (ME) and visual impairment. Thrombosis of the retinal vein leads to increase in the retinal capillary pressure, resulting in increased capillary permeability and leak-



**Fig. 1.** BRVO in the fundus. Right: photo showing BRVO in the fundus. Left: photo enlarged near the macula. In this case, BRVO occurred at the upper side of the retina; thus, the upper side was defined as the occlusion side. RT and CT were measured at a distance of 500  $\mu\text{m}$  from the fovea. BRVO, branch retinal vein occlusion; RT, retinal thickness; CT, choroidal thickness.

age of fluid and blood into the retina. Additionally, retinal ischemia can exacerbate this process by the production of vascular endothelial growth factor (VEGF), which promotes retinal capillary permeability and leakage in the extracellular space, aggravating ME [4]. The current standard treatment for BRVO-ME is the administration of anti-VEGF drugs, which has reportedly good outcomes [5–13]. However, ME often recurs, and there are many cases in which the anti-VEGF drugs are required multiple times.

While ME represents the changes in retinal thickness (RT), some studies have reported on the relationship between BRVO-ME and changes in the choroidal thickness (CT) [14, 15]. However, studies assessing these changes during the recurrence of ME, after successful treatment with anti-VEGF have not been reported. Hence, we examined the relationship between ME recurrence and changes in CT.

## Materials and Methods

This was a retrospective study using data from patients who received intravitreal injection of aflibercept (IVA) at Juntendo University Urayasu Hospital from January 2017 to October 2018 for the treatment of either naive BRVO-ME within 6 months from onset or recurrent ME within 6 months after treatment initiation. Measurement at recurrence refers to all recurrences within a period of time, not the first recurrence only. IVA was administered once during the induction period; thereafter, reinjection was performed as needed during medical examinations performed once a month. The criterion for reinjection was prolonged ME or recur-

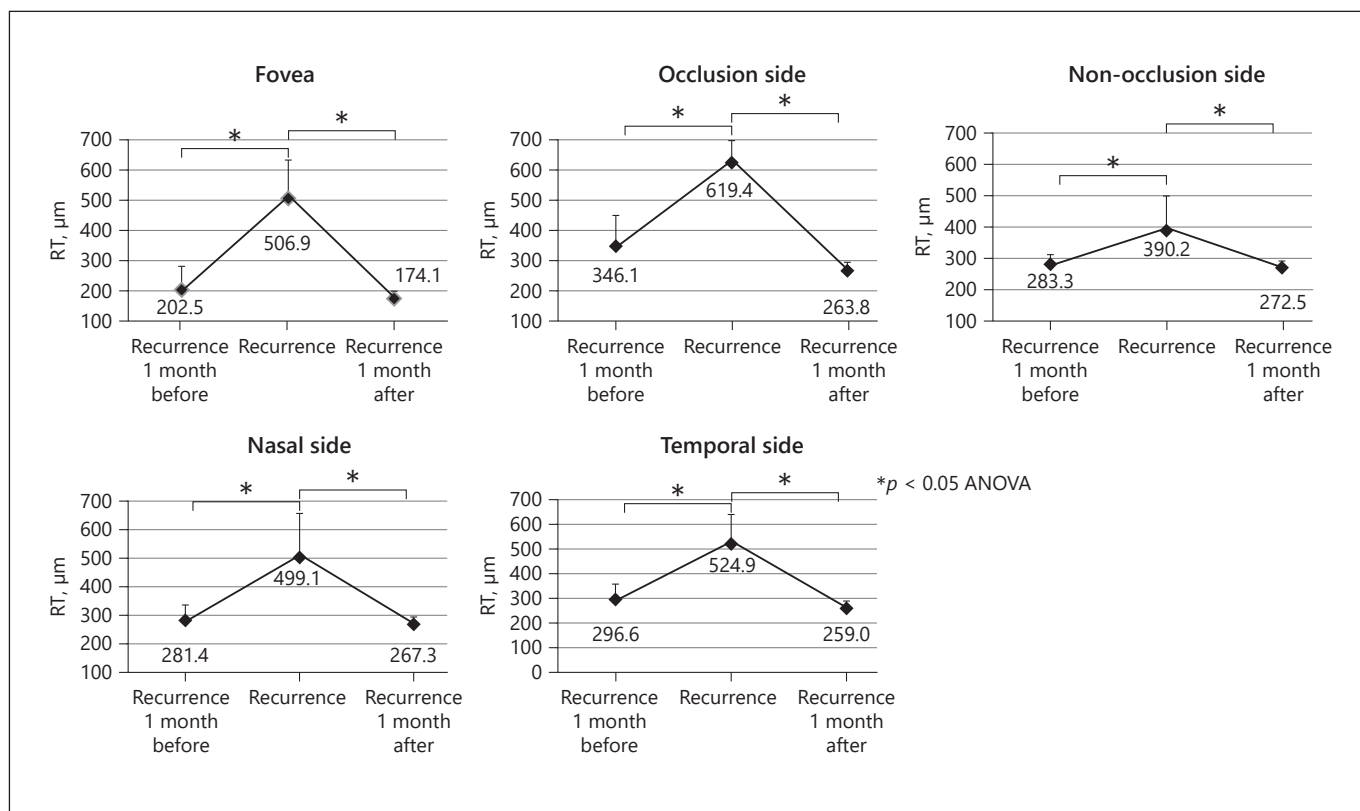
rence of foveal RT measuring  $>300 \mu\text{m}$ . The exclusion criteria included a history of internal eye surgery, history of retinal photocoagulation, myopia of at least  $-6 \text{ D}$ , choroidal excavation, and other diseases of the fundus, including diabetic retinopathy.

