Comparison of Changes in Number of Hyperreflective Dots After İntravitreal Ranibizumab or Dexamethasone İmplant in Patients with Branch Retinal Vein Occlusion

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Abstract

Purpose: To compare the effect of intravitreal ranibizumab (IVR) or intravitreal dexamethasone implants (IVD) on regression of hyperreflective dots (HRDs) on optical coherence tomography (OCT) B-scan in patients with branch retinal vein occlusion (BRVO).

Methods: 37 eyes of 37 patients with cystoid macular edema who received IVR or IVD and followed up for at least 12 months were included in this study. The patients were divided into three groups according to intravitreal treatment. Group 1 consisted of 12 eyes who received only IVD, group 2 consisted of 10 eyes who received only IVR on a pro re nata and group 3 consisted of 15 eyes who received both IVD and IVR. OCT parameters (CMT, number of HRDs, status of external limiting membrane (ELM) and ellipsoid zone (EZ)) and best-corrected visual acuity (BCVA) were compared between the groups over the follow-up time. HRDs were categorized as HRD in inner retinal layers (from the internal limiting membrane to the inner nuclear layer) or HRD in outer retinal layers (from the outer plexiform layer to the outer border of the photoreceptor layer).

Results: There was no significant difference between groups in terms of BCVA, CMT, HRDs in the inner and the outer retinal layers at baseline visit. (p 0.05 for all) Comparing the baseline values in all groups, a significant decrease was observed in CMT in the first year. (For group 1; p=0.013, group 2; p=0.010; group 3, p<0.001) The BCVA was significantly increased after 1 year in all groups. (p=0.001, p=0.006, p<0.001) The mean number of HRDs in inner and outer retinal layers were significantly decreased in group 1 and group 3. (For group 1; p<0.001, p=0.001, for group 3; p<0.001, p<0.001) However, there was no significant difference in terms of the mean number of HRDs in inner and outer retinal layers for group 2. (p=0.134, p=0.477) At the first year, the number of HRDs in inner and outer retinal layers was significantly lower in group 1 and group 3 than group 2. (For inner HRDs; group 1 vs. group 2 p=0.007, group 2 vs. group 3 p<0.001. For outer HRDs group 1 vs. group 2 p<0.001, group 2 vs. group 3 p<0.001.) The BCVA was higher in group 3 than group 2 at 1year. (p=0.048). There was no significant difference in terms of post-treatment CMT and the number of HRDs between group 1 and group3 in posthoc tests (p=0.621, p=0.876, and p=0.632).

Conclusion: The reduction in HRDs at 12 months and better BCVA after IVD intimates that the HRDs should be considered as inflammatory markers in the follow-up of CME in BRVO. Thus, IVD injection could be more appropriate for patients with higher HRDs after BRVO.

Introduction

Branch retinal vein occlusion (BRVO) is the second common cause of retinal vascular diseases, and with the development of macular edema (ME), the visual acuity was reduced. Increased vascular permeability and inflammatory cytokines are responsible for the pathogenesis of ME.(1, 2) Intravitreal injection of anti-

vascular endothelial growth factor (anti-VEGF) (bevacizumab, ranibizumab (IVR), and dexamethasone implant reported for the treatment of ME, which often achieved the better visual acuity gain.(3–5)

In patients with BRVO, ME is the main cause of visual impairment. Although ME decreases dramatically following intraocular injection of anti-VEGF agents, repeated recurrence and resistance of edema is a major problem in some BRVO patients. It is known that factors or cytokines other than VEGF may be associated with inflammation and retinal hypoxia in BRVO and that the pathogenesis of macular edema is complicated.(6) The anatomical healing could be monitorized via optical coherence tomography (OCT) among which hyperreflective dots (HRDs) on OCT appear as well-circumscribed, highly reflective marks of 20 μm to 40 μm in diameter. HRDs are seen in retinal vascular diseases, including BRVO and diabetic retinopathy (DR). (7, 8) These studies suggest that HRD could represent a clinical marker of inflammation, particularly activated microglia.(7, 9)

The aim of this study was to compare the effect of IVR or intravitreal dexamethasone implants (IVD) on regression of HRDs in BRVO.

