Predicting the visual acuity for retinal vein occlusion after ranibizumab therapy with an original ranking for macular microstructure

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Abstract. The study investigated predictive factors for best-corrected visual acuity (BCVA) after ranibizumab treatment in patients with macular edema (ME) associated with retinal vein occlusion (RVO) with an original ranking for the impairment of macular microstructure. In this retrospective study, 31 eyes of 31 patients with RVO received 3 monthly consecutive ranibizumab injections and another 3 months of follow-up. An original method was applied to rank the impairment of the external limiting membrane (ELM) and the ellipsoid zone (previously called the photoreceptor inner and outer segment junction, IS/OS) integrity on the baseline optical coherence tomography (OCT) images. Univariate and multivariate linear regression analyses were performed to assess the association between the baseline factors and post-treatment BCVA. ELM integrity and baseline BCVA were shown to be independent factors in the prediction of post-treatment BCVA. Comparison of post-treatment BCVA between original ELM ranks after adjusting for the baseline BCVA revealed the ELM integrity beneath the center of the fovea was important to post-treatment BCVA. ELM integrity in particular beneath the center of the fovea and baseline BCVA may be more useful than other factors in the prediction of visual function in patients with ME secondary to RVO after ranibizumab injections.

Introduction

Retinal vein occlusion (RVO) is one of most common vision-threatening retinal vascular diseases and can be divided

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into two primary categories: i) Central retinal vein occlusion (CRVO) and ii) branch retinal vein occlusion (BRVO) (1). Previous studies have confirmed that the increased expression of angiogenic growth factors such as vascular endothelial cell growth factor (VEGF) caused by hypoxia secondary to RVO leads to vascular hyperpermeability with subsequent breakdown of the blood-retina barrier and macular edema (ME). The development of ME contributes to visual deterioration (2-5).

The introduction of VEGF inhibitors is the beginning of a new era in the treatment of ME secondary to RVO targeting the disease at the molecular level (6). Ranibizumab has been applied successfully to reduce ME due to RVO (7-13). However, treatment success is often temporary. Some patients experience no effect on the resolution of ME, and some patients have a poor visual outcome despite complete resolution of the ME under ranibizumab therapy, despite multiple intravitreal injections. Therefore, the predictive factors for visual outcome after ranibizumab therapy have become very important (7,14-22).

Some factors are thought to be associated with the post-treatment best-corrected visual acuity (BCVA) prognosis of ME due to RVO under intravitreal anti-VEGF agent injections, such as the baseline BCVA, age, and macular microstructure (2). Optical coherence tomography (OCT) is a noninvasive method that visualizes the macular microstructure clearly. Spectral domain optical coherence tomography (SD-OCT) machines now attain 5 μm resolution, which allows layer-by-layer evaluation of the retina, such as the ellipsoid zone, external limiting membrane (ELM), retina pigment epithelium (RPE), and choroid (23). Among these ocular structures, the central foveal thickness (CFT), ellipsoid zone, and ELM integrity were reported to be associated with post-treatment BCVA (24-27).

However, previously, the extent of the ellipsoid zone and ELM damage was assessed mainly by dividing the hyperreflective line within the 1 mm diameter circle centered on the fovea into completely visible, partially visible, and invisible (25). Thus, the important effect of integrity beneath the center of the fovea was not considered adequately, which is very important to visual acuity. In the present study, an original ranking was applied that the integrity of the ELM and the ellipsoid zone at baseline was categorized into four ranks: i) Completely visible line; ii) partially detectable line with undamaged center
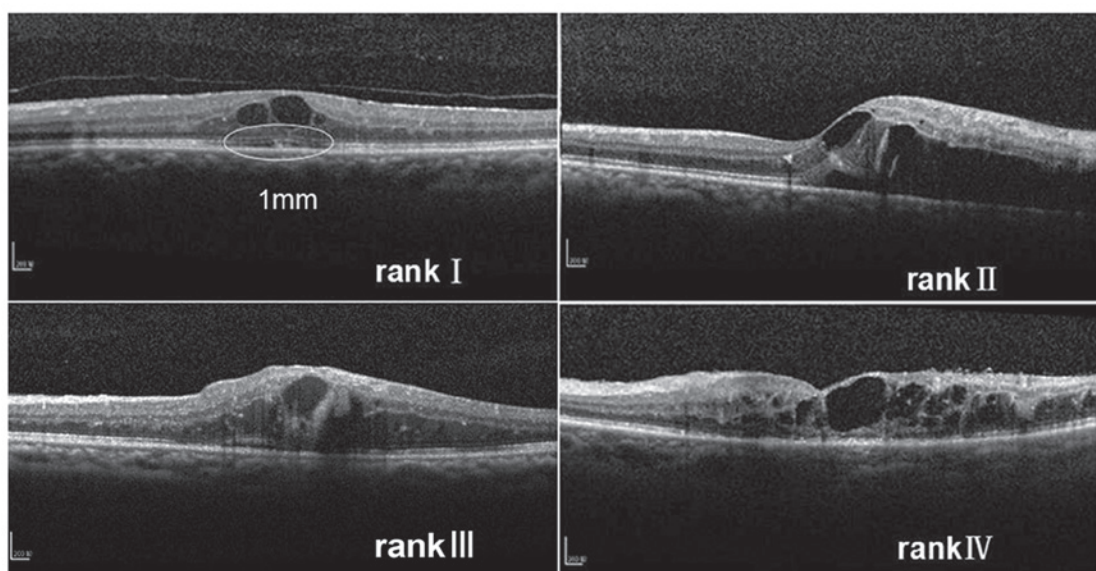
Figure 1. The representative figures of ranks of ELM integrity based on hyperreflective line within 1 mm diameter circle centered the fovea at baseline: Rank I, completely visible line; rank II, partially detectable line with undamaged center of fovea; rank III, partially detectable line with damaged center of fovea; rank IV, completely invisible line.