In our cohort, RT was measured using Cirrus high-definition optical coherence tomography (Carl Zeiss Meditec AG, Jena, Germany), while CT was measured with a 5-line high-definition enhanced depth image mode. The measurements taken via optical coherence tomography were all obtained at any time between 14:00 and 16:00 to reduce the effects of choroidal diurnal variation [16, 17]. RT and CT were measured at the fovea and at defined points 500  $\mu\text{m}$  from the fovea in the occlusion, non-occlusion, nasal, and temporal sides (Fig. 1). The measurements were recorded before and after the first IVA, before and after the recurrence of ME, and after reinjection. RT was measured as the distance between the surface of the internal limiting membrane and the inner border of the retinal pigment epithelium, and CT was the distance from the outer border of the retinal pigment epithelium to the inner border of the sclera. The visual acuity was measured using a Landolt chart, and it was converted to the logarithm of the minimal angle of resolution.

The Institutional Review Board of Juntendo University Urayasu Hospital approved this study (reference number 2014-047). The procedures used in this study conformed to the tenets of the Declaration of Helsinki. All participants provided written informed consent for inclusion in this study.

## Analysis

The data were analyzed using GraphPad Prism 7. Changes in CT and RT at baseline and 1 month after the first injection were examined using the Wilcoxon signed-rank test, while changes in thickness before recurrence, at the time of recurrence, and after reinjection were examined using repeated measure ANOVA and Dunnett's test of multiple comparisons.  $p$  values  $<0.05$  were considered statistically significant.



**Fig. 2.** Changes in RT before and after ME recurrence and before and after reinjection ( $n = 14$ ). RT significantly increased upon recurrence of ME and significantly decreased after reinjection at all sites. RT, retinal thickness; ME, macular edema; CRT, central retinal thickness.

