Morphological Predictors of Short-Term Response to Intravitreal Bevacizumab in Macular Edema Due to Retinal Vein Occlusion

Preditores Morfológicos de Resposta ao Bevacizumab Intravítreo para Tratamento do Edema Macular Secundário a Oclusão Venosa da Retina

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ABSTRACT

INTRODUCTION: Our purpose was to identify morphological predictive factors of short-term macular functional and anatomical outcomes after monthly intravitreal bevacizumab for the treatment of macular edema (ME) due to central (CRVO) and branch retinal vein occlusion (BRVO).

METHODS: Retrospective study of patients with ME secondary to CRVO or BRVO under monthly treatment with intravitreal injections of bevacizumab. Only treatment naïve patients, with center-involved ME of ≥305 μm in women and ≥320 μm in men on baseline Spectral-domain OCT (SD-OCT) (Heidelberg Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) were included. Resolution of ME was defined as central macular thickness (CMT) less than 300 μm, no subretinal and no intraretinal fluid. Demographic and clinical parameters, best-corrected visual acuity (BCVA) in ETDRS logarithmic scale and SD-OCT images were reviewed at baseline and at 4 months. SD-OCT morphologic features in the central 1.0-mm diameter circle were checked for disorganization of the retinal inner layers (DRIL), ellipsoid zone (EZ) and external limiting membrane (ELM) disruption, presence and location of intraretinal hyperreflective foci (HRF) cysts, subretinal and intraretinal fluid, and vitreoretinal interface status.

RESULTS: The study enrolled 61 eyes of 61 patients, 29 (47.5%) with CRVO and 32 (52.5%) with BRVO. At 4 months, patients had received a mean number of 3.2±2.7 bevacizumab injections. Mean BCVA was 32±27 ETDRS letters at baseline and improved to 44±27 at 4 months (p<0.001). BCVA improvement was similar in CRVO and BRVO eyes (p=0.68). A greater BCVA improvement was correlated with a worse baseline value (r=-0.45, p<0.001). CMT reduced significantly from 592 ± 223 μm at baseline to 327 ±117 μm after loading dose (p<0.001) and twenty-three (37.7%) patients presented a complete resolution of ME at the 4th month timeline. The number of eyes with ME resolution were similar between those with CRVO and BRVO (p=0.590).

The BCVA at the 4th-month follow-up was significantly lower in patients who presented at baseline with DRIL (39±27 *vs* 64±17 ETDRS letters, p=0.006), disrupted EZ (40±26 *vs* 64±21 ETDRS

letters, *p*=0.016) and disrupted ELM (40±2 *vs* 64±20 6 ETDRS letters, *p*=0.016). Patients who presented DRIL at baseline have less 25.1 letters in BCVA at 4-months than patients who did not (95% confidence interval [CI] 8.1 – 42.3; *p*=0.004). Similarly, EZ and EML disruption predicted a decrease of 24.5 letters in final BCVA comparing to patients with integrity of these layers (EZ 95% CI 5.6 – 43.5; *p*=0.010 MLE 95% CI 5.6 – 43.5; *p*=0.010). None of the analyzed baseline morphological factors were predictive of ME resolution. However, absence of DRIL (*p*=0.003), presence of HRF in the inner retinal layers (*p*<0.001) and preserved EZ (*p*=0.030) and ELM (*p*=0.004) were significantly more frequent among those with ME resolution.

CONCLUSION: Intravitreal injection of bevacizumab for ME due to CRVO and BRVO resulted in a significant functional and anatomical improvement. In our study, patients with DRIL and disrupted EZ and ELM at baseline presented a significant lower BCVA at the end of the follow-up. Identification of baseline biomarkers for ME poor response to anti-VEGF will enable disease stratification and prognosis and improve treatment decisions.

KEYWORDS: Bevacizumab; Macular Edema; Retinal Vein Occlusion; Tomography, Optical Coherence.