of fovea; iii) artially detectable line with damaged center of fovea; and iv) completely invisible line.

In this study, we applied the original ranking to investigate the effects of clinical baseline factors of eyes with ME secondary to RVO on post-treatment BCVA after 3 consecutive monthly ranibizumab injections and another 3 months of follow-up in order to find independent baseline characteristics that may predict a positive functional therapeutic response.

Materials and methods

In this retrospective study, 31 patients (16 CRVO, 15 BRVO) with ME due to RVO received 3 monthly consecutive intravitreal injections of 0.5 mg ranibizumab and further 3 months of follow-up. During the follow-up period, subjects were eligible to receive monthly intraocular ranibizumab if they had BCVA ≤20/40 or CFT ≥250 μm.

This study was approved by the Institutional Review Board and followed the tenets of the Declaration of Helsinki. Informed consent was obtained after patients were informed about the possible risks.

Patients were included if they met the inclusion criteria as follows: i) CFT on OCT was more than 300 μm; ii) the patient had not received an intravitreal injection; iii) 3 monthly consecutive ranibizumab injections and iv) other 3 months follow-up were completed, and no other treatment except ranibizumab injections was required. Patients were excluded if they had any of the following ocular diseases: Age-related macular degeneration (AMD), diabetic retinopathy (DR), choroidal neovascularization, a history of ocular trauma, and a history of intraocular surgery except cataract surgery. We also discharged patients if their baseline OCT scan did not provide an identifiable macular microstructure.

The patient's age, sex, and duration of RVO were recorded. A comprehensive ophthalmologic examination was performed. BCVA was measured with a Snellen chart and converted to a logarithm of the minimal angle of resolution (logMAR) units for statistical analysis. Eyes that had post-treatment BCVA of better than 0.30 logMAR were grouped in the good function group; the other eyes were grouped in the poor function group (28). Slit-lamp and fundus examinations were included. All patients underwent color fundus photography (Topcon Corp., Tokyo, Japan) and fluorescein angiography (FA; Heidelberg Engineering Inc., Heidelberg, Germany) to diagnose RVO and discover ischemic features. In addition, we performed SD-OCT imaging at baseline to evaluate the status of the ellipsoid zone, ELM, CFT, and subretinal hemorrhage within a 1 mm diameter circle centered on the fovea. All evaluations were obtained by authors masked to the patient's BCVA.

We obtained in each study eye 2 SD-OCT (spectralis; Heidelberg Engineering Inc.) scans 6 mm in crosshair fashion centered on the fovea (horizontal and vertical). For horizontal and vertical SD-OCT scans, the ART function (averaging of scans) was activated, and 25 SD-OCT scans were averaged. For maximal definition of the retinal layers, we used noise-reduction software (Heidelberg Engineering Inc.). The integrity of the ELM and the ellipsoid zone was categorized into four ranks depending on the microstructure within the 1 mm diameter circle centered on the fovea at baseline: i) Completely visible line, ii) partially detectable line with undamaged center of fovea, iii) partially detectable line with damaged center of fovea and iv) completely invisible line. If the ranking between the horizontal and vertical scans was different, the higher ranking was selected (Fig. 1).

