Optical Coherence Tomography Biomarkers in Patients With Macular Edema Secondary to Retinal Vein Occlusion

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Research Article

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Abstract

Purpose: To evaluate the impact of optical coherence tomography biomarkers on intravitreal dexamethasone (DEX) implant clinical outcomes in patients with macular edema (ME) secondary to retinal vein occlusion (RVO). Additionally, the effect of DEX on central retinal thickness (CRT) and visual acuity (BCVA) was also evaluated.

Methods: Retrospective study conducted on a cohort of patients with ME secondary to RVO, either naïve or previously treated, who underwent treatment with DEX implant and had a minimum follow-up of 6 months. Success was defined as a CRT < 250µm or a relative reduction of CRT $\geq 10\%$ from baseline.

Results: Fifty-seven eyes were included in the study. Baseline BCVA was significantly lower in the eyes with disrupted external limiting membrane (ELM) (mean 40.3 ± 21.3 letters) than in those with non-disrupted (mean 68.6 ± 10.7 letters) or partially-disrupted ELM (mean 59.6 ± 13.2 letters), $p=0.0001$ and $p=0.0011$, respectively. Among the 35 eyes with subretinal fluid (SRF) at baseline, those with a SRF thickness > median (119 µm) had a worse baseline BCVA than those with a SRF thickness $\leq$ median (Hodges-Lehmann median difference: -15.0 letters, 95% CI: -30.0 to -5.0 letters, $p=0.0061$). The eyes with disorganization of the retinal inner layers (DRIL) had lower baseline BCVA than those without DRIL (Hodges-Lehmann median difference: -12.0 letters, 95% CI: -25.0 to -5.0 letters, $p=0.0042$). CRT was significantly decreased from 567.6 ± 226.2 µm at baseline to 326.9 ± 141.0 µm at month 6 ($p<0.0001$). At month-6, 26 (45.6%); 24 (42.1%), and 20 (35.1%) eyes achieved a BCVA improvement ≥ 5 , ≥ 10 , and ≥ 15 letters respectively. Forty (70.2%) eyes were classified as success at month-6. Logistic regression analysis found none factor significantly associated with success in the multivariate analysis.

Conclusions: the results of this study suggested a positive impact of DEX on CRT and BCVA in eyes with RVO-ME with no differences between central RVO and branch RVO eyes or between treatment-naïve eyes and those previously treated. DEX implant significantly reduced the presence of cysts and their volume. Additionally, greater amount of SRF, presence of DRIL, presence of HRF (>20), or disrupted ELM were significantly associated with worse baseline BCVA.

Introduction

Retinal vein occlusion (RVO) is a prevalent and disabling condition that may affect approximately 0.5% of people aging from 31 to 101 years [1]. RVO can be divided into two main types: branch retinal vein occlusion (BRVO) and central retina vein occlusion (CRVO) according to anatomic location of occlusion. BRVO is more common and have a better prognosis than CRVO [1, 2].

Systemic risk factors of RVO occurrence include arterial hypertension, age, diabetes, and hypercoagulability [3].

Both forms may impair blood retinal barrier function, which leads to macular edema (ME) with the consequent visual impairment or visual loss [4]. Inflammation plays an important role in pathogenesis of

RVO. Upregulation of inflammatory mediators may facilitate the occurrence of ME [5].

Different treatment options are currently available to address ME secondary to RVO (RVO-ME), including laser photocoagulation, intravitreal injections of vascular endothelial growth factors inhibitors (anti-VEGF), or intravitreal corticosteroids sustained release implants.

The introduction of intravitreal therapies has entailed a significant improvement in functional and anatomic outcomes among patients with RVO-ME [6].

Corticosteroids, beside inhibiting the vascular endothelial growth factor (VEGF) pathway [7, 8], are able to downregulate other proinflammatory mediators [9].

Sustained release intravitreal dexamethasone (DEX) implant (Ozurdex; Allergan, Inc., Irvine, CA, USA) was introduced as a therapeutic option for treating RVO-ME patients. The results of the GENEVA study found significantly better functional and anatomic outcomes after DEX administration in eyes with RVO-ME [10, 11].

However, independently of the treatment administered, not all of the patients obtain functional improvements after RVO-ME resolution, mainly due to structural deficiencies in neuro retinal layers. For example, foveal photoreceptor layer disruption was associated with worse functional outcomes in patients with RVO [12].

Optical coherence tomography (OCT) has dramatically changed the approach of retinal diseases. It allows quantitative and qualitative analysis of imaging biomarkers such as intraretinal hyperreflective foci (HRF); disorganization of the retinal inner layers (DRIL); external limiting membrane (ELM) disruption; ellipsoid zone (EZ) disruption; and retinal and choroidal thickness [13–18].

We have evidence suggesting that OCT biomarkers may help to predict treatment clinical outcomes, although predictive value of OCT biomarkers varies among studies, likely because of differences in protocols, study populations, and treatment patterns; which finally results in controversy regarding the validity of these findings [13–20].

Identification of imaging features on OCT that may predict clinical outcomes, is crucial for determining the best therapeutic approach.

In an attempt to identify the predictive power of different OCT biomarkers and their impact on treatment outcomes, the current study evaluated quantitative and qualitative OCT features in a cohort of patients, either treatment naïve or previously treated, with RVO-ME. Additionally, we also evaluated the effectiveness of DEX implant on these parameters.

Methods

This was a retrospective study conducted on a cohort of patients with RVO, either BRVO or CRVO, who received treatment with DEX implant between January 2014 and September 2018.

The study complied with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Hospital General de Valencia, which waived the need for informed consent for participating in the study.

Patients

Eligible patients had a clinical diagnosed of ME secondary to RVO, either naïve or previously treated, who underwent treatment with DEX implant and had a minimum follow-up of 6 months.

Patients with ME secondary to other any condition different to RVO (i.e., diabetes, uveitis, etc.), any intercurrent disease, either ophthalmic or systemic, that could prevent visual acuity (VA) recovery, or uncontrolled glaucoma (defined as a medically treated intraocular pressure > 24mmHg) were excluded of the study.

OCT measurements

All the patients underwent OCT imaging using the 3D-TopCon (3D OCT-2000 Spectral Domain OCT, Topcon Medical Systems, Inc., Oakland, USA). The imaging acquisition protocol has been described elsewhere (17). In brief, the software of the OCT generated automatically the central retinal thickness (CRT). Macular scans covered a 9x9 mm area centered on the fovea.

OCT images were evaluated by a well-trained ophthalmologist (retina specialist), who were blind to patient information (both demographic and clinic).

