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Comparison of changes in number of hyperreflective dots after intravitreal ranibizumab or dexamethasone implant in patients with branch retinal vein occlusion

Aylin Karalezli[1], Sema Tamer Kaderli[2]*, Ahmet Kaderli[1], Cansu Kaya[1], Sabahattin Sul[1]

Abstract:

PURPOSE: To compare the effect of intravitreal ranibizumab (IVR) or intravitreal dexamethasone implants (IVD) on the regression of hyperreflective dots (HRDs) in patients with branch retinal vein occlusion (BRVO).

MATERIALS AND METHODS: Thirty-seven eyes 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 treatments. Group 1 consisted of 12 eyes who received only IVD, Group 2 consisted of 10 eyes who received only IVR, and Group 3 consisted of 15 eyes who received both IVD and IVR. The number of HRDs and best-corrected visual acuity (BCVA) were compared between the Groups through the follow-up time.

RESULTS: The mean number of HRDs in inner and outer retinal layers was significantly decreased in Group 1 and Group 3 (For Group 1; $P < 0.001$, $P = 0.001$, for Group 3; $P < 0.001$, $P < 0.001$). At the 1st year, the number of HRDs in inner and outer retinal layers was significantly lower in Group 1 and Group 3 than Group 2 (All $P < 0.05$). The BCVA was higher in Group 3 than Group 2 at 1st year ($P = 0.048$).

CONCLUSION: The HRDs should be considered inflammatory markers in the follow-up of CME in BRVO.

Keywords:

Branch retinal vein occlusion, hyperreflective dots, intravitreal dexamethasone, intravitreal ranibizumab, optic coherence tomography

Introduction

Branch retinal vein occlusion (BRVO) is the second most 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 intravitreal 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, recurrence and resistance of edema is a

[1]Department of Ophthalmology, Mugla Sitki Kocman University School of Medicine, Mugla, Turkey, [2]Department of Ophthalmology, Mugla Sitki Kocman Education and Training Hospital, Mugla, Turkey

***Address for correspondence:**
Dr. Sema Tamer Kaderli, Mentese Street 18/7, Mentese, Mugla, Turkey.
E-mail: sematamerkaderli@hotmail.com

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major problem in some BRVO patients. It is known that cytokines other than VEGF may be associated with inflammation and retinal hypoxia in BRVO and the pathogenesis of ME is complicated.[6] The anatomical healing could be monitored via optical coherence tomography (OCT) among which hyperreflective dots (HRDs) on OCT appear as well-circumscribed, highly reflective marks of 20–40 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 the regression of HRDs in BRVO.

Materials and 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 (Approval number: 15/II, Date: 14.07.2021). The patient consent is waived by IRB. Cases with clinically significant treatment-naive ME due to BRVO that had been present for < 3 months, the best-corrected visual acuity (BCVA) of between 1.30 (logarithm of minimum angle of resolution [logMAR]) and 0.30 (logMAR), and a central macular thickness (CMT) >300 μm on OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) were included in this study. Cases with a history or symptoms of chorioretinal diseases (e.g., posterior uveitis, DR, and choroidal neovascularization), insufficient quality images, media opacity (e.g., cataract and 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 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 >300 μm 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 3 monthly injections if they met the following criteria: CMT >300 μm 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 every 3 months after the initial 3 monthly IVR injections if they met the following criteria: CMT >300 μm 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. After three consecutive ranibizumab injections, patients with a poor response to IVR (reduction of CMT <50 μm) who accepted dexamethasone therapy were switched to dexamethasone implants. Written and verbal informed consent, clearly explaining all potential risks and possible benefits of IVR or dexamethasone, was discussed with and obtained from every patient. As a result of the informed consent, intravitreal treatment was applied to cases those who accepted related therapy.

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 logMAR 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. Images with good-quality scores were included in this study. OCT parameters (CMT, number of HRDs) and BCVA logMAR were compared between the Groups and over the follow-up time. Each patient was consulted by the internal medicine unit for blood pressure control and follow-up.

The OCT volume scan was performed on a 6x6mm macular cube with 20 averaged frames per B-scan centered over the fovea separated by 125 μm. The integrated follow-up mode of the device was used to ensure that the exact same retinal area was imaged at every follow-up visit. In the B-scan images of the OCT after black-on-white converting, HRD were represented as follows: discrete and well-circumscribed particles 20–40 μm 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 retinal pigment epithelium.[8] The eye-tracking system of the device was used to assure that the correct position was maintained during the scanning process. The central foveal horizontal B-scan was selected for each patient, and the same scan was used for all follow-up visits, as defined by the eye-tracker system. 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 [OPL] to the outer border of the photoreceptor layer) [Figure 1].