All statistical analyses were performed using SPSS ver. 18.0 (SPSS, Inc., Chicago, IL, USA). Continuous values were compared using an independent-sample t-test or a one-way analysis of variance (ANOVA). A paired sample t-test was used to compare the post-treatment with the baseline values. A non-parametric test was used if the continuous variables were abnormally distributed. Categorical variables were assessed

Table I. Baseline characteristics of patients with ME secondary to RVO.

No. of eyes (left/right)	31 (19/12)
Age (years)	61.4±9.7
Sex (Male/Female)	13/18
CRVO/BRVO	16/15
Duration of symptoms (days)	104.0±89.0
Baseline BCVA (logMAR)	0.60±0.26
Optical coherence tomography	
Initial ELM integrity	I 10, II 9, III 8, IV 4
Initial ellipsoid zone integrity	I 6, II 9, III 11, IV 5
Baseline central fovea thickness (μm)	646.4±197.0
Hemorrhage under the fovea (yes/no)	5/26
Fluorescein angiography	
Ischaemic/non-ischaemic type	13/18
Intact/broken foveal capillary ring	25/6

BCVA, best-corrected visual acuity; CRVO/BRVO, central retinal vein occlusion/branch retinal vein occlusion; ELM, external limiting membrane; ME, macular edema.
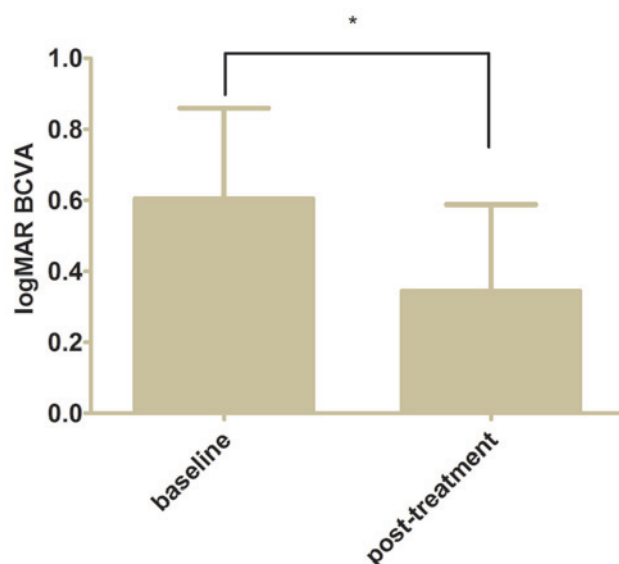

Figure 2. The mean BCVA changes from baseline to post-treatment, showing the post-treatment logMAR BCVA was significantly better than the baseline logMAR BCVA. *P<0.05; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimal angle of resolution.

using the chi-squared test. To determine the independent baseline factors that predict post-treatment BCVA, univariate regression analysis was performed, followed by stepwise multivariate regression analysis, logMAR BCVA at 6 month after the first intravitreal injection was treated as a dependent variable. Analysis of covariance was used to calculate and compare post-treatment BCVA after adjusting for other variables between ELM ranks. A P<0.05 was considered to indicate a statistically significant analysis.

Results

A total of 31 eyes of 31 patients with RVO (13 men and 18 women) were included in this study. Table I shows the baseline characteristics of the 31 eyes. The mean age of the patients was 61.4±9.7 years. Of all 31 RVO eyes, 16 eyes were CRVO, and 15 eyes were BRVO. The mean interval from diagnosis to the 1st injection for the patients with RVO was 104.0±89.0 days.

The mean post-treatment logMAR BCVA of the eyes was 0.34±0.24 from 0.60±0.26 at baseline (Fig. 2, P<0.05). The mean CFT decreased to 206.7±37.6 μm from 646.4±197.0 μm at baseline following 3 monthly ranibizumab injections and further 3 months of follow-up (Fig. 3, P<0.05).