Methods

Cases consisting of 37 patients who were referred to our retina department were retrospectively reviewed. This study adhered to the principles of the Declaration of Helsinki. Approval from the institutional review board/ethics committee was obtained. Cases with clinically significant treatment-naive ME due to BRVO that had been present for < 3months and the best-corrected visual acuity (BCVA) of between 1.30 (logMAR) and 0.30 (logMAR), and a central macular thickness (CMT) > 300μm on OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) were included in this study. Cases with history or symptoms of chorioretinal diseases (e.g., posterior uveitis, DR, choroidal neovascularization), insufficient quality images, media opacity (e.g., cataract, vitreous hemorrhage) were excluded from the study.

The patients were divided into three groups according to intravitreal treatment for ME due to BRVO. The patients in the group 1 received repeated pro re nata (PRN) IVD (700-μg dexamethasone implant, Ozurdex; Allergan, Inc, Irvine, CA) injections once in every 3 months after the initial injection if they met the following criteria: CMT > 300μm or a decrease in BCVA attributable to ME. The patients in the group 2 received repeated PRN IVR (0.5 mg ranibizumab, Lucentis, Genentech, South San Francisco, CA) injections after the initial three monthly injections if they met the following criteria: CMT > 300μm or BCVA < 20/20 with recurrent ME, or a decrease in BCVA attributable to ME. The patients in the group 3 received repeated PRN IVD injections once in every 3 months after the initial three monthly IVR injections if they met the following criteria: CMT > 300μm or BCVA < 20/20 with recurrent ME, or a decrease in BCVA attributable to ME and not to other ocular conditions, such as media opacity.

During 12 months of follow-up, all cases underwent full ophthalmic examinations, including BCVA, dilated fundus examination with slit-lamp biomicroscopy, and OCT at baseline and at every monthly visit after intravitreal injections. The BCVA was measured with a Snellen chart, and the decimal values were converted to the logarithm of minimal angle of resolution units for statistical analyses. Fundus

fluorescein angiography was also performed at baseline. The ischemic type of BRVO was described as higher than five disk areas of retinal capillary nonperfusion based on fluorescein angiography. CMT was calculated automatically as the average retinal thickness within a circle of a 1,000 mm diameter centered on the fovea. Only images with a quality score > 16 dB were selected. OCT parameters (CMT, number of HRDs) and best-corrected visual acuity (BCVA) (logMAR) were compared between the groups and over the follow-up time.

In the B-scan images of the OCT after black-on-white converting, HRD were represented as follows: discrete and well-circumscribed particles 20 to 40 mm in diameter, as measured using a caliper tool in the Spectralis OCT software, with no back shadowing, and high reflectivity equal or more prominent than that of the retinal pigment epithelium.(8) The number of HRDs was represented as the average of the number on the same scan as counted independently by two retinal specialists (S.S and A.K), who were masked to all clinical information. Inter-investigator reliability (κ) was evaluated. HRDs were categorized as HRD in inner retinal layers (from the internal limiting membrane to the inner nuclear layer) or HRD in outer retinal layers (from the outer plexiform layer to the outer border of the photoreceptor layer). (Fig. 1)

The SPSS 22.0 (SPSS, Inc, Chicago, IL) software program was used for statistical analyses. Continuous variables were given as mean ± SD, whereas qualitative variables were shown as frequencies (absolutes) and percentages (%). Variables that were quantitative in the form of measurement were checked by the Shapiro Wilk test for the normality hypothesis. Comparisons between categorical variables were evaluated using contingency tables and chi-square test or Fisher's test, when necessary. The paired t-test was used to compare the number of HRD, BCVA, and CMT between baseline and 12 months after the treatment. The one-way analysis of variance (ANOVA) with post-hoc Bonferroni correction was used for comparisons of parameters between groups after treatment at 1 year. A p value of lower than 0.05 was considered as statistically significant. For evaluation of interobserver concordance of the HRDs counting, an intraclass correlation coefficient was calculated.