RESUMO

INTRODUÇÃO: O nosso objetivo foi identificar preditores morfológicos de resposta anatómica e funcional a curto prazo ao tratamento do edema macular (EM) secundário a oclusão de ramo (OVRR) e da veia central da retina (OVCR) com bevacizumab.

MÉTODOS: Estudo retrospetivo de doentes com EM secundário a OVRR e OVCR sob tratamento mensal com injeções intravítreas de bevacizumab. Apenas doentes *treatment naïve* e com edema macular central com ≥305 µm nas mulheres ≥320 µm em homens na tomografia de coerência óptica (SD-OCT) (Heidelberg Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) foram incluídos. A resolução do EM foi definida como uma espessura macular central inferior a 300 µm e ausência de líquido intra e subretiniano. Foram colhidos dados demográficos, relativos à melhor acuidade visual corrigida (MAVC) na escala ETDRS e as imagens do SD-OCT foram analisadas na *baseline* e aos 4 meses. As imagens do SD-OCT, no anel de 1,0 mm central, foram analisadas quanto à presença de: desorganização das camadas internas da retina (DRIL), disrupção da zona elipsoide (ZE) e da membrana limitante externa (MLE), presença e localização de focos hiperrefletivos intrarretinianos (HRF), líquido intra e subretinano e status da interface vítreo-retiniana.

RESULTADOS: Foram incluídos 61 olhos de 61 doentes, dos quais 29 (47,5%) apresentaram OVCR e 32 (52,5%) OVRR. Aos 4 meses o número médio de injeções intravítreas realizadas foi de 3,2±2,7 injeções. A MAVC melhorou de 32±27 letras ETDRS na baseline para 44±27 letras ETDRS aos 4 meses (*p*<0,001). A melhoria da MAVC foi idêntica em olhos com OVCR e OVRR (*p* = 0,680). Uma MAVC inferior na *baseline* correlacionou-se com um maior ganho de letras ETDRS ao fim de 4 meses (r = -0,45, *p*<0,001).

A MAVC aos 4 meses foi significativamente mais baixa nos indivíduos que apresentavam na baseline presença de DRIL (39±27 *vs* 64±17 ETDRS letras, *p*=0,006), disrupção da ZE (40±26 *vs* 64±21 letras ETDRS, *p*=0,016) e da MLE (40±2 *vs* 64±20 6 letras ETDRS, *p*=0,016). Os pacientes que apresentavam DRIL na baseline têm em média menos 25,2 letras na MACV ao fim de 4 meses (Intervalo de confiança [IC] 95%, 8,1 – 42,3; *p*=0,004). Do mesmo modo, a disrupção da ZE e da MLE predizem uma diminuição de 24,5 letras na AV final (EZ IC 95%, 5,6 – 43,5; *p*=0,010; MLE IC 95%, 5,6 – 43,5; *p*=0,010).

Vinte e três (37,7%) doentes apresentaram resolução completa do EM aos 4 meses. O número de olhos com resolução de EM foi semelhante entre aqueles com OVCR e OVRR (*p* = 0,590). Nenhum dos fatores clínicos ou morfológicos analisados na baseline foram preditivos de resolução do EM. No entanto, ausência de DRIL (*p* = 0,003), presença de HRF nas camadas internas da retina (*p* <0,001) e integridade da ZE (*p* = 0,03) e MLE (*p* = 0,004) foram significativamente mais frequentes entre aqueles com resolução do EM.

CONCLUSÃO: O tratamento do EM secundário a OVCR e OVRR com injeções intravítre-

as de bevacizumab traduziu-se em ganho anatómico e funcional significativo. No nosso estudo, doentes com DRIL e disrupção da ZE e MLE na baseline apresentaram uma MAVC inferior no *follow-up*. A identificação de biomarcadores que antecipem a resposta do EM ao tratamento com anti-VEGF ajudará a programar o tratamento destes doentes e, adicionalmente, permitirá a estratificação e o estabelecimento do prognóstico da doença.