Table II shows the general characteristics, BCVA, OCT, and FA data for the good function and poor function groups at baseline. There was no significant difference in the general characteristics between the groups, while significant differences in the baseline ELM integrity, ellipsoid zone integrity, and BCVA between the groups were observed. The results revealed the baseline ELM integrity, ellipsoid zone integrity, and BCVA of the good function were significantly better than those of the poor function group (P<0.01). Differences in the baseline CFT and FA data between groups were found but were not statistically significant.
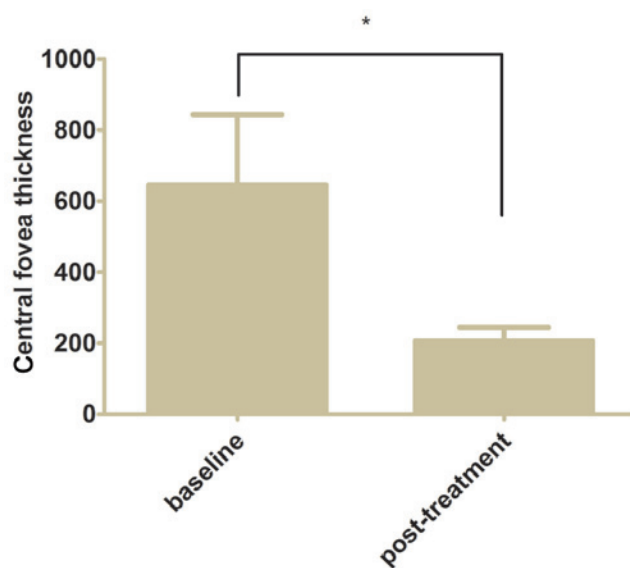

Figure 3. The mean CFT changes from baseline to post-treatment, demonstrating the post-treatment CFT was significantly thinner than the baseline CFT. *P<0.05; CFT, central foveal thickness.

Univariate and multivariate regression analyses were performed to determine the baseline factors significantly associated with post-treatment BCVA in all patients. Univariate regression analyses showed that the ellipsoid zone, ELM, baseline BCVA, sex, and RVO type were associated significantly with post-treatment BCVA (P<0.05). We then performed stepwise multivariate regression analyses to determine the baseline factors independently associated with post-treatment BCVA. The result showed that the ELM integrity and the baseline BCVA were the independent factors associated with post-treatment BCVA (B=0.149, P<0.01; B=0.262, P=0.045, respectively). Both were positively associated with post-

Table II. Comparison of baseline characteristics between good function and poor function group.

Baseline predictors	Good function group N=19	Poor function group N=12	P-value
Age (years)	60.1±10.1	63.5±9.2	0.354
Sex			0.123
Male	10	3	
Famale	9	9	
Eye			0.206
Left	10	9	
Right	9	3	
Type			0.179
CRVO	8	8	
BRVO	11	4	
Duration of symptoms (days)	88.7±84.9	128.2±93.7	0.236
Initial ELM integrity	I8, II9, III2, IV0	I2, II0, III6, IV4	0.001[a]
Initial ellipsoid zone integrity	I5, II9, III5, IV0	I1, II0, III6, IV5	<0.01[a]
Baseline central fovea thickness (μm)	640.2±143.7	656.2±268.1	0.951
Baseline BCVA	0.47±0.13	0.82±0.26	<0.01[a]
Hemorrhage under the fovea (Yes/No)			0.949
Yes	3	2	
No	16	10	
Ischaemic/non-ischaemic type			0.981
Yes	8	5	
No	11	7	
Intact/broken foveal capillary ring			0.762
Yes	4	2	
No	15	10	

BCVA, best-corrected visual acuity; CRVO/BRVO, central retinal vein occlusion/branch retinal vein occlusion; ELM, external limiting membrane; [a]P<0.01.
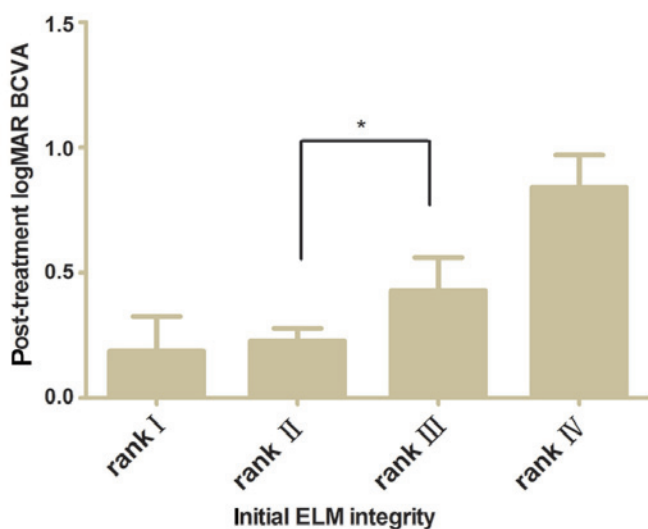

Figure 4. Comparison of post-treatment BCVA between ELM ranks after adjusting for initial BCVA, showing the post-treatment BCVA difference after adjusting for baseline BCVA between ranks II and III was significant (P=0.05). *P<0.05; BCVA, best-corrected visual acuity; ELM, external limiting membrane.

treatment BCVA. Tables III and IV show the detailed results of the regression analysis.