Results

The baseline (pre-treatment) comparisons and clinical characteristics were summarized and detailed in Table 1. There was no significant difference between groups in terms of BCVA, CMT, status of ELM and EZ, HRDs in the inner retinal layers and the outer retinal layers at baseline. (p□0.05 for all parameters)

Table 1
The baseline demographics and BCVA of the patients.

	Mean ± SD			
	Group 1 (n = 12)	Group 2 (n = 10)	Group 3 (n = 15)	p
Age, y	63.9 ± 6.9	62.4 ± 5.5	64.0 ± 5.6	0.775
Sex (F/M)	3/9	1/9	3/12	0.643
Lens status (Phakic/Pseudophakic)	4/8	4/8	6/9	0.562
Hypertension, n(%)	9(75)	9(90)	12(80)	0.664
Ischemic type, n(%)	7(58.3)	6(60)	8(53.3)	0.787
CMT (μm)	466 ± 123.4	479 ± 141.1	453 ± 107.6	0.870
IOP (mmHg)	14.1 ± 2.8	13.8 ± 3.03	13.6 ± 2.9	0.884
BCVA (logMAR)	0.6 ± 0.16	0.65 ± 0.13	0.58 ± 0.15	0.504
ELM status	6(50)	4(40)	6(40)	0.839
Intact, n(%)	6(50)	6(60)	9(60)	
Disrupted, n(%)				
EZ status	5(41.6)	3(30)	5(33.3)	0.829
Intact, n(%)	7(58.4)	7(70)	10(66.7)	
Disrupted, n(%)				

Data are presented as mean ± standard deviation. F; female, M; male, BCVA; best-corrected visual acuity, logMAR; logarithm of the minimum angle of resolution, CMT; central macular thickness, IOP; intraocular pressure, ELM; external limiting membrane, EZ; elipsoid zone

The comparison of BCVA and OCT parameters after treatments during follow-up time was summarized in Table 2. Compared to the baseline values in all groups, a significant decrease was observed in CMT in the first year. (For group 1; $p = 0.013$, group 2; $p = 0.010$; group 3, $p < 0.001$) The BCVA was significantly increased after 1 year in all groups. ($p = 0.001$, $p = 0.006$, $p < 0.001$) The mean number of HRDs in inner and outer retinal layers were significantly decreased in group 1 and group 3. (For group 1, $p < 0.001$, $p = 0.001$ for group 3; $p < 0.001$, $p < 0.001$) However, there was no significant change in terms of the mean number of HRDs in inner and outer retinal layers group 2. ($p = 0.134$, $p = 0.477$)

Table 2
Comparison of BCVA and OCT parameters after treatments during follow-up.

		Mean ± SD					
		Baseline	Month 1	Month 3	Month 6	Month 12	P*
Group 1	BCVA(logMAR)	0.59 ± 0.15	0.44 ± 0.11	0.31 ± 0.11	0.44 ± 0.12	0.31 ± 0.11	**0.001**
	CMT(µm)	466 ± 123	364.3 ± 134	334.3 ± 52.6	339.1 ± 82	297.4 ± 94.6	**0.013**
	HRDs in IRL(n)	8 ± 1.7	5.6 ± 1.9	4.4 ± 1.5	4.8 ± 2.2	3.5 ± 1.4	**< 0.001**
	HRDs in ORL(n)	5.9 ± 3.0	2.8 ± 2.5	2.6 ± 2.4	3.3 ± 2.1	1.2 ± 0.96	**0.001**
Group 2	BCVA(logMAR)	0.65 ± 0.13	0.58 ± 0.14	0.45 ± 0.13	0.55 ± 0.15	0.38 ± 0.14	**0.006**
	CMT(µm)	479 ± 141	321 ± 49.8	357 ± 102	361 ± 42.9	353 ± 87.9	**0.010**
	HRDs in IRL(n)	8.1 ± 2.1	6.9 ± 2.1	6.6 ± 1.7	5.8 ± 1.9	6.7 ± 1.5	0.134
	HRDs in ORL(n)	6.1 ± 2.5	6.3 ± 3.2	5.7 ± 2.1	4.4 ± 2.9	5.4 ± 1.8	0.477
Group 3	BCVA(logMAR)	0.58 ± 0.15	0.54 ± 0.16	0.40 ± 0.12	0.53 ± 0.16	0.25 ± 0.11	**< 0.001**
	CMT(µm)	453 ± 107	324 ± 94.2	341 ± 95	342.4 ± 50	270 ± 32.7	**< 0.001**
	HRDs in IRL(n)	8 ± 3.1	7.2 ± 2.9	6.2 ± 2.1	4 ± 1.6	3.1 ± 2.3	**< 0.001**
	HRDs in ORL(n)	5.8 ± 2.2	4.6 ± 2.6	4.4 ± 2.7	1.8 ± 1.9	1.8 ± 1.6	**< 0.001**