PALAVRAS-CHAVE: Bevacizumab; Edema Macular; Oclusão Venosa da Retina; Tomografia de Coerência Óptica.

INTRODUCTION

Retinal vein occlusion (RVO) is one of the most prevalent retinal vascular diseases and a leading cause of visual morbidity.[1,2]

Visual loss in RVO is attributable predominantly to macular edema (ME).[1,3] In RVO, the vascular occlusion increases retinal capillary pressure, inducing an upregulation of vascular endothelial growth factor (VEGF) which, subsequently, results in increased capillary permeability, leaking fluid and blood to the retina.[3-5]

Over the last decade, intravitreal anti-vascular endothelial growth factor (anti-VEGF) has revolutionized the treatment of ME secondary to RVO and significantly improved the visual prognosis of these patients.[1,3,6] Clinical studies demonstrated beneficial effects of anti-VEGF therapy both on ME resolution and best corrected visual acuity (BCVA) in patients with central (CRVO) and branch retinal vein occlusion (BRVO).[1,7-13] Among anti-VEGF therapies, bevacizumab although an off-label treatment, is reported in several retrospective and prospective studies as an effective option in the improvement of BCVA and reduction of central macular thickness (CMT) in RVO.[14]

Nowadays, the current standard to evaluate ME response to treatment relays on BCVA and spectral domain optical coherence tomography (SD-OCT) parameters, including CMT and the presence of intra and subretinal fluid. However, previous investigations using OCT revealed that CMT is only modestly correlated with current visual acuity or its variation.[15] Moreover, despite ME resolution, BCVA does not always improve.[16] The clinical response to anti-VEGF treatment is heterogenous, while some eyes present a great and sustained response to anti-VEGF treatment on OCT, others have persistent ME.[17]

Therefore, there is an urgent need to identify predictors of functional and anatomical outcomes in patients with ME secondary to RVO.

Previous studies show that OCT findings other than ME may constitute important factors of prognosis in RVO. Recently, it has been demonstrated that disorganization of retinal internal layers (DRIL) and ellipsoid zone (EZ) disruption can be related with visual acuity outcomes.[18,19] Furthermore, DRIL seems also to be a major risk factor for ME recurrence.[20]

This is an issue of interest, since biomarkers predicting final BCVA and ME resolution may contribute to disease phenotype profiling, improvement of treatment decisions, such as an optimized use of intravitreal injections, risk stratification and prognosis assessment.

Therefore, the purpose of this study was to identify in a Portuguese cohort predictive factors for macular functional and anatomical improvement after intravitreal bevacizumab for the treatment of ME due to RVO and BRVO.

METHODS

We retrospectively analyzed data gathered during the regular clinical visits of patients diagnosed with CRVO and BRVO at the Department of Ophthalmology of Centro Hospitalar e Universitário de São João, a tertiary referral center from Porto, Portugal. The study was conducted in accordance with the tenets of the Declaration of Helsinki and approved by the Institutional Review Board and Ethics Committee of our hospital.

Patients newly diagnosed with RVO between July 2016 and December 2020 were revised.

PATIENT ELIGIBILITY

The study included patients newly diagnosed with ME secondary to CRVO or BRVO. Only treatment naïve patients, with center-involved ME of ≥305 μm in women and ≥320 μm in men on baseline SD-OCT (Heidelberg Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) were included.

Exclusion criteria were any retinal disease other than CRVO/BRVO, past history of uveitis, cataract surgery within 6 months, prior vitrectomy and media opacity precluding high quality images assessment.

TREATMENT PROTOCOL

Patients received consecutive monthly intravitreal injections of Bevacizumab (Avastin®) until the first follow-up appointment (at 4- months). A dose of 1.25 mg in a 0.05 mL total volume was injected intravitreally via the pars plana.