A comparison of post-treatment BCVA between the ELM ranks after adjusting for baseline BCVA was performed. The baseline BCVA was shown to be associated with post-treatment BCVA independently. Fig. 4 shows the post-treatment BCVA difference between ranks II and III was significant (P<0.05).

Discussion

In the present study, we investigated the baseline factors with an original ranking on OCT images to predict post-treatment BCVA after ranibizumab treatment in patients with ME associated with RVO. Our results showed the ELM integrity and the baseline BCVA were the independent factors that predict post-treatment BCVA, indicating patients with good baseline ELM integrity in particular beneath the center of the fovea and baseline BCVA would obtain good post-treatment BCVA after intravitreal VEGF inhibitor therapy.

RVO is an important cause of visual impairment, and ME secondary to RVO is the second most common major retinal vascular disease after DR 3-5. Previously, there were no effec-

Table III. Univariate analysis results of baseline predictors for post-treatment BCVA.

Baseline predictors	N/mean ± SD	Post-treatment BCVA	
		B (95% CI)	P-value
Age (years)	61.4±9.7	0.003 (-0.006, 0.013)	0.460
Sex		0.188 (0.018, 0.358)	0.032
Male	13		
Female	18		
Eye		-0.138 (-0.317, 0.042)	0.127
Left	19		
Right	12		
Type		-0.174 (-0.344, -0.004)	0.045[b]
CRVO	16		
BRVO	15		
Duration of symptoms (days)	104.0±89.0	0.000 (-0.001, 0.001)	0.544
Initial ELM integrity	I 10, II 9, III 8, IV 4	0.189 (0.138, 0.241)	<0.01[a]
Initial ellipsoid zone integrity	I 6, II 9, III 11, IV 5	0.186 (0.126, 0.246)	<0.01[a]
Baseline central fovea thickness (μm)	646.4±197.0	0.000 (0.000, 0.001)	0.124
Baseline BCVA	0.60±0.26	0.642 (0.374, 0.909)	<0.01[a]
Hemorrhage under the fovea		-0.024 (-0.272, 0.223)	0.841
Yes	5		
No	26		
Ischaemic/non-ischaemic type		-0.008 (-0.192, 0.177)	0.932
Yes	13		
No	18		
Intact/broken foveal capillary ring		0.040 (-0.190, 0.270)	0.726
Yes	6		
No	25		

BCVA, best-corrected visual acuity; CRVO/BRVO, central retinal vein occlusion/branch retinal vein occlusion; ELM, external limiting membrane; SD, standard deviation; [a]P<0.01, [b]P<0.05.

Table IV. Multivariate analysis results of baseline predictors for post-treatment BCVA.

Baseline predictors	N/mean ± SD	Post-treatment BCVA	
		B (95% CI)	P-value
Initial ELM integrity	I 10, II 9, III 8, IV 4	0.149 (0.087, 0.212)	<0.01
Baseline BCVA	0.60±0.26	0.262 (0.007, 0.517)	0.045

BCVA, best-corrected visual acuity; CRVO/BRVO, central retinal vein occlusion/branch retinal vein occlusion; ELM, external limiting membrane; SD, standard deviation.

tive treatments for ME secondary to CRVO, while only grid laser photocoagulation was available to treat ME secondary to BRVO, but it reduced edema very slowly and provided benefit for only a few patients (29,30). In 2009, the Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) study recommended 1 mg intravitreal triamcinolone acetonide (TA) for ME secondary to CRVO, although the risk of cataract and high intraocular pressure increased. TA injections were

not superior to grid laser for ME secondary to BRVO (31). High VEGF concentrations were present in the eyes of patients with RVO, resulting in neovascularization and ME, and VEGF inhibitors can block this pathogenesis, representing the safe, latest, and effective treatment for RVO. VEGF inhibitors included bevacizumab and ranibizumab, which were reported to be superior in BCVA gains and CFT decrease to other treatment. Among these VEGF inhibitors, ranibizumab have been

approved in the United States and the European Union for the treatment of ME secondary to RVO (7,14-21).