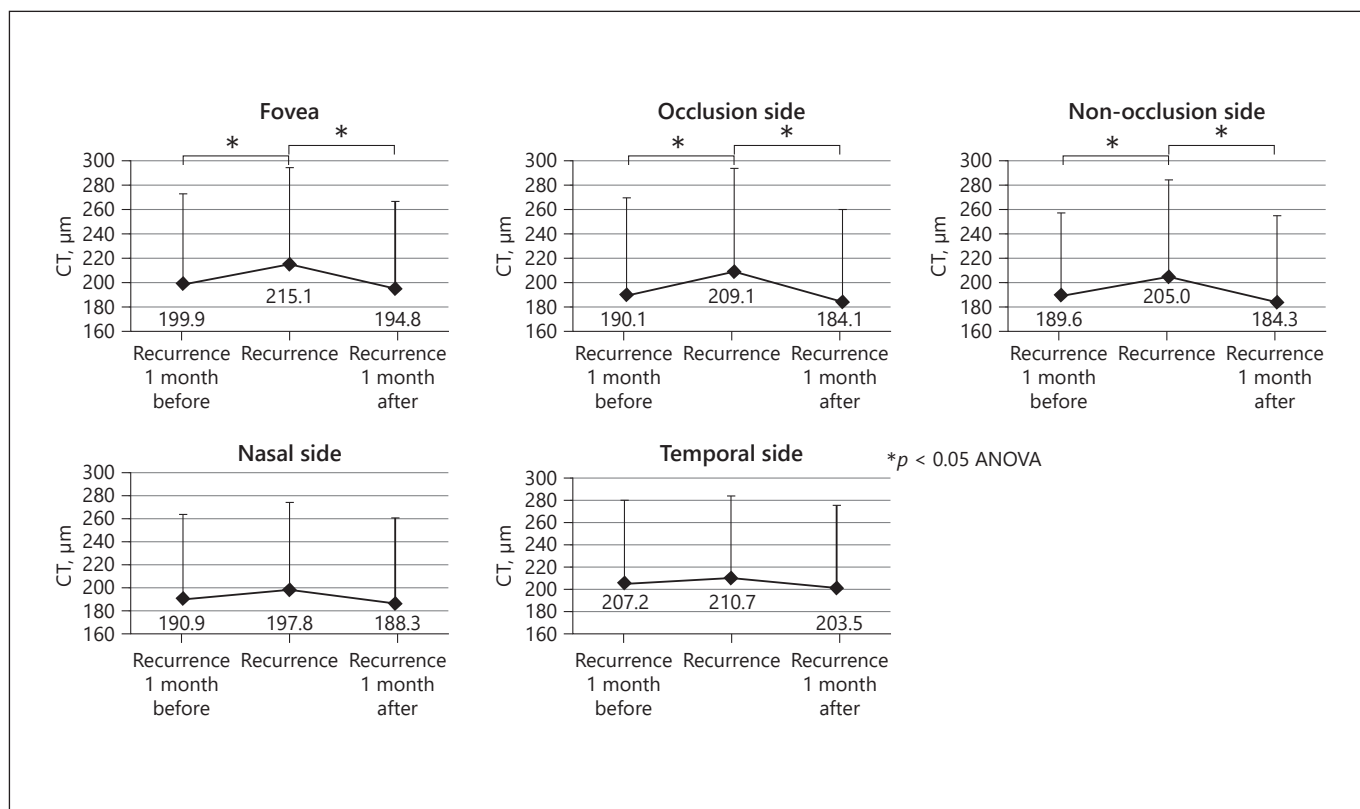
## Results

Overall, 11 cases with 11 eyes were included; the patients' medical histories at baseline are shown in Table 1. Table 2 shows the changes in RT and CT at each site before and after the first injection. Both CT and RT were significantly reduced at 1 month after the first injection compared with those at baseline for all sites, including the fovea. Recurrences during the 6-month study period occurred once in 8 cases and twice in 3 cases. Figure 2 shows the changes in RT before and after the 14 recurrences and after reinjection at the time of recurrences. RT significantly increased after recurrence and decreased significantly after reinjection following recurrence. Conversely, for CT, although there was significant thickening at the time of recurrence and thinning after reinjection in the subfoveal choroid area and the occlusion and non-occlusion sides, there were no significant changes in recurrence and reinjection on the nasal and temporal sides (Fig. 3).

## Discussion

In this study, we showed that IVA treatment for BRVO-ME led to choroidal thickening and re-thinning as a result of ME recurrence and reinjection, respectively. Although studies have reported on the relationship between BRVO-ME and the choroid, to the best of our knowledge, there have been no reports on the relationship between ME recurrence and CT.