BCVA; Best corrected visual acuity, logMAR; logarithm of the minimum angle of resolution, CMT; central macular thickness, HRD; hyperreflective dot, IRL; inner retinal layer, ORL; outer retinal layer. Bold values are statistically significant. P*; a paired t-test was used to compare the number of HRD, BCVA, and CMT between baseline and 12 months after the treatment. ,

At the first year, the number of HRDs in inner and outer retinal layers was significantly lower in group 1 and group 3 than group 2. (Table 3) The BCVA was higher in group 3 than group 2 at first year. (p = 0.048). There was no significant difference in terms of posttreatment CMT and the number of HRDs between group 1 and 3 in posthoc tests (p = 0.621, p = 0.876, and p = 0.632). The number of injection was significantly lower in group 1. (Table 3) The disruption of ELM and EZ presence was higher in group 2. (Table 3)

Table 3
Comparison of BCVA and OCT parameters between the groups at 1 year.

	Mean ± SD						
	Group 1	Group 2	Group 3	P^A	P^B	P^C	p^D
BCVA	0.31 ± 0.11	0.38 ± 0.14	0.25 ± 0.11	0.706	0.572	**0.048**	-
CMT	297.4 ± 94.6	353 ± 87.9	270 ± 32.7	0.190	0.621	**0.02**	-
HRDs in IRL(n)	3.5 ± 1.4	6.7 ± 1.5	3.1 ± 2.3	**0.007**	0.876	**< 0.001**	-
HRDs in ORL(n)	1.2 ± 0.96	5.4 ± 1.8	1.8 ± 1.6	**< 0.001**	0.632	**< 0.001**	-
Number of iv injection(n)	3.4 ± 0.7	7.3 ± 1.4	5.2 ± 0.8	**< 0.001**	**< 0.001**	**< 0.001**	-
ELM status	7(58.3)	2(20)	10(66.6)				0.06
Intact, n(%)	5(41.7)	8(80)	5(33.4)				
Disrupted, n(%)							
EZ status	8(66.6)	3(30)	11(73.3)				0.102
Intact, n(%)	4(33.4)	7(70)	4(26.7)				
Disrupted, n(%)							

BCVA; Best corrected visual acuity, logMAR; logarithm of the minimum angle of resolution, CMT; central macular thickness, HRD; hyperreflective dot, IRL; inner retinal layer, ORL; outer retinal layer, ELM; external limiting membrane, EZ; elipsoid zone.

Posthoc tests: p^A; Group1 vs. group2, p^B; Group 1 vs. group 3, p^C; Group 2 vs. group 3, p^D; chi-square test. Bold values are statistically significant.

Discussion

In this study, we attempted to investigate the effect of dexamethasone implant and ranibizumab on the regression of HRDs in patients with ME secondary to BRVO. We demonstrated that the mean number of HRDs in inner and outer retinal layers was significantly decreased in patients who administered IVD at 1 year after treatment. Furthermore, the reduction in HRDs and better BCVA after IVD intimates that the HRDs should be considered as inflammatory markers in the follow-up of ME in BRVO. Thus, IVD injection could be more appropriate for patients with higher HRDs after BRVO.