RVO-ME was classified, according to the Otani et al classification (21), in sponge-like retinal swelling (SLRS); cystoid ME (CME); and serous retinal detachment (SRD). If SLRS was combined with CME or SRD, the pattern was classified as either CME or SRD, as appropriate, and when SLRS, CME, and SRD were all present, the type was classified as SRD. Other qualitative and quantitative evaluations of Spectral Domain (SDm) OCT images performed at baseline assessed the presence of several morphologic features including the presence of subretinal fluid (SRF) and its height, cystoid changes in the outer nuclear layer (ONL) and in the inner nuclear layer (INL) and maximal cyst size; presence of septae; presence of DRIL, presence of HRF (number and location); subfoveal choroidal thickness (CST), and choroidal thickness measured at 500 μ m and 1500 μ m nasal (CTN) and temporally (CTT); and ELM continuity. ELM continuity classification was based on the textural and morphologic properties in the vicinity of the ELM surface in the central 2000 μ m. Three different scenarios were considered, namely (1) Non-disrupted, whether discontinuity was less than 500 μ m; (2) Partially disrupted, if it was between 500 μ m and 1000 μ m; and (3) disrupted when discontinuity was greater than 1000 μ m.

Definitions

Treatment naïve patient was defined as a patient who, up to that moment, had never received any treatment (pharmacological, laser, and/or surgical).

Anatomic success was defined as a CRT < 250 or a relative reduction of CRT $\geq 10\%$ from baseline [18].

Rescue therapy was administered on a pro re nata regime, according to specific retreatment criteria, including loss of visual acuity (VA) of more than 5 ETDRS letters, increase in CRT of > 50 μm , and/or presence of intraretinal (IRF)/subretinal (SRF) fluid compared to the previous visit [22].

The number of HRF was defined as Few (≥ 2 to ≤ 10); Moderate (> 10 to ≤ 20); or Many (> 20); and its locations as between the internal limiting membrane and the INL; between the outer plexiform layer and ELM; and in all retinal layers.

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Outcomes

The primary endpoint was the mean change in CRT from baseline to month-6.

Secondary outcomes included mean change in best corrected visual acuity (BCVA); proportion of eyes gaining ≥ 5 , ≥ 10 , and ≥ 15 letters in BCVA; the impact of the different OCT biomarkers on functional and anatomic outcomes; and the impact of treatment on the different OCT biomarkers.

Statistical analysis

MedCalc® Statistical Software version 19.8 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2021) and the SPSS IBM Corp. Released 2019. (/IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) were used to perform the statistical analysis.

Although sample size was not calculated before the study, we have conducted a post hoc analysis for testing the adequacy of sample. The post hoc power analyses was determined for an alpha level of 0.05, the study sample size, and the effect size observed in the study [23].

Descriptive statistics number (percentage), mean [standard deviation (SD)], mean [95% confidence interval (95% CI)], mean [standard error (SE)], median (interquartile range), or median (95% CI) were used, as appropriate.

Of the total amount of follow-up measurements, 4% was missing and they were allocated using an algorithm of multiple imputation [24].

Data were tested for normal distribution using a D'Agostino-Pearson test.

A repeated measures ANOVA or a Friedman's two-way analysis test as appropriate, were used to assess changes in BCVA and CRT within the groups throughout the study.

The one-way ANOVA test or the Kruskal-Wallis test were used to compare differences between groups. Post hoc analysis for pair wise comparisons were done with the Scheffé's method (ANOVA) or the Conover method (Kruskal-Wallis).

The Mann–Whitney U test was used in the evaluation of the baseline clinical and demographic parameters between naïve and previously treated eyes and between CRVO and BRVO eyes.

A logistic regression model, for both univariate and multivariate analysis, was used to estimate and test factors for their association with success criterion. A backward strategy was adopted, with a statistically significant cut-off for variable screening of 0.05.

Factors associated with success in the univariate analysis at $p \leq 0.2$ were included in the multivariate analysis.

The analysis of covariance (ANCOVA) was used in the evaluation of the changes in BCVA and CRT between the different diagnosis and ELM status. The first model included "diagnosis" as a factor and age, sex, duration of RVO-ME, treatment status (naïve or previously treated), and ELM status as covariates. The second model included "Treatment status" as factor and age, sex, duration of macular edema, diagnosis (CRVO or BRVO), type of macular edema (ME), and ELM status as covariates. The third model included "ELM status" (classified as non-disrupted, partially disrupted, and disrupted) as factor and age, sex, duration of RVO-ME, treatment status, and diagnosis as covariates. Categorical variables were compared using a Chi-square test and a Fisher's exact test, as needed. P value of less than 0.05 was considered significant.

Results

Fifty-seven eyes (29 treatment naïve and 28 previously treated) fulfilled the inclusion/exclusion criteria requirements. Fifteen (26.3%) eyes had a clinical diagnosed of CRVO and 42 (73.7) ones of BRVO. In the overall study sample, mean age was 72.4 ± 9.3 years and duration of the RVO-ME was 61.3 ± 81.6 days.

With the exception of the number of intravitreal injections previously administered (when comparing treatment naïve versus [vs] previously treated, $p < 0.0001$) there were no significant differences in any of the baseline study variables. The table 1 summarizes the main baseline clinical and demographic characteristics of the study population.

Baseline BCVA was significantly lower in the eyes with disrupted ELM (mean 40.3 ± 21.3 letters) than in those with non-disrupted (mean 68.6 ± 10.7 letters) or partially-disrupted ELM (mean 59.6 ± 13.2 letters), $p = 0.0001$ and $p = 0.0011$, respectively; and significantly greater in non-disrupted group than in the partially disrupted one (0.0370).

Among the 35 eyes with SRF, those eyes with a SRF thickness > median (119 μm) had a worse baseline BCVA than those with a SRF thickness $\leq$ median (Hodges-Lehmann median difference: -15.0 letters, 95% CI: -30.0 to -5.0 letters, $p=0.0061$).

The eyes with DRIL had a lower BCVA at baseline than those without DRIL (Hodges-Lehmann median difference: -12.0 letters, 95% CI: -25.0 to -5.0 letters, $p=0.0042$). Moreover, baseline BCVA was significantly lower in eyes with more than 20 HRF >20 than in those with less than 10 HRF ($p=0.0388$, Kruskal-Wallis test).

In the overall study sample, CRT was significantly decreased from $567.6 \pm 226.2 \mu\text{m}$ at baseline to $267.7 \pm 120.6 \mu\text{m}$; $406.4 \pm 197.0 \mu\text{m}$; and $326.9 \pm 141.0 \mu\text{m}$ at months 2, 4, and 6, respectively ($p < 0.0001$, $p=0.0011$, and $p < 0.0001$, respectively) (Figure 1). There were no significant differences in CRT reduction, at all the different time points, between CRVO and BRVO eyes (Figure 2A) or between treatment-naïve eyes and those previously treated (Figure 2B).