Lee et al. [14] reported that subfoveal CT is significantly increased in the eye with RVO than in the fellow eye; we also observed similar changes at baseline although CT was not compared with that in the fellow eye in all directions at baseline. Nevertheless, after the first injection, the choroid was thinner in all directions. Thus, we believe that the choroid may have thickened at any point 500  $\mu\text{m}$  from the fovea. It is believed that choroidal thickening in RVO is caused by choroidal vascular hyperpermeability due to the increase in intraocular VEGF [18], and it was reported that an increase in the level of VEGF



**Fig. 3.** Changes in CT before and after ME recurrence and before and after reinjection ( $n = 14$ ). CT significantly increased upon recurrence of ME and significantly decreased following reinjection at the fovea and occlusion and non-occlusion sides. There were no significant changes in CT of the nasal and temporal sides upon recurrence of ME and after reinjection. CT, choroidal thickness; ME, macular edema; SFCT, subfoveal choroidal thickness.

**Table 1.** Clinical and demographic characteristics at baseline

	N = 11
Sex (men)	6 (54.5%)
Age, years	66.3±9.8
Hypertension presence/absence	8/3
Dyslipidemia presence/absence	3/8
Duration from BRVO onset, months	2.1±1.7
Visual acuity (logMAR)	0.52±0.24
CRT, μm	691.5±254.4
BRVO type major/macular	11/0
SFCT of the affected eye, μm	261.9±93.4

Data are either presented as numbers and proportions or means ± standard deviations. BRVO, branch retinal vein occlusion; logMAR, logarithm of the minimal angle of resolution; CRT, central retinal thickness; SFCT, subfoveal choroidal thickness.

**Table 2.** Changes in the RT and CT before and after the first IVA

	Baseline	1 month after the first injection	p value
<i>RT</i>			
CRT	691.5±254.4	188.6±33.8	<0.001
Occlusion side	769.6±170.9	303.2±50.0	<0.001
Non-occlusion side	593.9±272.8	277.3±21.8	<0.001
Nasal side	644.4±256.4	275.5±40.2	<0.001
Temporal side	704.8±182.5	274.4±21.4	<0.001
<i>CT</i>			
SFCT	249.8±72.9	208.5±70.3	0.001
Occlusion side	259.5±74.8	202.5±76.7	0.001
Non-occlusion side	233.4±74.5	201.9±69.5	0.005
Nasal side	232.0±71.2	201.2±67.0	0.005
Temporal side	241.1±75.9	205.4±60.9	0.003

Data are presented as means ± standard deviations. RT, retinal thickness; CT, choroidal thickness; IVA, intravitreal injection of aflibercept; CRT, central retinal thickness; SFCT, subfoveal choroidal thickness.

may increase the production of nitric oxide, which may also induce choroidal thickening [19]. The increase in intraocular VEGF will determine the timing of edema recurrence and may result in increased CT. In a previous study, it was reported that cases with an increased CT in the affected eye at baseline had a greater response to VEGF treatment [20]. In this study, all cases responded to treatment, and the baseline choroids of affected eyes were thicker than those of the fellow eyes. In cases where the choroid is not thickened at baseline, ME may be caused by other factors such as microaneurysm rather than the increase in VEGF. According to a report by Hasegawa et al. [20], in cases where the choroid was not thickened, improvement of edema was achieved by performing photocoagulation on microaneurysms detected on fluorescein angiography [19]. In this study, there were no cases with microaneurysm at baseline because BRVO was targeted during the acute phase. In the future, it may be necessary to examine changes in CT in cases with first treatment for long standing BRVO or cases in which ME has recurred many times.

The anti-VEGF drug used in this study was aflibercept; however, ranibizumab is another commonly used anti-VEGF drug. There are controversial findings on the effectiveness of intravitreal injection of ranibizumab in age-related macular degeneration (AMD), with some reporting significant reduction in CT following treatment [21, 22], and others reporting no significant effect [23, 24]. On the other hand, IVA treatment of AMD has been effective in thinning the choroid [25], suggesting that the effect on the choroid might differ depending on the type of anti-VEGF drug administered. Kaya et al. [26] have reported that the intravitreal injection of either aflibercept or ranibizumab decreases CT in patients with AMD, with more prominent results observed in those who received IVA.