DATA COLLECTION

The medical files of all eligible patients were reviewed and data on demographic, clinical parameters, risk factors for RVO, BCVA in ETDRS (Early Treatment of Diabetic

Retinopathy) scale and SD-OCT images both at baseline and 4- months post-treatment start, were collected.

SD-OCT was acquired with Spectralis HRA-OCT (Heidelberg Engineering, Heidelberg, Germany). The 20x15º macular cube raster scan and horizontal 6 mm high resolution linear fovea-centered scans were used. For analysis purpose only high-quality images were considered. SD-OCT morphologic features in the central 1.0-mm diameter circle were checked for DRIL, EZ and external limiting membrane (ELM) disruption, presence and location of intraretinal hyperreflective foci (HRF), subretinal and intraretinal fluid, and vitreoretinal interface status.

DRIL was defined as a disruption of any of the two boundaries between the ganglion cell-inner plexiform layer, inner nuclear layer and outer plexiform layer, as previously described.[18] EZ and ELM disruptions were considered as any interruption of these band's continuity. Resolution of ME was defined as CMT lower than 300 µm, no subretinal and no intraretinal fluid.

STATISTICAL ANALYSIS

Normality of quantitative data was assessed using the Shapiro-Wilk test. Categorical variables are expressed as frequencies (percentage). Continuous variables are expressed as mean ± standard deviation (SD) or median and range according to normality. The paired t-test was used to compare data at baseline and at the end of the follow-up. For comparison between groups, independent-sample T test or Mann-Whithney test for continuous variables or chi-square test for categorical variables were applied. The Pearson's correlation coefficient was used to assess the strength of the correlation between baseline BCVA and its variation. A *p* value of $p<0.05$ was considered significant.

Statistical analysis was performed with the statistical software SPSS Version 26.

RESULTS

CLINICALC HARACTERISTICS AT BASELINE

The study enrolled 61 eyes of 61 patients, of which 29 (47.5%) presented a CRVO and 32 (52.5%) a BRVO. Table 1 illustrates the distribution of baseline characteristics of the study population. Half of the sample was composed by females (55.7%) and the mean age at diagnosis was 69 ± 14 years. In the majority of the cases, the RVO presented as a symptomatic event (44%). Regarding RVO risk factors, 70.5% of the sample had arterial hypertension, 42.6% dyslipidemia and 11.4% ocular hypertension or glaucoma.

At 4 months follow-up, patients had received a mean number of 3.2±2.7 bevacizumab injections.

Table 1. Demographic and clinical characteristics of the study group.

Demographics	
Age, years	69 ± 14
Female, n (%)	34 (55.7)
Study eye, % right eye	33 (54.1)
Symptoms	
Asymptomatic, n (%)	17 (27.9)
Symptomatic, n (%)	44 (72.1)
Duration of symptoms, days	15 [1-90]
Risk factors for RVO	
Arterial hypertension, n (%)	43 (70.5)
Dyslipidemia, n (%)	26 (42.6)
Ocular hypertension/glaucoma n(%)	7 (11.4)
Retinal vein occlusion Type	
Central vein occlusion, n (%)	29 (47.5)
Branch vein occlusion, n (%)	32 (52.5)
Number of bevacizumab injections	3.2±2.7
Central vein occlusion	3.0 ±0.7
Branch vein occlusion	3.3 ± 0.8
Follow-up time, months	4

FUNCTIONAL AND ANATOMIC OUTCOMES AFTER TREATMENT

Mean BCVA was 32±27 ETDRS letters at baseline and improved to 44±27 at 4 months ($p<0.001$). BCVA improvement was identical in CRVO and BRVO eyes ($p=0.680$) (Fig. 1). A greater BCVA improvement was correlated with a worse baseline value (r=-0.45, <0.001) (Fig. 2).