In the overall study population, there was significant reduction in CRT, cyst volume, and SRF thickness ($p < 0.0001$ each, respectively). However, there were no significant changes in nasal, temporal, or subfoveal choroidal thickness (Table 2). No differences were observed between any of the study variables either between CRVO and BRVO. Nevertheless, BCVA improvement was significantly greater in the treatment naïve eyes than in the previously treated ones (median difference 18.0; 95% CI: 4.0 to 35.0, $p=0.0129$ (Table 2).

At month-6, 26 (45.6%); 24 (42.1%), and 20 (35.1%) eyes achieved a BCVA improvement ≥ 5 , ≥ 10 , and ≥ 15 letters respectively. However, 20 (35.1%) eyes experienced a BCVA worsening ≥ 5 letters. The table 3 shows the proportion of eyes achieving certain change in BCVA according to different baseline characteristics.

Once adjusted by different covariates, there were no significant differences in BCVA, CRT, or CST mean changes according to diagnosis, treatment status, or ELM status (table 4).

At month-6, 18 (31.6%) showed not recurrence of RVO-ME. Among them, 2 (13.3%) were eyes with CRVO-ME and 16 (38.1%) ones with BRVO-ME, $p=0.0787$.

The presence and volume of the cysts were significantly reduced in the overall study population, as well as in the eyes with CRVO-ME and BRVO-ME. Additionally, the number of HRF was significantly reduced ($p=0.0028$) in the CRVO-ME eyes (Table 5). However, ELM status did not change throughout the study (Table 5).

Forty (70.2%) eyes were classified as success at month-6, 10 (66.7%) in the eyes with ME secondary to CRVO (CRVO-ME); 30 (71.4%) in those with ME secondary to BRVO (BRVO-ME); 22 (71.0%) in the treatment naïve eyes; and 18 (69.2%) in the previously treated ones (Figure 3).

Median (95% CI) duration of RVO-ME before treatment was 32.0 (20.6 to 56.0) days, with 28 (49.1%) eyes with a duration of edema ≤ 30 days, 9 (15.8%) eyes with RVO-ME duration >30 and ≤ 60 days, and 20 (35.1%) ones with a RVO-ME duration > 60 days.

There were no significant differences in CTR reduction or in mean change in BCVA between eyes with a RVO-ME duration $\leq$ median ($-253.4 \pm 267.4 \mu\text{m}$ and 0.9 ± 29.5 letters, respectively) and those with a RVO-ME duration $>$ median ($-227.5 \pm 321.8 \mu\text{m}$ and 3.0 ± 29.0 letters, respectively), $p=0.5494$ and $p=0.8730$, respectively (Mann-Whitney U test).

Logistic regression analysis found that the presence of 10-20 HRF at baseline and the change in septum status (present at baseline versus absent at month6) were predictors of anatomic success in the univariate analysis; while baseline disrupted ELM was predictor of achieving a BCVA ≥ 15 letters at month 6. However, none factor was significantly associated with either anatomic or functional success in the multivariate analysis (Table 6).

The mean number of DEX implant administered throughout the study was 1.46 ± 0.50 . Twenty-one (36.8%) eyes underwent a unique DEX implant during the study follow-up, while 36 (63.2%) required rescue therapy (27 eyes received an additional DEX implant and 9 eyes received anti-VEGF injections).

Discussion

The results of the current study showed that the DEX implant Ozurdex® significantly reduce the CRT in patients with RVO-ME, with no differences between eyes with BRVO-ME and those with CRVO-ME or between treatment naïve and previously treated eyes.

Regarding function, there was a BCVA mean gain of $+ 5.4$ letters at month-2, and at month-6, 20 (35.1%) eyes had achieved a BCVA improvement ≥ 15 letters. Although there was no difference in mean change in BCVA between eyes with CRVO-ME and those with BRVO-ME, the mean change in BCVA was significantly greater in the treatment naïve eyes than in the previously treated ones.

Additionally, 40 (70.2%) eyes were classified as success at month-6 (CRT $\leq 250 \mu\text{m}$ or CRT reduction $> 10\%$, at the end of the follow-up period), with no differences between CRVO/BRVO (mean difference 4.7%, $p = 0.7350$) and between naïve/previously treated (mean difference 1.8%, $p = 0.8834$) groups.

DEX implant was the first medical therapy approved for treatment of RVO-ME. Different studies have shown clinically significant functional and anatomic improvements after the administration of the DEX implant in patients with RVO [10, 11, 25–29].

However, these studies did not provide information about potential biomarkers that can predict clinical outcomes in RVO-ME patients.

In a previous study published by our group we found a significant improvement of ELM integrity after DEX implant administration in patients with ME secondary to retinal vascular disease (diabetic macular

edema or RVO-ME) [18]. However, this study failed to confirm that finding. It may be partially explained by the fact that our previous study included eyes with diabetic macular edema, while the current study only included eyes with RVO. Additionally, in our previous study [18] we assessed the changes in ELM from a quantitative point of view, while in the current one the changes in ELM have been qualitatively evaluated.

In patients with ME secondary to diabetic retinopathy, ELM integrity was associated with the final BCVA improvement [30, 31], which may suggest a relationship between ELM status and photoreceptor damage.

In agreement with this assumption, we found a significantly lower baseline BCVA in those eyes with disrupted ELM than in those with non-disrupted or partially disrupted ELM, and lower baseline BCVA in eyes with partially disrupted ELM than in those with non-disrupted ELM. However, in the current study, the enhance of ELM integrity was not associated with a better functional outcome. This may be due to the fact that even though there was an anatomical improvement, there is a tipping point from which photoreceptor damage cannot be recovered, which would highlight the relevance of an early therapeutic approach.

Regarding the effect of DEX implant on cysts, as compare to baseline (0/57 eyes), we found a greater proportion of eyes without cysts at month 2 (31/57, $p < 0.0001$), month 4 (10/57, $p = 0.0005$), and month 6 (20/57, $p < 0.0001$). However, no significant changes were observed in DRIL and/or HRF.

It is no easy to compare our studies with the currently available scientific evidence, since most of the evidence evaluated ME secondary to diabetic retinopathy (DME).

The presence of DRIL [32] or integrity of the ellipsoid zone [33] have been associated with better clinical outcomes in DME patients who underwent DEX implant. Additionally, DEX treatment was also capable to ameliorate DRIL status [32].

However, despite the association between OCT biomarkers and BCVA at baseline, the current study did not observe any relationship between the different OCT biomarkers (DRIL, HRF, cyst, and ELM status) evaluated at baseline and the clinical outcomes.

We found worse baseline BCVA in those eyes with thicker SRF, presence of DRIL, disrupted ELM, or HRF > 20 . However, due probably to the limited sample, we did not find significant associations between these OCT biomarkers and the changes in BCVA.