However, not all patients benefit from VEGF inhibitors, and sometimes, BCVA does not improve even if there is a significant decrease in CFT 2. Several studies have been conducted to identify predictive factors for good treatment response, and some baseline factors were thought to contribute to post-treatment BCVA after intravitreal injections of anti-VEGF agent for patients with ME due to RVO. The factors included age, baseline BCVA, ischemic areas, response to first injection, duration of occlusion, history of hypertension, hemorrhage under the fovea, and baseline OCT findings, which were thought to be one of most important predictors (2,10,26,32).

Today, images with high resolution of the neural retina can be obtained in a non-invasive manner with OCT scanning, and the microstructure of the retina such as the ellipsoid zone, ELM, and RPE can be defined on OCT imaging (23). Changes in the macular microstructure can be detected by OCT in most eyes with RVO during an early stage and are believed to be important predictors for post-treatment BCVA after intravitreal injections of an anti-VEGF agent (22,27,28,33,34).

In some studies, the CFT measured with OCT was found to be able to predict the post-treatment BCVA outcome in ME due to RVO after anti-VEGF agent injections (33,34). However, some researchers concluded that the correlation between baseline CFT and BCVA after anti-VEGF agent injections was not significant (35). Similarly, a contradictory conclusion regarding the association between baseline CFT and BCVA after VEGF inhibitor injections in patients with AMD appeared. To interpret this contradiction, Oishi *et al* (36) pointed out the pattern of correlation was V-shaped, and there was a negatively linear correlation in eyes with CRT >203 μm and a positively linear trend in eyes with CRT ≤203 μm. However, in the present study, the baseline CFT was more than 203 μm, and the correlation was not significant.

Previously, the integrity of the ellipsoid zone and the ELM was shown to be significantly associated with post-treatment BCVA after anti-VEGF agent injections in patients with RVO and AMD (22,24,25,28,35,36). Some studies demonstrated the integrity of the ellipsoid zone was more highly associated with post-treatment BCVA than the ELM (24,28,35); however, some studies reported the ELM was more useful in the prediction of post-treatment BCVA (22,25,36). In the present study, the integrity of the ellipsoid zone and the ELM correlated significantly with post-treatment BCVA in univariate regression analysis, respectively, but the integrity of the ellipsoid zone was excluded from the independent variables in multivariate regression analysis. We found the ELM was more useful in the prediction of post-treatment BCVA in patients with ME due to RVO, and we agreed with the interpretation that ellipsoid zone status may be too sensitive to evaluate diseases that cause severe retinal damage such as AMD, retinal detachment (RD), and RVO 36. The ELM may be more useful in the evaluation of retinal damage of ME secondary to RVO than the ellipsoid zone.

This study revealed a significant correlation of baseline BCVA and post-treatment BCVA after intravitreal VEGF inhibitor injections for ME secondary to RVO in univariate and multivariate regression analysis, in accordance with previous studies (26).

The strengths of our study are as follows: i) The bias resulting from the type of agents was controlled; ranibizumab was the single anti-VEGF agent for intravitreal injections unlike most previous studies and ii) previously, the extent of the ellipsoid zone and ELM damage was assessed mainly by dividing the hyperreflective line into completely visible, partially visible, and invisible. Thus, the important effect of integrity beneath the center of the fovea was not considered adequately. In addition, the previous assessments were mainly based on post-treatment OCT imaging instead of baseline OCT imaging, so they could not be real predictors. In contrast, in the present study the integrity of the ELM and the ellipsoid zone at baseline was categorized into four ranks: i) Completely visible line), ii) partially detectable line with undamaged center of fovea), iii) partially detectable line with damaged center of fovea, and iv) completely invisible line. The results revealed the post-treatment BCVA in ELM rank II was significantly better than that of ELM rank III (P<0.05), which was attributed to the important effect of the ELM integrity beneath the center of the fovea.

In this study, we did not find a significant association between FA data and post-treatment BCVA, perhaps because the evaluation of the ischemia severity from baseline FA data was difficult, and nonischemic types could be incorrectly assessed as it would become ischemic type later. Of course, the small sample size and the retrospective design of this study might have affected our findings. Additional prospective investigation especially with large samples are needed to illuminate the predictors for BCVA after anti-VEGF agent treatment in patients with ME secondary to RVO.

In conclusion, the ELM integrity and the baseline BCVA may be more useful than other factors in the prediction of the post-treatment BCVA of patients with ME associated with RVO after intravitreal injections of ranibizumab, and the ELM integrity beneath the center of fovea should be the focus to predict post-treatment BCVA.

Acknowledgements

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