Previous studies explain the possible constitution of HRDs detected on OCT, but these dots are still unknown. Bolz et al. reported that the isolated HRDs were found on OCT, but they could not be found on

fundus photographs taken simultaneously with OCT. However, they demonstrated that the confluent accumulated HRDs on OCT were detected as hard exudates in the corresponding fundus photograph. Therefore they supported that these isolated dots characterized by the same hyperreflectivity was accumulated dots might be small intraretinal protein and/or lipid deposits as precursors of hard exudates.(10) In contrast, several other studies have asserted that HRDs are associated with inflammatory responses in the retina.(11–13) Coscas et al. suggested that these HRDs were most likely microglia cells activated by inflammation, which subsequently swell and spread to outer retinal layers.(7) Furthermore, in another study, authors reported that, in patients with BRVO, HRD disappeared immediately after intravitreal bevacizumab treatment, suggesting that HRF could represent inflammatory cells, particularly activated microglia, rather than lipid extravasation.(14)

The RIDE and RISE phase III clinical trials also showed that resolution of hard exudates (deposition of lipoproteins) after IVR was not evident before 6 months of treatment. By contrast, these studies recognized diminished numbers of HRD within 6 months of treatment, especially in eyes that received dexamethasone implants.(15) Similar to their results, in our study, the decrement of HRDs was properly early after IVD treatment. (Within 3 months) Vogel et al. suggested that the HRDs on the OCT are cellular, rather than accumulations of proteins or lipids, given their discrete, granular, and demarcated presentation and consistent size in a study with patients with central serous chorioretinopathy via adaptive optics scanning light ophthalmoscopy findings. They support the hypothesis that HRF could be activated microglia.(16)

Lee et al. reported a strong correlation between sCD14 and HRDs in the inner retina and also they suggested that the HRDs observed on OCT may be due to activated microglia in diabetic ME.(17) These studies suggested that HRDs could reflect the presence of activated microglia due to retinal inflammation. Zeng et al showed that, as DR in human donor eyes progresses, activated microglia infiltrate and migrate to the outer retinal layer. Singhal et al demonstrated that the number of activated microglia decreases after intravitreal triamcinolone injection.(18) Retinal glial cells, contribute to the development of ME.(19) In a healthy retina, resting microglia are essentially located in the inner retina, but with inflammation, the activated glial cells migrate to the site of injury.(20) The activated microglia also discharge proinflammatory and proangiogenic mediators.(21) Vujosevic et al stated the migration of HRDs from the inner to the outer retina layers through the DR progression. (22) The contribution of activated microglia to the progression of BRVO was also shown in animal model.(23)

The zonulae adherents between the photoreceptors and Muller cells, creating the ELM, can block the transfer of macromolecules, and that the healthy ELM restricts the migration through the outer retinal layers. A breakdown of ELM permits these inflammatory molecules through the outer layers of retina and leads to both photoreceptor disorganization which is in line with the results of a previous report, documenting the outer retinal discontinuity in eyes with retinal vein occlusion. (24) We hypothesized that the inflammatory microenvironment in the outer retinal layer might be responsible for the damage of photoreceptor status. We observed that the eyes with received only IVR had significantly more HRDs in the outer retinal layers and more ELM disruption and inner segment/outer segment disruption at the final

visit. The pathologic association of increased HRDs in outer retinal layers with disruption of the ELM and EZ and poor visual acuity, may be a clinical prognostic marker of outer blood-retinal breakdown and consequent photoreceptor dysfunction. The abovementioned conclusions may also describe the fact why visual acuity does not always increase after intravitreal treatment, even in the decrease of CMT.