Evidence regarding the importance of HRF is eluding. Several studies have shown that the presence of HRF in various retinal layers was positively associated with final BCVA [13, 34] while, on the other hand, other studies showed that the presence of HRF was not associated with final BCVA [35]. In our study a significant association between HRF and final visual acuity has not been established; however, we found worse baseline BCVA in eyes with over 20 HRF, and also in eyes with more disrupted ELM. Although we do not localize the HRF within the retinal layers, it is known that a disrupted ELM cannot block the migration of extravasated lipoproteins in the inner retinal layers to the outer retinal layers of the ELM, and makes it possible to pass these extravasated blood constituents of the HRF through the outer retinal layer [36].

Murakami *et al* [37] reported that HRF in the outer retinal layers were associated with either a disrupted ELM or EZ and poor prognoses in diabetic ME.

The relationship between SRF and visual function is controversial.

According to CATT (Comparison of Age-related Macular Degeneration Treatments Trials) study results, in eyes with age-related macular degeneration, SRF was associated with better visual acuity, whereas eyes with subfoveal intraretinal fluid had worst visual acuity [38].

Conversely, in patients with ME secondary to uveitis, SRF was associated with thicker retinas and worse baseline BCVA [39]. This finding agrees with our results. However, unlike what happened in our study, where the presence of SRF was not associated with better anatomic or functional outcomes throughout the study, they found better BCVA improvement in eyes with SRF at baseline [39].

Additionally, larger intraretinal cysts, thicker SRF, higher percentage of DRIL, and percentage of ELM disruption have been associated with worse baseline BCVA in patients with RVO-ME. However, only percentage of ELM disruption independently impacted baseline BCVA [40].

The results of the current study are in agreement with a previous study conducted by our group that found no differences in BCVA improvements between the eyes with severe ELM disruptions at baseline and those with no or less severe ELM disruption at baseline [18].

Since we found significant associations between different OCT biomarkers (DRIL, ELM status, SRF thicknesses, or HRF) and the baseline BCVA, the lack of relationship between these biomarkers and clinical outcomes needs to be further investigated.

CRT was significantly reduced at all the different time-point measures, not only in the overall study populations, but also in the CRVO and BRVO eyes, and in the treatment naïve and previously treated ones. We did not find any differences at any of the different time-points according to the diagnosis (CRVO vs BRVO) or to the treatment status (treatment naïve vs previously treated).

This study did not find any relationship between the time elapsed from RVO diagnosis to the first intravitreal DEX implant and the changes in CRT or BCVA. Conversely, the LOUVRE study found that the mean gain in BCVA was greater in patients with recent-onset ME [41]. Such a difference may be explained by the fact that in our study the median time from diagnosis to treatment was 32 days, while in the LOUVRE study the cut-off point was established in 3 months. In our study 13 (22.8%) eyes had duration of ME at baseline ≥ 90 days. Although CRT reduction and BCVA improvement were lower in those eyes with ME duration ≥ 90 days ($163.5 \pm 261.6 \mu\text{m}$ and 7.0 ± 27.6 letters, respectively) than in those with ME duration < 90 days ($263.5 \pm 300.6 \mu\text{m}$ and 4.6 ± 29.2 letters, respectively), such differences were not statistically significant ($p = 0.3816$ and $p = 0.1558$, respectively, Mann-Whitney U test).

Several limitations should be taken into consideration when interpreting the results of this study. The main one is its retrospective design, which entail potential bias and confounding factors. In order to

minimize its impact, we applied strict inclusion/exclusion criteria. The second limitation is the lack of sample size calculation. In fact, the power for detecting the observed differences in BCVA change, between baseline and month-6, was 13% in CRVO vs BRVO eyes and 97% between treatment naïve and previously treated eyes. Additionally, the power for detecting the observed differences in CRT reduction at month 6, between CRVO vs BRVO and between treatment naïve vs previously treated eyes, was 13% each, respectively.

An additional limitation is the fact that we have measured the presence or absence of DRIL, but not whether their extension changed over the course of the study. This fact, therefore, may explain the lack of significant changes after treatment. Finally, we did not evaluate the safety profile of DEX, but treatment related adverse events associated with DEX are well known and have been exhaustively reported [42].

Conclusions

Despite these limitations, the results of this study suggest a positive impact of DEX on CRT in eyes with RVO-ME. DEX implant significantly reduced the presence of cysts and their volume. Additionally, greater amount of SRF, presence of DRIL, presence of HRF (> 20), or disrupted ELM were significantly associated with worse baseline BCVA.

We also found a significant improvement in BCVA at month-2 after DEX implantation and approximately 1/3 of the eyes showed no recurrence of the ME. However, we did not find any relationship between the OCT biomarkers and the clinical outcomes.

In order to identify the best patient profile candidate to benefit from DEX treatment, further research will be needed to elucidate the complex relationship between the different OCT biomarkers and the clinical outcomes.

List Of Abbreviations

ANCOVA

Analysis of covariance

ANOVA

Analysis of variance

Anti-VEGF

Vascular endothelial growth factors inhibitors

BRVO

Branch retinal vein occlusion

BCVA

Best corrected visual acuity

CATT

Comparison of Age-related Macular Degeneration Treatments Trials

CI
Confidence interval
CME
Cystoid macular edema
CRT
Central retinal thickness
CRVO
Central retinal vein occlusion
CST
Subfoveal choroidal thickness
CTN
Nasal choroidal Thickness
CTT
temporal choroidal thickness
DEX
Dexamethasone intravitreal implant
DRIL
Disorganization of the retinal inner layers
ELM
External limiting membrane
ETDRS
Early Treatment Diabetic Retinopathy Study
EZ
Ellipsoid zone
HRF
Hyperreflective foci
INL
Internal limiting membrane
IRF
Intraretinal fluid
ME
Macular edema
OCT
Optical coherence tomography
RVO
Retinal vein occlusion
RVO-ME
Macular edema secondary to retinal vein occlusion.
SD
Standard Deviation

SDm
Spectral domain
SE
Standard error
SLRS
Sponge-like retinal swelling
SRD
Serous retinal detachment
SRF
Subretinal fluid
VA
Visual acuity
VEGF
vascular endothelial growth factor

Declarations

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Statement of Ethics

“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. The protocol was approved by the Ethics Committee of the Hospital General de Valencia, which waived the need for written informed consent of the participants for the study”.

Consent for publication

Not applicable in this study.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Authors Contribution

Verónica Castro-Navarro: Conception and design of the work, interpretation of the data, and revision of the work.

Clara Monferrer-Adsuara: Conception and design of the work, interpretation of the data, and revision of the work.

Catalina Navarro-Palop: Acquisition and interpretation of data for the work.

Javier Montero-Hernández: Acquisition and interpretation of data for the work.

Enrique Cervera-Taulet: Acquisition and interpretation of data for the work.