The SPSS 22.0 (SPSS, Inc., Chicago, IL, USA) software program was used for statistical analyses. Continuous variables were given as mean ± standard deviation, 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 with *post hoc* Bonferroni correction was used for comparisons of parameters between Groups after treatment at 1 year. A $P \leq 0.05$ was considered statistically significant. For the evaluation of interobserver concordance of the HRDs counting, an intraclass correlation coefficient was calculated.

Results

The baseline (pretreatment) comparisons and clinical characteristics are summarized and detailed in Table 1. There was no significant difference between Groups in terms of BCVA, CMT, the status of External limiting membrane (ELM) and Ellipsoid zone (EZ), HRDs in the inner retinal layers and the outer retinal layers at baseline ($P > 0.05$ for all parameters). The macular ischemia was not seen in any patient. Interinvestigator reliability between two retina specialist for the counting of HRDs was assessed with a κ value, which was 0.857 ($P < 0.001$).

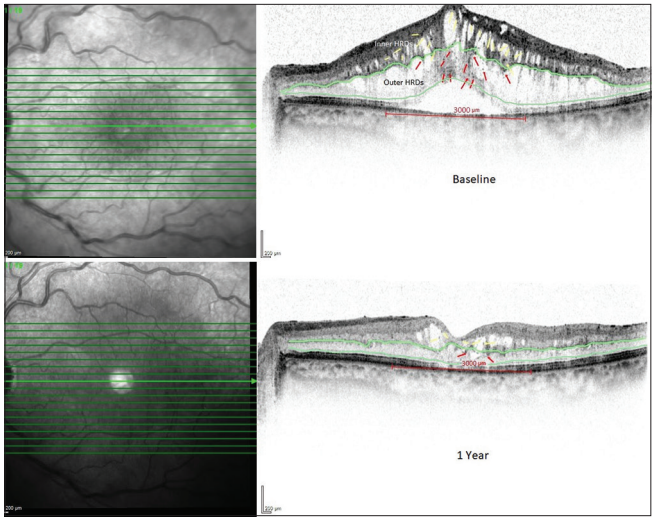

Figure 1: A representative case of BRVO with ME at baseline and 1 year after the IVD in Group 1. Red lines indicate 3000 mm reference lines. SD-OCT images from a 62-year-old woman treated with IVD who had BRVO with ME. Compared with the baseline image, SD-OCT at 1 year after IVD injection showed reduced inner retinal HRDs (Yellow arrows) and outer retinal HRDs (Red arrows). BRVO = Branch retinal vein occlusion, ME = Macular edema, IVD = Intravitreal dexamethasone implants, SD-OCT = Spectral domain optical coherence tomography, HRDs = Hyperreflective dots

The comparison of BCVA and OCT parameters after treatments during follow-up time is summarized in Table 2. Compared to the baseline values in all Groups, a significant decrease was observed in CMT in the 1st 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 was 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 ($P = 0.134$, $P = 0.477$). The changes of HRDs in inner and outer retinal layers and CMT at each Group over the follow-up time were shown in Figure 2.

At the 1st 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 ($P = 0.048$). There was no significant difference in terms of posttreatment CMT and