At the time of recurrence and reinjection, significant changes were observed in the fovea and the occlusion and non-occlusion sides of the choroid but not on the nasal and temporal sides. This might have resulted from site specific differences in reactivity to VEGF or existing differences in the levels of VEGF concentrations in each of these areas. Nevertheless, a decrease in CT occurred at all sites after the first injection. Despite this observation, in cases with recurrent ME, choroidal change is site dependent, probably due to a difference in the pathogenesis of ME in treatment-naive and recurrent cases.

This study had several limitations that merit mentioning. This was a retrospective study that included a small number of enrolled patients; however, the enrolled patients were managed with a strict regimen. Thus, the

small sample size did not seem to affect the study results. Future studies should aim to enroll a larger number of patients to validate our findings. Additionally, in this study, we did not determine the number of recurrences per patient, which may have affected the outcomes. Moreover, the research period was short (i.e., 6 months), which may have further impacted our findings.

## Conclusion

In BRVO, CT around the macula changed with recurrence and improvements in ME. However, there were differences depending on the site. These findings may suggest a difference in the pathology of ME at initial occurrence and recurrent stages. Further studies on the reactivity of the choroid to IVA treatment may aid in assessing the response to treatment in patients with BRVO. It may also provide a deeper understanding of the pathological causes for primary and secondary ME.

## Acknowledgement

We would like to thank Editage ([www.editage.com](http://www.editage.com)) for English language editing.

## Statement of Ethics

The Institutional Review Board of Juntendo University Urayasu Hospital approved this study (reference number 2014-047). The procedures used in this study conformed to the tenets of the Declaration of Helsinki. All participants provided written informed consent for inclusion in this study.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

## Funding Sources

The authors did not receive any funding.

## Author Contributions

All authors take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Y.S. Contribution to scientific experiments: Y.S., K.T., and K.M. Drafting of the manuscript: Y.S. Critical revision of the manuscript for important intellectual content: T.S. and N.E.