Availability of the data

The data that support the findings of this study are available from the corresponding author, [VCN], upon reasonable request.

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Tables

Table 1. Baseline demographic and clinical characteristics in the overall study population; in the central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) samples; and in the treatment naïve and previously treated patients.

Variable	Overall (n=57)	CRVO (n=15)	BRVO (n=42)	P*	Naïve (n=31)	Previously treated (n=26)	P*
Type of RVO, n (%)		N.A.	N.A.				
CRVO	15 (26.3)			N.A.	9 (21.0)	6 (23.1)	0.7647
BRVO	42 (73.7)				22 (71.0)	20 (76.9)	
Treatment status, n (%)					N.A.	N.A.	
Naïve	31 (54.4)	9 (60.0)	22 (52.4)	0.7647 ^a			N.A.
Previously treated	26 (45.6)	6 (40.0)	20 (47.6)				
Age, years							
Mean (SD)	72.4 (9.3)	70.6 (9.1)	73.0 (9.4)	0.3994	72.3 (10.5)	72.5 (7.9)	0.8225
95% CI	69.9 to 74.9	65.6 to 75.7	70.1 to 76.0		68.4 to 76.1	69.3 to 75.7	
Sex, n (%)							
Women	34 (59.6)	10 (66.7)	24 (57.1)	0.5224	19 (61.3)	15 (57.7)	0.7846
Men	23 (40.4)	5 (33.3)	18 (42.9)		12 (38.7)	11 (42.3)	
Eye, n (%)							
Right	25 (43.9)	5 (33.3)	20 (47.6)	0.3428	14 (45.2)	11 (42.3)	0.8303
Left	32 (56.1)	10 (66.7)	22 (52.4)		17 (54.8)	15 (57.7)	
NOII							
Mean (SD)	1.3 (1.7)	1.1 (1.5)	1.4 (1.8)	0.5850	0.0	2.9 (1.4)	<0.0001
95% CI	0.8 to 1.8	0.2 to 1.9	0.8 to 1.9		0.0 to 0.0	2.3 to 3.4	
Type of RVO-ME, n (%)				0.3056 ^b			0.1474 ^b
SLRS	2 (3.5)	1 (6.7)	1 (2.4)		2 (6.5)	0 (0.0)	
CME	20 (35.1)	3 (20.0)	17 (40.5)		6 (19.4)	14 (53.8)	
						12 (46.2)	

SRD	35 (61.4)	11 (73.3)	24 (57.1)		23 (74.2)		
Duration of RVO-ME, days							
Mean (SD)	61.3 (81.6)	60.7 (70.8)	61.5 (85.9)	0.8632	62.5 (94.3)	59.9 (65.2)	0.5424
95% CI	39.7 to 83.0	21.5 to 99.9	34.8 to 84.3		27.9 to 97.1	33.6 to 86.2	
BCVA**							
Mean (SD)	55.2 (19.4)	55.5 (15.7)	55.1 (20.7)	0.6738	55.0 (19.0)	55.5 (20.3)	0.7524
95% CI	50.1 to 60.4	46.8 to 64.2	48.7 to 61.6		48.1 to 62.0	47.3 to 63.7	
CRT, μm							
Mean (SD)	567.6 (226.2)	549.8 (158.7)	573.9 (247.3)	0.8420	617.7 (280.0)	507.9 (117.1)	0.2846
95% CI	507.6 to 627.6	461.9 to 637.7	496.9 to 651.0		515.0 to 720.4	460.6 to 555.1	
NMCST500, μm							
Mean (SD)	175.1 (53.6)	180.2 (53.0)	173.7 (54.3)	0.6570	180.2 (54.6)	169.1 (52.8)	0.3610
95% CI	160.9 to 189.4	150.9 to 209.5	156.4 to 190.3		160.2 to 200.2	147.8 to 190.4	
NMCST1500, μm							
Mean (SD)	180.6 (58.4)	188.3 (60.6)	177.9 (78.1)	0.5742	183.5 (58.9)	177.2 (58.7)	0.5859
95% CI	165.1 to 196.1	154.7 to 221.8	159.8 to 196.0		161.9 to 205.1	153.5 to 200.9	
TMCST500, μm							
Mean (SD)	189.6 (76.5)	205.5 (118.5)	183.9 (55.4)	0.9278	186.4 (65.5)	193.5 (89.1)	0.6137
95% CI	169.3 to 209.9	139.8 to 275.1	166.7 to 201.2		162.3 to 210.4	157.5 to 229.4	
TMCST1500, μm							
Mean (SD)	184.1 (56.5)	194.1 (75.7)	180.5 (48.4)	0.5804	189.2 (61.4)	178.0 (50.4)	0.2866
95% CI	169.1 to 199.1	152.1 to 236.0	165.5 to 195.6		166.7 to 211.8	157.6 to 198.4	
CST, μm							

Mean (SD)	184.1 (57.0)	184.1 (67.3)	184.1 (53.7)	0.9494	186.8 (54.6)	180.8 (60.6)	0.5749
95% CI	169.0 to 199.2	146.9 to 221.4	167.3 to 200.8		166.8 to 206.9	156.3 to 205.3	
HRF, n (%)				0.3247 ^b			0.5098 ^b
< 10	16 (28.1)	3 (20.0)	13 (31.0)		8 (25.8)	8 (30.8)	
10-20	23 (40.4)	11 (73.3)	12 (28.6)		12 (38.7)	11 (42.3)	
>20	18 (31.6)	1 (6.7)	17 (40.5)		11 (35.5)	7 (26.9)	
DRIL, n (%)							
Yes	34 (59.6)	10 (66.7)	24 (57.1)	0.5582 ^a	20 (64.5)	14 (53.8)	0.4323 ^a
No	23 (40.4)	5 (33.3)	18 (42.9)		11 (35.5)	12 (46.2)	
Cysts volume, µm ³							
Mean (SD)	317.9 (145.4)	285.7 (121.8)	329.7 (152.8)	0.3268	318.9 (154.6)	316.9 (137.1)	0.9084
95% CI	279.0 to 356.9	218.2 to 353.1	281.5 to 378.0		261.2 to 376.6	261.5 to 372.2	
Cysts, n (%)				0.2838 ^b			0.4658 ^b
<100 µm	2 (3.6)	1 (6.7)	1 (2.4)		1 (3.3)	1 (3.8)	
100-200 µm	12 (21.4)	5 (33.3)	7 (17.1)		8 (26.7)	4 (15.4)	
>200 µm	42 (75.0)	9 (60.0)	33 (80.5)		21 (70.0)	21 (80.8)	
ELM, n (%)							
Non-disrupted	13 (22.8)	2 (13.3)	11 (26.2)		5 (16.1)	8 (30.8)	
Partially disrupted	24 (42.1)	6 (40.0)	18 (42.9)	0.2059 ^b	16 (51.6)	8 (30.8)	0.6727 ^b
Disrupted	20 (35.1)	7 (46.7)	13 (31.0)		10 (32.39)	10 (38.5)	
SRF, n (%)				0.3600 ^a			
Yes	35 (61.4)	11 (73.3)	24 (57.1)		23 (74.2)	12 (46.2)	0.0548 ^a
No		4 (26.7)			8 (25.8)	14 (53.8)	

	22 (38.6)		18 (42.9)				
SRF, μm							
Mean (SD)	147.1 (112.2)	103.8 (38.8)	166.9 (129.0)	0.1097	158.4 (129.6)	125.3 (67.1)	0.3943
95% CI	108.5 to 185.6	77.8 to 129.9	112.4 to 221.4		102.3 to 214.4	82.7 to 168.0	

* Mann-Whitney test

** Letters in the Early Treatment Diabetic Retinopathy Study (ETDRS) charts.

^aFisher exact test.