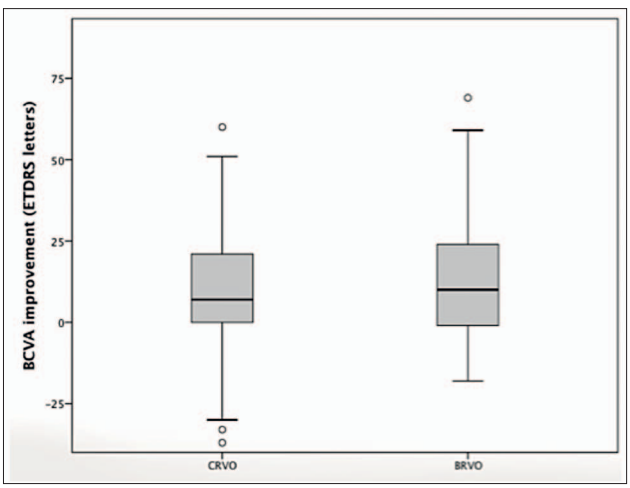

Figure 1. BCVA improvement was identical in CRVO and BRVO eyes ($p=0.680$).

BCVA, best corrected visual acuity; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion.

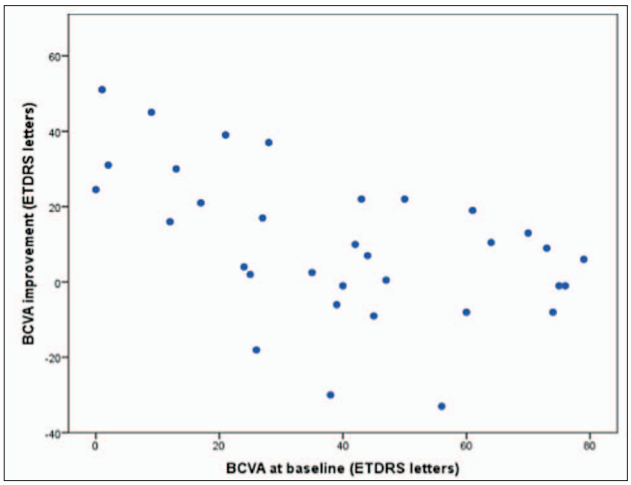

Figure 2. Patients with a low BCVA at baseline presented a greater improvement of BCVA after treatment (r=-0.45, <0.001).

BCVA, best corrected visual acuity.

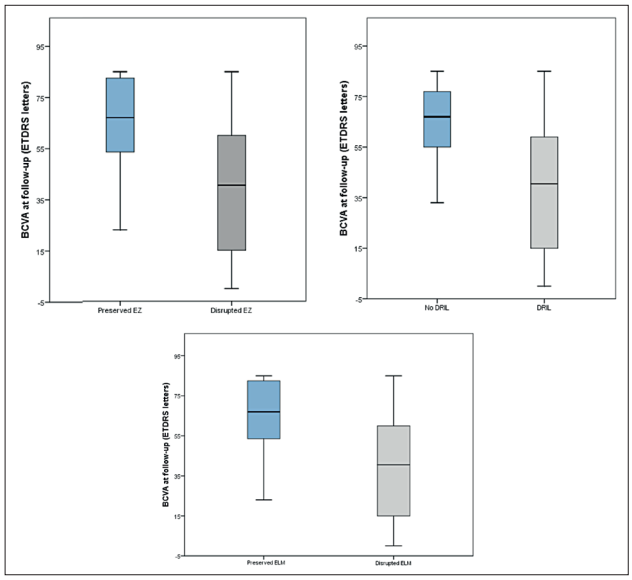

Figure 3. Association of baseline SD-OCT parameters with follow-up BCVA.

BCVA, best corrected visual acuity; DRIL, disorganization of the retinal inner layers; EZ, ellipsoid zone; ELM, external limiting membrane.

CMT at baseline was 592 ± 223 µm, reducing significantly to 327 ±117 µm at the 4th month (p<0.001). Baseline CMT thickness was higher in eyes with CRVO than BRVO (659 ± 221 *vs* 536 ± 213 µm, p=0.040).