## References

- 1 Hayreh SS. Ocular vascular occlusive disorders: natural history of visual outcome. *Prog Retin Eye Res.* 2014 Jul;41:1–25.
- 2 Rogers SL, McIntosh RL, Lim L, Mitchell P, Cheung N, Kowalski JW, et al. Natural history of branch retinal vein occlusion: an evidence-based systematic review. *Ophthalmology.* 2010 Jun;117(6):1094–e5.
- 3 Wong TY, Scott IU. Clinical practice. Retinal vein occlusion. *N Engl J Med.* 2010 Nov;363(22):2135–44.
- 4 The Royal College of Ophthalmologists. Clinical guidelines: retinal vein occlusion (RVO) guidelines. 2015 Jul
- 5 Campochiaro PA, Hafiz G, Shah SM, Nguyen QD, Ying H, Do DV, et al. Ranibizumab for macular edema due to retinal vein occlusions: implication of VEGF as a critical stimulator. *Mol Ther.* 2008 Apr;16(4):791–9.
- 6 Argon laser photocoagulation for macular edema in branch vein occlusion. The Branch Vein Occlusion Study Group. *Am J Ophthalmol.* 1984 Sep;98(3):271–82.
- 7 Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. *Ophthalmology.* 2011 Oct;118(10):2041–9.
- 8 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 Aug;118(8):1594–602.
- 9 Nghiem-Buffer S, Fajnkuchen F, Buffet M, Ayrault S, Le Gloahec-Lorcy A, Grenet T, et al. Intravitreal ranibizumab and/or dexamethasone implant for macular edema secondary to retinal vein occlusion. *Ophthalmologica.* 2014 Nov;232(4):216–22.
- 10 Brynskov T, Kemp H, Sørensen TL. Intravitreal ranibizumab for retinal vein occlusion through 1 year in clinical practice. *Retina.* 2014 Aug;34(8):1637–43.–
- 11 Tan MH, McAllister IL, Gillies ME, Verma N, Banerjee G, Smithies LA, et al. Randomized controlled trial of intravitreal ranibizumab versus standard grid laser for macular edema following branch retinal vein occlusion. *Am J Ophthalmol.* 2014 Jan;157(1):237–e1.
- 12 Berger AR, Cruess AF, Altomare F, Chaudhary V, Colleaux K, Greve M, et al. Optimal treatment of retinal vein occlusion: Canadian expert consensus. *Ophthalmologica.* 2015 Jun;234(1):6–25.
- 13 Sakanishi Y, Lee A, Usui-Ouchi A, Ito R, Ebihara N. Twelve-month outcomes in patients with retinal vein occlusion treated with low-frequency intravitreal ranibizumab. *Clin Ophthalmol.* 2016 Jun;10:1161–5.
- 14 Kim KH, Lee DH, Lee JJ, Park SW, Byon IS, Lee JE. Regional choroidal thickness changes in branch retinal vein occlusion with macular edema. *Ophthalmologica.* 2015 Aug;234(2):109–18.
- 15 Lee EK, Han JM, Hyon JY, Yu HG. Changes in choroidal thickness after intravitreal dexamethasone implant injection in retinal vein occlusion. *Br J Ophthalmol.* 2015 Nov;99(11):1543–9.
- 16 Brown JS, Flitcroft DI, Ying GS, Francis EL, Schmid GF, Quinn GE, et al. In vivo human choroidal thickness measurements: evidence for diurnal fluctuations. *Invest Ophthalmol Vis Sci.* 2009 Jan;50(1):5–12.
- 17 Tan CS, Ouyang Y, Ruiz H, Sadda SR. Diurnal variation of choroidal thickness in normal, healthy subjects measured by spectral domain optical coherence tomography. *Invest Ophthalmol Vis Sci.* 2012 Jan;53(1):261–6.
- 18 Tsuiki E, Suzuma K, Ueki R, Maekawa Y, Kitaoka T. Enhanced depth imaging optical coherence tomography of the choroid in central retinal vein occlusion. *Am J Ophthalmol.* 2013 Sep;156(3):543–e1.
- 19 Mrejen S, Spaide RF. Optical coherence tomography: imaging of the choroid and beyond. *Surv Ophthalmol.* 2013 Aug;58(5):387–429.
- 20 Hasegawa T, Kawano T, Maruko I, Koizumi H, Iida T. Clinical findings of eyes with macular edema associated with branch retinal vein occlusion refractory to ranibizumab. *Retina.* 2018 Jul;38(7):1347–53.
- 21 Yamazaki T, Koizumi H, Yamagishi T, Kinoshita S. Subfoveal choroidal thickness after ranibizumab therapy for neovascular age-related macular degeneration: 12-month results. *Ophthalmology.* 2012 Aug;119(8):1621–7.
- 22 Kang HM, Kwon HJ, Yi JH, Lee CS, Lee SC. Subfoveal choroidal thickness as a potential predictor of visual outcome and treatment response after intravitreal ranibizumab injections for typical exudative age-related macular degeneration. *Am J Ophthalmol.* 2014 May;157(5):1013–21.
- 23 Ellabban AA, Tsujikawa A, Ogino K, Ooto S, Yamashiro K, Oishi A, et al. Choroidal thickness after intravitreal ranibizumab injections for choroidal neovascularization. *Clin Ophthalmol.* 2012 May;6:837–44.
- 24 Ogasawara M, Maruko I, Sugano Y, Ojima A, Sekiryu T, Iida T. [Retinal and choroidal thickness changes following intravitreal ranibizumab injection for exudative age-related macular degeneration]. *Nippon Ganka Gakkai Zasshi.* 2012 Jul;116(7):643–9.
- 25 Koizumi H, Kano M, Yamamoto A, Saito M, Maruko I, Sekiryu T, et al. Subfoveal choroidal thickness during aflibercept therapy for neovascular age-related macular degeneration: twelve-month results. *Ophthalmology.* 2016 Mar;123(3):617–24.
- 26 Kaya F. Change in choroidal thickness after intravitreal injection for treatment of neovascular age-related macular degeneration: ranibizumab versus aflibercept. *J Fr Ophthalmol.* 2017 Dec;40(10):832–8.