^bChi-squared from trend test.

RVO: Retinal vein occlusion; CRVO: Central retinal vein occlusion; BRVO: Branch retinal vein occlusion; NA: Not applicable; SD: Standard deviation; 95% CI: 95% Confidence interval; NOII: Number of intravitreal injections; RVO: retinal vein occlusion; ME: macular edema; SLRS: Sponge-like retinal swelling; CME: Cystoid macular edema; SRD: Serous retinal detachment; CRT: Central retinal thickness; NMCST: Nasal mean choroidal subfoveal thickness; TMCST: Temporal mean choroidal subfoveal thickness; 500: ring of 500 microns; 1500: Ring of 1500 microns; CST: Choroidal subfoveal thickness; HRF: Hyperreflective foci; DRIL: Disorganization of retinal inner layers; ELM: External limiting membrane; SRF: Serous retinal fluid.

Table 2. Overview of the unadjusted mean changes from baseline to the last follow-up visit at month 6 between eyes with central retinal vein occlusion related macular edema (CVRO-ME) and those with macular edema secondary to branch retinal vein occlusion (BRVO-ME), and between treatment-naïve eyes and those previously treated.

Variables	Overall (n=57)					
	Mean difference (95% CI) from baseline					p ^b
BCVA	2.0 (-5.7 to 9.7)					0.6114
CRT, μm	-240.7 (-318.4 to -162.9)					<0.0001
CST, μm	1.7 (-17.8 to 21.3)					0.8594
NMCST500, μm	12.6 (-5.2 to 30.5)					0.1615
NMCST1500, μm	1.8 (-18.5 to 22.2)					0.8581
TMCST500, μm	7.4 (-14.4 to 29.3)					0.4992
TMCST1500, μm	12.6 (-8.0 to 33.2)					0.2257
Cyst volume, μm ³	-195.8 (-255.5 to -136.1)					<0.0001
SRF, μm	-114.3 (-159.8 to -68.7)					<0.0001
	CRVO (n=15)		BRVO (n=42)		Difference between treatment groups*	
	Mean difference (95% CI) from baseline	p ^a	Mean difference (95% CI) from baseline	p ^a	Median difference** (95% CI)	p ^b
BCVA	-9.5 (-25.5 to 6.5)	0.2248	6.1 (-2.8 to 14.9)	0.1739	16.0 (0.0 to 35.0)	0.0798
CRT, μm	-194.2 (-340.7 to 47.7)	0.0130	-257.3 (-351.9 to -162.6)	<0.0001	-45.5 (-227.0 to 127.0)	0.6311
CST, μm	15.0 (-30.2 to 60.2)	0.4883	-3.0 (-25.2 to 19.2)	0.7859	-16.0 (-68.0 to 30.0)	0.4967
NMCST500, μm	25.9 (-10.6 to 62.5)	0.1502	7.9 (-13.3 to 29.0)	0.4556	-11.0 (-54.0 to 30.0)	0.6768
NMCST1500, μm	13.5 (-35.2 to 62.1)	0.5619	-2.3 (-25.1 to 20.4)	0.8370	-6.5 (-61.0 to 39.0)	0.7788
TMCST500, μm	7.7 (-56.2 to 71.7)	0.7990	7.3 (-14.1 to 28.7)	0.4943	-11.5 (-55.0 to 31.0)	0.5259

TMCST1500, μm	19.1 (-38.2 to 76.4)	0.4856	10.3 (-10.8 to 31.3)	0.3302	-11.0 (-60.0 to 48.0)	0.5992
Cyst volume, μm^3	-140.1 (-267.5 to -12.7)	0.0335	-216.2 (-285.5 to -146.8)	<0.0001	-68.0 (-207.0 to 85.0)	0.3323
SRF, μm	-58.3 (-116.6 to 0.0)	0.0500	-139.9 (-200.5 to -79.4)	0.0001	-3.0 (-60.0 to -52.0)	0.6015
Naïve (n=31)		Previously treated (n=26)		Difference between treatment groups*		
	Mean difference (95% CI) from baseline	p^a	Mean difference (95% CI) from baseline	p^a	Median difference (95% CI)**	p^b
BCVA	11.0 (0.4 to 21.6)	0.0428	-8.8 (-19.2 to 1.6)	0.0928	-18.0 (-35.0 to -4.0)	0.0129
CRT, μm	-269.8 (-399.4 to -140.3)	0.0002	-205.9 (-286.9 to -124.9)	<0.0001	41.5 (-120.0 to 197.0)	0.6251
CST	1.4 (-23.2 to 25.9)	0.9110	2.2 (-31.1 to 35.5)	0.8932	4.0 (-41.0 to 46.0)	0.8413
NMCST500	12.9 (-8.8 to 34.5)	0.2342	12.3 (-18.8 to 43.5)	0.4218	-3.0 (-40.0 to 33.0)	0.8039
NMCST1500	4.0 (-21.5 to 29.6)	0.7494	-0.8 (-35.4 to 33.8)	0.9620	-9.0 (-52.0 to 32.0)	0.6307
TMCST500	7.6 (-23.0 to 38.3)	0.6137	7.2 (-26.2 to 40.6)	0.6630	0.0 (-36.0 to 43.0)	0.9872
TMCST1500	21.3 (-5.2 to 47.8)	0.1105	2.2 (-31.7 to 36.1)	0.8951	-4.0 (-47.0 to 39.0)	0.8538
Cyst volume, μm^3	-218.8 (-304.5 to -133.2)	<0.0001	-169.2 (-256.9 to -81.5)	0.0005	70.5 (-80.0 to 181.0)	0.3653
SRF, μm	-128.9 (-202.3 to -55.5)	0.0015	-92.3 (-133.9 to -50.7)	0.0004	0.0 (-64.0 to 48.0)	0.8969

^a Two-way analysis of variance (ANOVA) test.