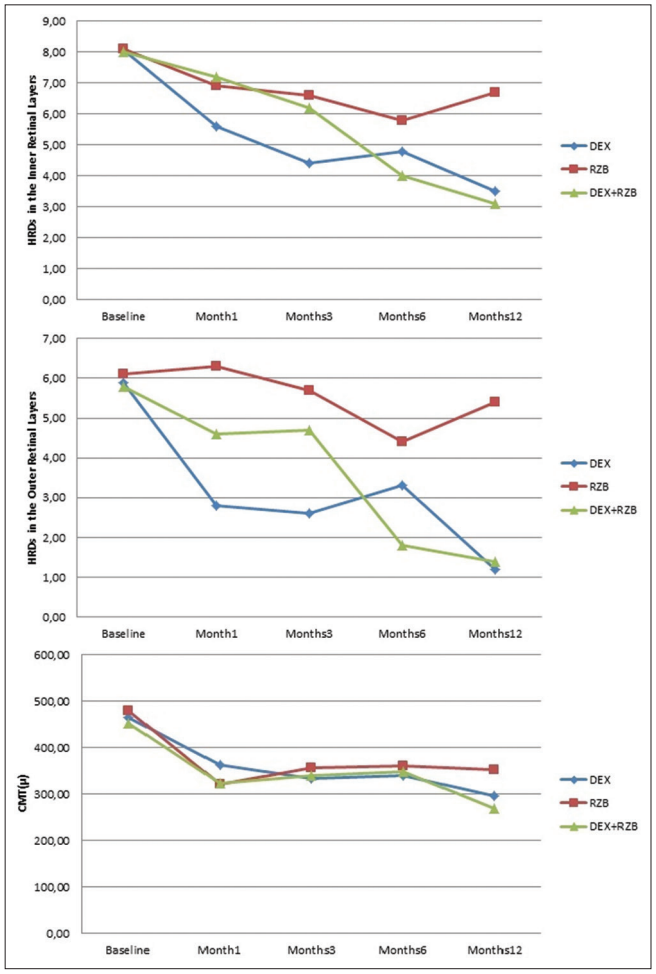

Figure 2: Mean numbers of HRDs in inner and outer retinal layers and CMT at each Group at baseline and 1, 3, 6, and 12 months after intravitreal therapy. HRDs = Hyperreflective dots, CMT = Central macular thickness

Table 1: The baseline demographics and best-corrected visual acuity of the patients

	Mean±SD			*P*
	Group 1 (*n*=12)	Group 2 (*n*=10)	Group 3 (*n*=15)	
Age, (years)	63.9±6.9	62.4±5.5	64.0±5.6	0.775
Sex (female/male)	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				
Intact, *n* (%)	6 (50)	4 (40)	6 (40)	0.839
Disrupted, *n* (%)	6 (50)	6 (60)	9 (60)	
EZ status				
Intact, *n* (%)	5 (41.6)	3 (30)	5 (33.3)	0.829
Disrupted, *n* (%)	7 (58.4)	7 (70)	10 (66.7)	

Data are presented as mean±SD. BCVA=Best-corrected visual acuity, logMAR=Logarithm of the minimum angle of resolution, CMT=Central macular thickness, IOP=İntraocular pressure, ELM=External limiting membrane, EZ=Ellipsoid zone, SD=Standard deviation

Table 2: Comparison of best-corrected visual acuity and optical coherence tomography parameters after treatments during follow-up

	Mean±SD					*P**
	Baseline	Month 1	Month 3	Month 6	Month 12	
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**

**P*: A paired *t*-test was used to compare the number of HRD, BCVA and CMT between baseline and 12 months after the treatment. Bold values are statistically significant. BCVA=Best corrected visual acuity, logMAR=Logarithm of the minimum angle of resolution, CMT=Central macular thickness, HRD=Hyperreflective dot, IRL=İnner retinal layer, ORL=Outer retinal layer, SD=Standard deviation

the number of HRDs between Groups 1 and 3 in *post hoc* tests ($P = 0.621$, $P = 0.876$, and $P = 0.632$). The number of injections was significantly lower in Group 1 [Table 3]. The disruption of ELM and EZ presence was higher in Group 2 [Table 3].

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 were 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.

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, might be small intraretinal protein and/or lipid deposits

Table 3: Comparison of best corrected visual acuity and optical coherence tomography parameters between the groups at 1 year

	Mean±SD			P^A	P^B	P^C	P^D
	Group 1	Group 2	Group 3				
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							
Intact, *n* (%)	7 (58.3)	2 (20)	10 (66.6)				0.06
Disrupted, *n* (%)	5 (41.7)	8 (80)	5 (33.4)				
EZ status							
Intact, *n* (%)	8 (66.6)	3 (30)	11 (73.3)				0.102
Disrupted, *n* (%)	4 (33.4)	7 (70)	4 (26.7)				

P^A=Group 1 versus group 2, P^B=Group 1 versus group 3, P^C=Group 2 versus group 3, P^D: Chi-square test. Bold values are statistically significant.
BCVA=Best-corrected visual acuity, logMAR=Logarithm of the minimum angle of resolution, CMT=Central macular thickness, HRD=Hyperreflective dot, IRL=İnner retinal layer, ORL=Outer retinal layer, ELM=External limiting membrane, EZ=Elipsoid zone