Twenty-three (37.7%) patients presented a complete resolution of ME at the 4th month timeline, being the number of eyes with ME resolution similar between those with CRVO and BRVO (11 (37.9%) *vs* 12 (37.5%), p=0.590).

PREDICTIVE ANALYSIS

DRIL, presence and location of HRF, and EZ and ELM disruption, were evaluated as possible markers for BCVA and ME resolution.

At baseline, DRIL was present in 48 (78.7%) patients, EZ and ELM disruptions in 50 (82%) and HRF were evident in 44 (72.1%).

The BCVA at the 4th-month follow-up was significantly lower in patients who presented at baseline DRIL (39±27 *vs* 64±17 ETDRS letters, p=0.006), disrupted EZ (40±26 *vs* 64±21 ETDRS letters, p=0.016) and disrupted ELM (40±2 *vs* 64±20 6 ETDRS letters, p=0.016) (Fig. 3). Final BCVA was not statistically different in patients who had HRF at presentation (33.9±30.2 *vs* 47.4±25.1 ETDRS letters, p=0.117).

Furthermore, the presence of DRIL, EZ and EML disruption predicts final BCVA. Patients who present DRIL at baseline have less 25.1 letters in BCVA at 4-months than patients who do not (95% Confidence Interval [CI] 8.1 – 42.3; p=0.004). Similarly, EZ and EML disruption predict a decrease of 24.5 letters in final BCVA comparing to patients with integrity of these layers (EZ CI 95% 5.6 – 43.5; p=0.010 MLE CI 95% 5.6 – 43.5; p=0.010). HRF presence did not predict visual acuity outcomes (p=0.120; Wald chi-square test).

Differently, none of the baseline morphological factors analyzed were different at baseline between patients with or without ME resolution. The presence of HRF (p=0.27), DRIL (p=0.09), EZ (p=0.31) or ELM disruption (p=0.31) at baseline is not different between patients who present or not ME resolution (Table 2). Likewise, the presence of DRIL (p=0.646),

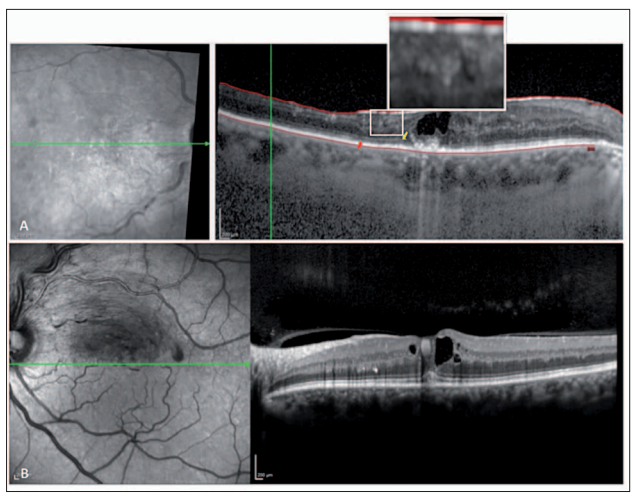

Figure 4. A. OCT scan image illustrative of DRIL (white box), ELM (yellow arrow) and EZ (red arrow) disruption. B. OCT scan illustrative of HRF.

DRIL, disorganization of the retinal inner layers; EZ, ellipsoid zone; ELM, external limiting membrane; HRF, hyperreflective foci.

HRF (p=0.313) and EZ (p=0.908) or ELM (p=0.908) disruption do not influence CMT at the 4th month follow-up.

However, absence of DRIL (p=0.003), presence of hyperreflective foci (HRF) in the inner retinal layers (p<0.001) and preserved EZ (p=0.030) and ELM (p=0.040) at 4 -months were significantly more frequent among those with ME resolution (Table 2).

Table 2. Comparation between patients with and without macular edema resolution.