^b Mann-Whitney U test.

*First column versus (VS) the second one.

** Hodges-Lehmann median difference (95% Confidence interval)

CRVO: Central retinal vein occlusion; BRVO: Branch retinal vein occlusion; CI: Confidence interval; BCVA: Best corrected visual acuity; CRT: Central retinal thickness; CST: Central subfoveal thickness; NRT: Nasal retinal thickness; 500: ring of 500 microns; 1500: Ring of 1500 microns; TRT: Temporal retinal thickness, SRF: Subretinal fluid.

Table 3. Change in best corrected visual acuity (BCVA) according to different baseline characteristics.

Change in BCVA from baseline to month 6*, n (%)					
	≥ 5	≥ 10	≥ 15	≤5	p ^a
Diagnosis					
CRVO	5 (19.2)	5 (20.8)	5 (25.0)	9 (42.9)	0.0728 ^b
BRVO	21 (80.8)	19 (79.2)	15 (75.0)	12 (57.1)	
Treatment status					
Naïve	18 (69.2)	18 (75.0)	14 (70.0)	9 (42.9)	0.0690 ^b
Previously treated	8 (30.8)	6 (25.0)	6 (30.0)	12 (57.1)	
EM duration**					
≤ 32 days	10 (38.5)	9 (37.5)	9 (45.0)	13 (61.9)	0.1010 ^b
> 32 days	16 (61.5)	15 (62.5)	11 (55.0)	8 (38.1)	
Type of RVO-ME					
SLRS	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	0.1877
CME	8 (30.8)	7 (29.4)	8 (40.0)	9 (42.9)	
SRD	18 (69.2)	17 (70.8)	12 (60.0)	10 (47.6)	
HRF, n (%)					0.7126
< 10	5 (19.2)	4 (16.7)	5 (25.0)	6 (28.6)	
10-20	14 (53.8)	13 (54.2)	7 (35.0)	7 (33.3)	
>20	7 (26.9)	7 (29.2)	8 (40.0)	8 (38.1)	
ELM, n (%)					0.3960
Non-disrupted	6 (23.1)	6 (25.0)	3 (15.0)	4 (19.0)	
Partially disrupted	15 (57.7)	13 (54.2)	10 (50.0)	7 (33.3)	
Disrupted	5 (19.2)	5 (20.8)	7 (35.0)	10 (47.6)	
DRIL, n (%)					
No	9 (34.6)	8 (33.3)	5 (25.0)	11 (52.4)	0.3391 ^b
Yes	17 (65.4)	16 (66.7)	15 (75.0)	10 (47.6)	
Cysts, n (%)***					0.2014
<100 μm	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)	
100-200 μm	7 (26.9)	6 (25.0)	3 (15.0)	3 (15.0)	
>200 μm	19 (73.1)	18 (75.0)	17 (5.5)	15 (75.0)	

* Letters in the Early Treatment Diabetic Retinopathy Study (ETDRS) charts.

** Median split.

***Fifty-six eyes.

^a Chi-squared test.

^b Chi-squared for trend test.

Table 4. Adjusted comparison of mean change from baseline to month-6 in different study variables according to baseline diagnosis and according to external limiting membrane (ELM) status. Statistical significance was assessed using the analysis of covariance (ANCOVA).

Model 1: "Diagnosis" as factor and age, sex, duration of macular edema, treatment status (naïve or previously treated), type of macular edema (ME), and ELM status as covariates.

Model 2: "Treatment status" (naïve or previously treated) as factor and age, sex, duration of macular edema, diagnosis, type of macular edema (ME), and ELM status as covariates.

Model 3: "ELM status" as factor and age, sex, duration of RVO-ME, treatment status (naïve or previously treated), type ME, and diagnosis as covariates.

Diagnosis			
	CRVO (n=15)	BRVO (n=42)	P
BCVA ¹			
Mean (SEM)	-3.8 (6.3)	4.0 (3.6)	0.2930
95% CI	-16.4 to 8.8	-3.3 to 11.4	
CRT ² , μm			
Mean (SEM)	-200.2 (74.1)	-255.1 (43.1)	0.5338
95% CI	-349.1 to -51.3	-341.7 to -168.5	
CST ³ , mm^3			
Mean (SEM)	5.5 (19.3)	0.4 (11.2)	0.8218
95% CI	-33.3 to 44.4	-22.2 to 23.0	
SRF ^{*4} , μ			
Mean (SEM)	-46.6 (42.3)	-49.2 (24.2)	0.9583
95% CI	-133.3 to 40.2	-98.8 to 0.32	
Cyst volume ⁵ , μm^3			
Mean (SEM)	-71.0 (78.7)	-199.3 (44.9)	0.1771
95% CI	-232.1 to 90.1	-291.3 to -107.3	
Treatment Status			
	Naïve (n=31)	Previously treated (n=27)	P
BCVA ¹			
Mean (SEM)	4.4 (4.5)	-1.0 (4.9)	0.4522
95% CI	-4.6 to 13.4	-10.9 to 9.0	
CRT ² , μm			
Mean (SEM)	-308.4 (58.3)	-165.5 (57.7)	0.0988
95% CI	-417.5 to -199.3	-281.3 to -49.5	
CST ³ , mm^3			
Mean (SEM)	-2.4 (14.2)	6.3 (15.1)	0.6974
95% CI	-30.8 to 26.1	-23.9 to 36.5	

SRF ^{*4} , μ			
Mean (SEM)	-22.7 (26.9)	-87.3 (33.2)	0.1498
95% CI	-77.9 to 32.3	-155.3 to 24.7	
Cyst volume ⁵ , μm^3			
Mean (SEM)	-186.0 (50.0)	-136.8 (61.7)	0.5482
95% CI	-288.3 to -83.6	-263.2 to -10.4	

ELM status				
	Non-disrupted	Partially disrupted	Disrupted	p
BCVA ¹				
Mean (SEM)	-3.5 (6.8)	4.6 (5.0)	2.3 (5.6)	0.2651
95% CI	-17.2 to 10.1	-5.4 to 14.7	-8.9 to 13.5	
CRT ² , μm				
Mean (SEM)	-273.6 (80.6)	-277.3 (59.3)	-175.3 (66.1)	0.2783
95% CI	-435.6 to -111.7	-396.8 to -158.1	-308.2 to -42.3	
CST ³ , μm				
Mean (SEM)	8.6 (21.0)	-7.3 (15.4)	8.0 (17.2)	0.5796
95% CI	-33.5 to 50.9	-38.3 to 23.8	-26.6 to 42.7	
SRF ^{*4} , μ				
Mean (SEM)	-19.0 (48.7)	-55.1 (29.2)	-57.7 (41.9)	0.6068
95% CI	-119.0 to 80.9	-115.1 to 4.9	-143.7 to 28.4	
Cyst volume ⁵ , μm^3				
Mean (SEM)	-173.5 (90.6)	-156.4 (54.4)	-181.6 (78.0)	0.8661
95% CI	-359.4 to 12.4	-268.0 to -44.8	-341.6 to -21.6	

* In the yes with serous retinal detachment (35 eyes). This variable was not adjusted by type of edema.