The increased VEGF expression contributes to the pathology of ME due to BRVO, and various intravitreal anti-VEGF injections have been widely used for treatment.(1, 25) In addition to increased VEGF expression, inflammatory cytokines and chemokines also play a crucial role in the pathogenesis of ME. The inflammatory cytokines like soluble intercellular adhesion molecule 1, interleukin 6 (IL-6), monocyte chemotactic protein 1 (MCP-1) are elevated in the aqueous humor of patients with BRVO, which enhance vessel permeability and play an essential role in the pathogenesis of ME. (1) After intravitreal injection, CMT was more decreased in the triamcinolone acetonide (IVTA) group compared with the bevacizumab group. IL-6, interferon-γ-inducible protein 10, MCP-1, Human Platelet Derived Growth Factor-AA, and VEGF were significantly decreased in the IVTA group, but only VEGF in the intravitreal bevacizumab group.(26) Corticosteroids repress the production of prostaglandins and leukotrienes, decreasing edema within a variety of mechanisms, essentially suppressing macrophage activity, vasoconstrictive effect, reduction of lymphokine, and VEGF. In opposite, anti-VEGF agents have been observed to reduce hyperpermeability through a decrease in the production of VEGF.(27) Therefore, IVD implants, which inhibit inflammatory cytokines, may be more effective as a therapeutic option for ME in patients with BRVO.

Our study confirmed the outcomes made in previous studies that HRDs correlated negatively with visual acuity.(28–31) Do et al reported that the final BCVA was associated with the baseline number of outer retinal HRDs in the IVB group. However, in the IVD group, the authors did not observe the correlation with the baseline number of outer retinal HRDs. They explained the disparity because the IVD injection reduced outer retinal HRDs more effectively than the IVB and suggested that IVD could resolve the inflammatory components more effectively than IVB with better visual outcomes.(9)

Hwang et al. also evaluated the correlation between the number of HRDs and the therapeutic responsiveness of bevacizumab or dexamethasone implant. They found that the number of HRDs on OCT can be a predictive prognostic factor of the treatment response to bevcizumab injection or IVD implant. A higher number of HRDs and higher rate of OPL disruptions was observed on SD-OCT in bevacizumab nonresponders than in responders in their studies. They supported that dexamethasone implant may be more effective in treating diabetic ME or retinal vein occlusion eyes with many HRDs and OPL disruptions on OCT.(30) In current study, the final BCVA and the presence intact ELM and EZ were higher in eyes received IVD than in eyes with only IVR treatment.

Chatziralli et al. described that the amount and location of HRDs are independent factors of worse final BCVA in patients with ME due to retinal vascular diseases, such as DR and BRVO. The decline of the numbers of HRDs was not influenced by the decision of treatment option (IVR or IVD) used to decrease the ME. In addition, they found that the number of HRDs was associated with the status of EZ and ELM. (31) In contrast, in our study we observed that the final visual acuity and the number of HRDs in outer

retinal layer were higher in patients who received IVD. We speculate that these different results may be due to the difference in the patient groups included.

The limitation of our study is its retrospective and nonrandomized nature. In addition, the manual measurement and classification of the position of the HRDs may have introduced a subjective element. However, the strengths of our study are the relatively homogenous involvements of patients with ME due BRVO, treated by two agents and combined treatment.

In conclusion, this study demonstrated that the outer HRDs are independent factors associated with the final BCVA in patients with ME due to DR and BRVO, suggesting HRDs as a potential biomarker of poor final visual outcome. Furthermore, the reduction of HRDs are more prominent in patients received dexamethasone implant treatment. The reduction in HRDs at 12 months and better BCVA after IVD intimates that the HRDs should be considered as inflammatory markers in the follow-up of CME in BRVO. Thus, IVD injection could be more appropriate for patients with higher HRDs after BRVO.

Declarations

Competing interest: Author Karalezli declares that she has no conflict of interest. Author Tamer Kaderli declares that she has no conflict of interest. Author Kaderli declares that he has no conflict of interest. Author Kaya declares that he has no conflict of interest. Author Sül declares that he has no conflict of interest.

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Data availability: The manuscript has no associated data in a data repository.

Consent to participate: Retrospective study design.