	Macular Edema Resolution (n=23)	Macular Edema Persistence (n= 38)	*p*
Age, years	68 ± 15	70 ± 14	0.63‡
Female, n(%)	10 (44)	24 (63)	0.71†
BCVA at baseline, ETDRS letters	32 ± 30	32 ± 24	0.99 §
BCVA at follow-up, ETDRS letters	53 ± 27	39 ± 25	0.05 §
ETDRS letters gain, ETDRS letters	21 ± 20	8 ± 23	0.04 ‡
Tomographic features at baseline			
CMT, µm	598 ± 267	588 ± 194	0.87 ‡
HRF, n(%)	17 (81)	28 (76)	0.40 †
Location of HRF, n(%)			0.27 †
- Inner retinal layers	11 (65)	15 (50)	.17 †
- Outer retinal layers	4 (24)	4 (13)	
- Both retinal layers	2 (12)	11 (37)	
DRIL, n(%)	15 (71)	31 (88)	0.09 †
EZ disruption, n(%)	17 (81)	33 (89)	0.31 †
ELM disruption, n(%)	16 (76)	33 (89)	0.31 †
Tomographic features at 4-months			
CMT, µm	266 ± 43	365 ± 194	
HRF, n(%)	13 (65)	30 (86)	0.01 †
Location of HRF			
- Inner retinal layers	5 (39)	12 (40)	<0.001 †
- Outer retinal layers	8 (62)	3 (10)	
- Both retinal layers	0 (0)	15 (50)	
DRIL, n(%)	7 (33)	26 (74)	0.003 †
EZ disruption, n(%)	11 (52)	28 (80)	0.03 †
ELM disruption, n(%)	8 (38)	27 (77)	0.04 †

Continuous variables are reported as mean ± SD. Data were derived from: ‡ Independent samples T test; †Chi-square; § Mann–Whitney test.

BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; CMT, central macular thickness; HRF, hyperreflective foci; DRIL, disorganization of retinal inner layers; EZ, ellipsoid zone; ELM, external limiting membrane.

DISCUSSION

Intravitreal anti-VEGF therapies had become an effective therapeutic option in ME secondary to RVO. However, not all patients experience a visual gain after this treatment,[16,21,22] being important to identify predictive factors for visual gain after anti-VEGF therapy.

OCT can be used for diagnosis, staging, observation, and the individual treatment response evaluation of macular edema in RVO. Until now, CMT and the presence or absence ME have been the major morphologic outcomes included in patient's follow-up. However, recent studies have shown different morphologic features on OCT and their correlation with functional outcomes.[15,18,19,23]

This study demonstrates that in ME secondary to CRVO and BRVO managed with bevacizumab, the presence of DRIL, EZ and ELM disruption at baseline may predict the final BCVA. None of the morphological factors analyzed were predictive of CMT or ME resolution. These results are significant given that except from baseline BCVA, only a few studies have identified imaging markers that consistently predict visual acuity outcomes in ME secondary to RVO.

Our results are in accordance with previous findings.[15,18,19] DRIL, integrity changes in the outer photoreceptor segment line and disrupted ELM illustrates damage to the retinal structure that may lead to irreversible cell loss and associated functional loss. A study with 91 eyes with ME secondary to CRVO, demonstrated that the extents of both DRIL and EZ disruption were associated with the BCVA and that the initial 3-month evolution of DRIL and EZ integrity are robust predictors of twelve-month visual acuity, independently of baseline visual acuity and CMT.[18] Another study of 136 eyes with macular edema due to RVO concluded that greater DRIL extent at baseline correlates with worse baseline visual acuity (point estimate, 0.04; 95% CI, 0.01– 0.07 per 100 µm, p= 0.003). The change in the DRIL

extent following the first three monthly anti-VEGF injections identified the eyes with a high likelihood of subsequent VA improvement or decline.[24]