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 HRDs could represent inflammatory cells, particularly activated microglia, rather than lipid extravasation.[14]

Zeng *et al*. showed that, as DR in human donor eyes progresses, activated microglia infiltrate and migrate to the outer retinal layer.[15] Singhal *et al*. demonstrated that the number of activated microglia decreases after intravitreal triamcinolone injection.[16] Retinal glial cells, contribute to the development of ME. After the retinal injury, retinal glial cells (Muller) upregulate inflammatory factors, including monocyte chemoattractant protein-1, which recruit phagocytotic monocytes and microglial cells to the injured area.[17] In a healthy retina, resting microglia are essentially located in the inner retina, but with inflammation, the activated microglial cells migrate to the site of injury.[18] The activated microglia also discharge proinflammatory and proangiogenic mediators.[19] Vujosevic *et al*. stated the migration of HRDs from the inner to the outer retina layers through the DR progression.[20] The contribution of activated microglia to the progression of BRVO was also shown in animal model.[21]

The zonula adherens between the photoreceptors and Muller cells, creating the ELM, can block the transfer of macromolecules (lipid and protein) and that the healthy ELM restricts the migration to the photoreceptors. A breakdown of ELM permits the migration of these inflammatory molecules and leads to both photoreceptor disorganization and thus poor visual acuity.[22] 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 which 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 pathological association of increased HRDs in outer retinal layers with disruption of the ELM and EZ and poor visual acuity may be a clinical prognostic markers of outer blood-retinal breakdown and consequent photoreceptor dysfunction. The above-mentioned conclusions may also describe the fact why visual acuity does not always increase after intravitreal treatments, even the decrease of CMT.

The increased VEGF, inflammatory cytokines, and chemokines contribute to the pathology of ME due to BRVO.[1,23] Sohn *et al*. reported that CMT was more decreased in the intravitreal triamcinolone acetonide (IVTA) Group compared to bevacizumab Group. The authors also stated that IL-6, interferon-γ-inducible protein 10 and VEGF were significantly decreased in the IVTA Group.[24] 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. On opposite, anti-VEGF agents have been observed to reduce hyperpermeability through a decrease in the production of VEGF.[25] Therefore, IVD implants, which inhibit inflammatory cytokines, may be more effective as a therapeutic option for ME in patients with BRVO.

Previous studies have attempted to compare the effect of two treatment alternatives that is, an anti-VEGF agent and an IVD implant on the number of HRDs over time.

Our study, in line with previous ones, demonstrated more reduction in HRDs number after IVD treatment in patients with ME due to BRVO. Furthermore, our study confirmed that HRDs correlated negatively with visual acuity.[26-29] Do *et al*. reported that 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 IVB or IVD. They found that the number of HRDs on OCT can be a predictive prognostic factor of the treatment response to IVB or IVD. A higher number of HRDs and higher rate of OPL disruptions were observed in IVB nonresponders than in responders in their study. They also supported that IVD may be more effective in treating diabetic ME or retinal vein occlusion eyes with many HRDs and OPL disruptions on OCT.[28] In our 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 HRDs are independent factors for worse final BCVA in a study in which they investigated the outcomes in patients with ME due to DR and BRVO. They reported that they achieved similar reductions in HRDs after IVD and IVR treatment. The mean BCVA showed significant improvement from baseline at all time points in both treatment.[29] In contrast, in our study, we observed that the number of HRDs in the inner and outer retinal layer was lower in patients who received IVD than in patients who received IVR after 1 year. Furthermore, the final BCVA was higher in patients treated with IVD than the patients treated with IVR in our study. We speculate that these different results may be related with the difference in the patient Groups included. While both DR and BRVO cases were included in the mentioned study, we only included BRVO patients.

Our study was limited in lower sample sizes and retrospective, 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 to BRVO, treated by two agents and combined treatment.

Conclusion

This study suggested that HRDs as a potential biomarker of poor final visual outcome in patients with ME due to BRVO. Furthermore, the reduction of HRDs was more prominent in patients who received IVD. Therefore, in patients with higher HRDs after BRVO, IVD treatment may be chosen for the treatment of cystoid macular edema (CME) secondary to BRVO, which has advantages such as fewer injections with good visual results.

Data availability statement

The manuscript has no associated data in a data repository.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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