Consent to publish: For this type of study (retrospective analysis), formal consent is not required.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Figures

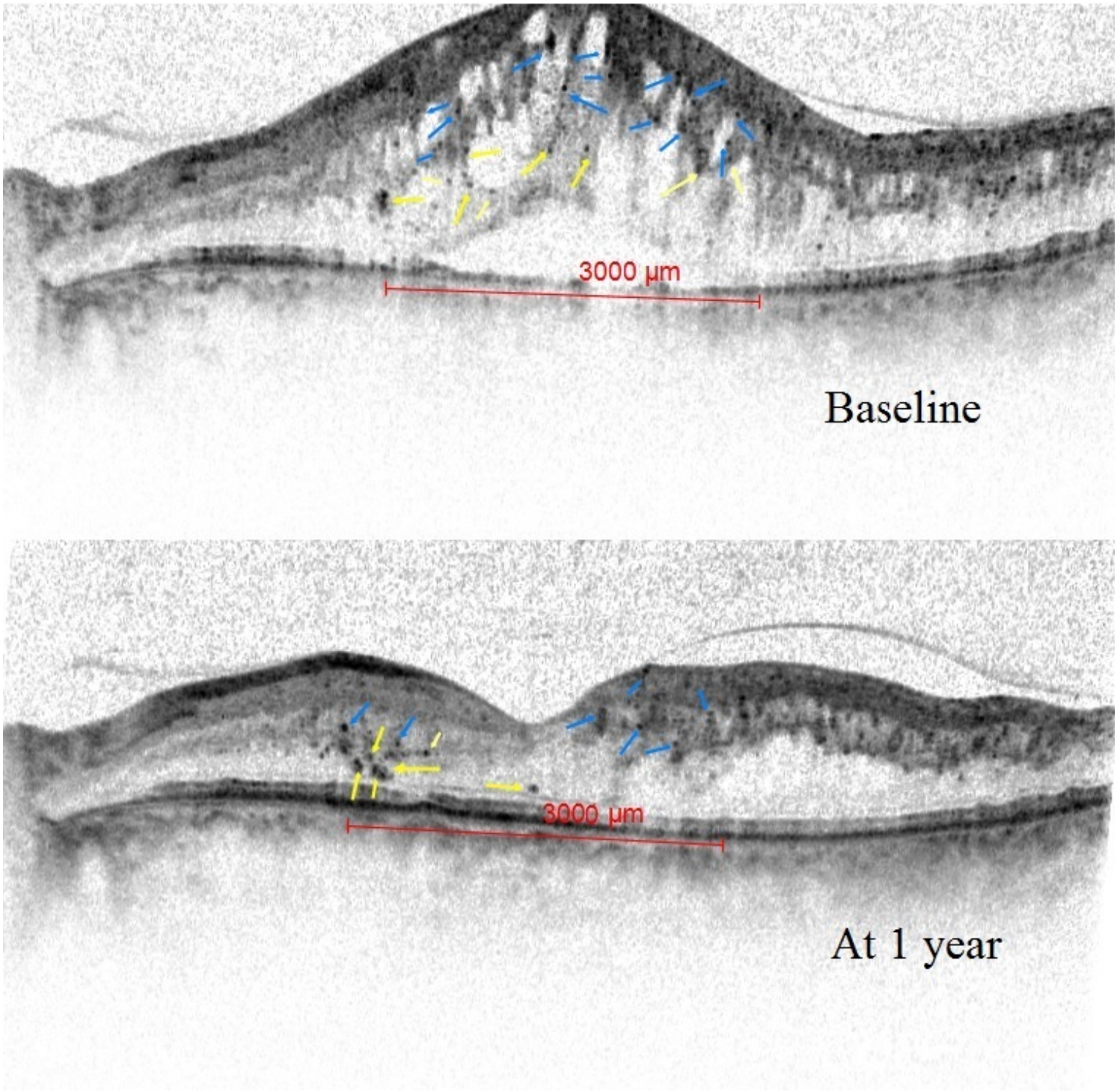

Figure 1

A representative case of BRVO with ME at baseline and 1 year after the IVD in group 1. Red lines indicate 3,000-mm reference lines. SD-OCT images from a 57-year-old man treated with IVD who had BRVO with ME. Compared with the baseline image, SD-OCT at 1 year after IVD injection showed reduced inner retinal HRDs (blue arrows) and outer retinal HRDs (Yellow arrows).