In our study, we did not find an association between the presence of HRF and the final BCVA. The origin of these foci is still unclear, but they may be present in the initial stage of the development of intraretinal hard exudates or subclinical features of lipoprotein extravasation after inner blood–retinal barrier disruption.[25] Previous findings showed that HRF are associated with poorer visual outcomes and that its reduction can be achieved with treatment.[26,27] Moreover, the location of HRF seems to be a prognostic factor. Kang et al. retrospectively reviewed 97 eyes with macular edema secondary to BRVO under bevacizumab treatment and concluded that the presence of HRF in outer retinal layers was predictive of disrupted ELM and photoreceptors inner and outer segments at the final visit and these patients had a poor final BCVA.[23]

A cohort of 682 patients (a subset of CRYSTAL and BRIGHTER cohorts) was analyzed in order to identify the best imaging biomarkers for assessing the structure function correlation. The predictors found were central retinal thickness, subretinal and intraretinal fluid and HRF.[1] Our lack of significance for HRF may reside on the short time of follow-up. Kang *et al*[23] evaluated HRF as a predictor for BCVA at a mean of 6 months of follow-up, Spooner *et al*[27] at 48 weeks and Chatziralli *et al*[26] at 9 months. It is possible that with a longer follow-up we could also reach an influence of HRF on final visual acuity.

Ischemia is another factor that may influence the predictive value of OCT markers for final outcomes. In this study, ischemia was not considered. Literature regarding this issue is not conclusive. While Yu *et al*[28] demonstrated that the development of DRIL was not influenced by baseline ischemia at ultra-widefield fluorescein angiography (UWFFA) in BRVO, Berry *et al*[19] concluded that ischemic features on UWFFA at baseline are predictive of the extent of DRIL in CRVO. More studies are necessary to understand the real effect of ischemia and if it is dependent or not on the type of RVO.

Additionally, our results show that a greater BCVA improvement was correlated with a worse baseline value (r=-0.45, p<0.001). This is another important issue to address since it proves that the decision to treat should not rely exclusively on baseline BCVA. A negative correlation of preoperative BCVA and its improvement has also been shown in previous reports.[29-31]

Regarding ME resolution, none of the baseline morphological factors analyzed were predictive. However, absence of presence of HRF in the inner retinal layers and preserved EZ and ELM at follow-up were significantly more frequent among those with ME resolution. This could be explained by the fact that bevacizumab not only provided a CMT decrease but also leaded to a restoration of the outer retinal integrity. In bevacizumab poorly responsive eyes, the persistent ME may lead to irreversible damage of outer retinal layers.

We analyzed data from a sample with a considerable size and used the same anti-VEGF in the same treatment regimen controlling bias regarding different types of treatments. Nonetheless, several limitations of this study merit discussion. First, it is a retrospective study. Second, our follow-up time is short, with a post-treatment evaluation only after loading-dose. Longer follow-up is needed to prove the utility of these markers. Furthermore, integration of other data, for example, macular ischemia assessment on fluorescein angiography or OCT angiography would probably provide additional data. Also, a qualitative assessment of the biomarkers was performed, with consequent variability between images evaluation. A quantitative analysis, with precise quantification of the extent of DRIL, EZ and ELM disruptions, might not only give us supplemental information but is also essential for its applicability in clinical practice.

In conclusion, we showed that intravitreal injection of bevacizumab for ME due to CRVO and BRVO resulted in a significant functional and anatomical improvement at short-term. Patients with DRIL and disrupted EZ and ELM at baseline presented a significant lower BCVA at the end of the loading dose intravitreal treatment. These results support the use of DRIL, EZ and ELM disruption as novel disease biomarkers in clinical practice, as well as end points in future clinical trials. Identification of baseline biomarkers of ME poor response to anti-VEGF will improve treatment decisions and, also, enable disease stratification and prognosis.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

CM, AFM: Conceptualization, Writing Original Draft.
CM, AFM, GG, CP, JNB: Methodology, Investigation.
SP, MF, EB, FFR, JNB: Conceptualization, Supervision, Project Ad-ministration.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

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Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

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