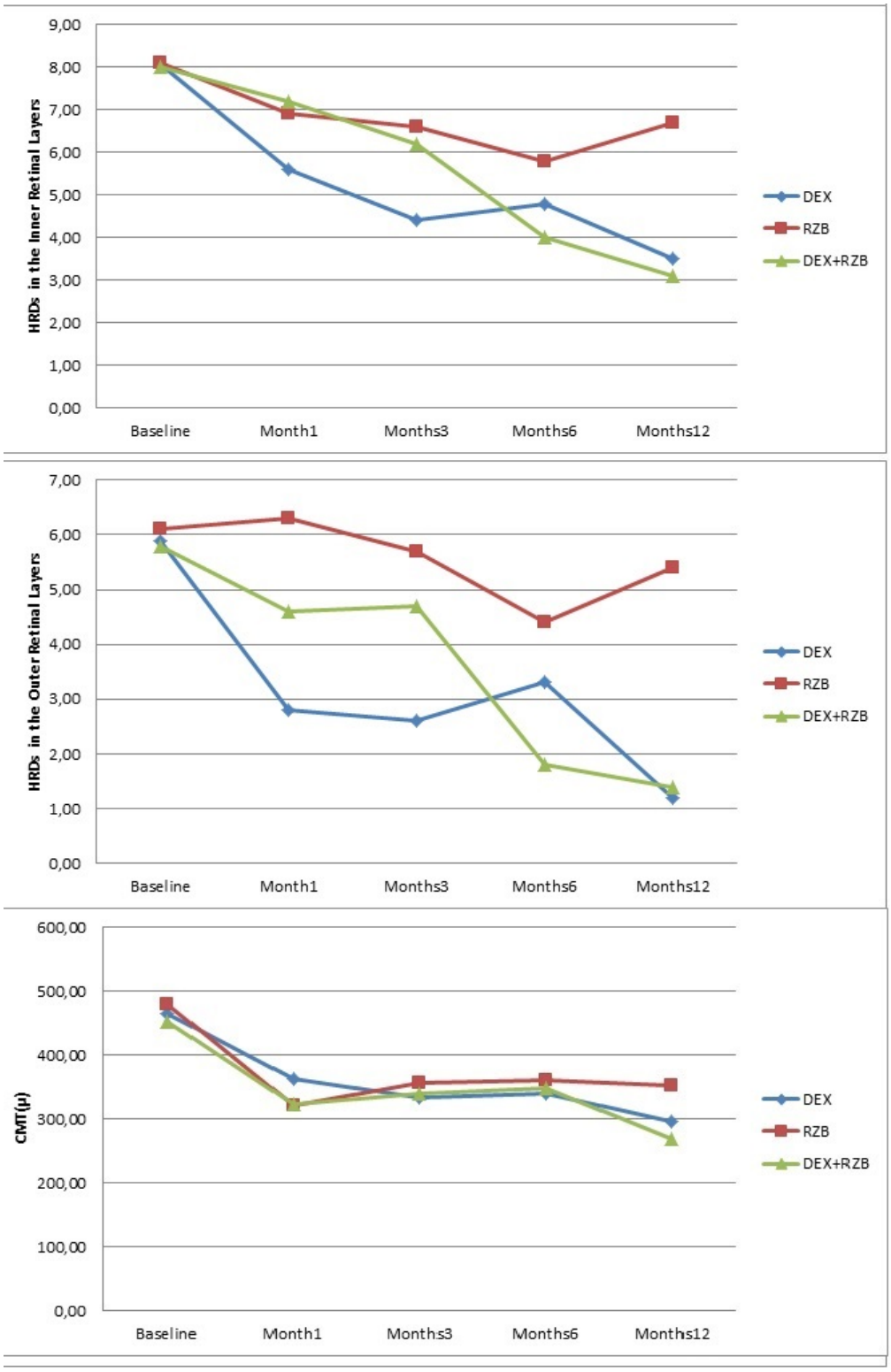

Figure 2

Mean numbers of HRDs in inner and outer retinal layers and central macular thickness (CMT) at each group at baseline and 1,3, 6, and 12 months after intravitreal therapy.