¹ Also adjusted by baseline BCVA.

² Also adjusted by baseline CRT.

³ Also adjusted by baseline CST.

⁴Also adjusted by baseline SRF.

⁵Also adjusted by baseline volume cysts.

Bonferroni correction was applied to the pairwise comparisons.

BRVO: Branch retinal vein occlusion; CRVO: Central retinal vein occlusion, Other: Uveitis and Irvine-gass;
BCVA= Best corrected visual acuity; SEM= Standard error of the mean; CI= Confidence interval; CRT =
Central retinal thickness; MV= Macular volume.

Table 5. Overview of optical coherence tomography (OCT) biomarkers over the course of the study.
Statistical significance was calculated using the Chi-squared test.

Overall (n=57)					
	Baseline	Month 2	Month 4	Month 6	p
DRIL, n (%)					
No	23 (40.4)	25 (43.9)	25 (48.1)	27 (47.4)	0.8365
Yes	34 (59.6)	32 (56.1)	27 (51.9)	30 (52.6)	
HRF, n (%)					
<10	16 (28.1)	32 (56.1)	25 (48.1)	24 (42.1)	0.0851
10-20	23 (40.4)	13 (22.8)	12 (23.1)	15 (26.3)	
>20	18 (31.6)	12 (21.1)	15 (28.8)	18 (31.6)	
Cyst, n (%)					
No Cysts	0 (0.0)	31 (54.4)	10 (19.2)	20 (35.1)	<0.0001
<100 μm ³	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	
100-200 μm ³	12 (21.4)	7 (12.3)	4 (7.7)	4 (7.0)	
>200 μm ³	42 (75.0)	19 (33.3)	38 (73.1)	33 (57.9)	
ELM status, n (%)					
Non-disrupted	13 (22.8)	10 (17.9)	8 (15.4)	15 (26.8)	0.8122
Partially disrupted	24 (42.1)	28 (50.0)	25 (48.1)	24 (42.9)	
Disrupted	20 (35.1)	18 (32.1)	19 (36.5)	17 (30.4)	
CRVO (n=15)					
	Baseline	Month 2	Month 4	Month 6	p
DRIL, n (%)					
No	5 (33.3)	2 (13.3)	4 (30.8)	4 (26.7)	0.6078
Yes	10 (66.7)	13 (86.7)	9 (69.2)	11 (73.3)	
HRF, n (%)					
<10	3 (20.0)	9 (60.0)	5 (38.5)	9 (60.0)	0.0028
10-20	11 (73.3)	4 (26.7)	2 (15.4)	2 (13.3)	
>20	1 (6.7)	2 (13.3)	6 (46.29)	4 826.7)	
Cyst, n (%)					
No Cysts	0 (0.0)	9 (60.0)	2 (15.4)	5 (33.3)	0.0016

<100 μm^3 [AMG1]	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	
100-200 μm^3	5 (33.3)	0 (0.0)	0 (0.0)	1 (6.7)	
>200 μm^3	9 (60.0)	6 (40.0)	11 (84.6)	9 (60.0)	
ELM status, n (%)					0.9950
Non-disrupted	2 (13.3)	3 (21.4)	2 (15.4)	3 (20.0)	
Partially disrupted	6 (40.0)	5 (35.7)	6 (46.2)	6 (40.0)	
Disrupted	7 (46.7)	6 (42.9)	5 (38.5)	6 (40.0)	
BRVO (n=42)					
	Baseline	Month 2	Month 4	Month 6	p
DRIL, n (%)					
No	18 (42.9)	23 (54.8)	21 (53.8)	23 (54.8)	0.6370
Yes	24 (57.1)	19 (45.2)	18 (46.2)	19 (45.2)	
HRF, n (%)					0.2755
<10	13 (31.0)	23 (54.8)	20 (51.3)	15 (35.7)	
10-20	12 (28.6)	9 (21.4)	10 (25.6)	13 (31.0)	
>20	17 (40.5)	10 (23.8)	9 (23.1)	14 (33.3)	
Cyst, n (%)					
No Cysts	0 (0.0)	22 (52.4)	8 (20.5)	15 (35.7)	<0.0001
<100 μm^3 [AMG2]	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	
100-200 μm^3	7 (17.1)	7 (16.7)	4 (10.3)	3 (7.1)	
>200 μm^3	33 (80.5)	13 (31.0)	27 (69.2)	24 (57.1)	
ELM status, n (%)					0.6724
Non-disrupted	11 (26.2)	7 (16.7)	6 (15.4)	12 (29.3)	
Partially disrupted	18 (42.9)	23 (54.8)	19 (48.7)	18 (43.9)	
Disrupted	13 (31.0)	12 (28.6)	14 (35.9)	11 (26.8)	

RVO: retinal vein occlusion; DRIL: Disorganization of inner retinal layers; HRF: Hyperreflective foci; CRVO: Central retinal vein occlusion; BRVO: Branch retinal vein occlusion.

[\[AMG1\]](#) Por favor, comprobar unidades.

[AMG2]Por favor, comprobar unidades.

Table 6. Univariate and multivariate analysis of baseline factors associated with anatomic success and best corrected visual acuity improvement ≥ 15 letters. Factors associated with success in the univariate analysis at $p \leq 0.1$ were included in the multivariate analysis.

	Anatomic success		BCVA gaining ≥ 15 letters	
	Univariate		Univariate	
Factor	OR (95% CI)	P	OR (95% CI)	P
Sex				
Ref: Women				
Men	0.48 (0.15 to 1.52)	0.2103	2.55 (0.83 to 7.79)	0.1013
Age*				
> 73 years	2.2 (0.69 to 7.25)	0.1779	0.57 (0.19 to 1.71)	0.3132
ME duration*				
> 32 days	0.40 (0.12 to 1.31)	0.1300	1.44 (0.48 to 4.29)	0.5148
ME Duration				
Ref: ≤ 30 days				
> 30 ≤ 60	0.27 (0.05 to 1.39)	0.1177	2.64 (0.57 to 12.25)	0.2555
> 60	0.33 (0.09 to 1.22)	0.0955	0.91 (0.26 to 3.139)	0.8745
ME duration				
Ref: ≤ 90 days				
> 90 days	0.39 (0.11 to 1.41)	0.1501	0.48 (0.12 to 1.98)	0.3082
RVO				
Ref: CRVO				
BRVO	1.88 (0.54 to 6.50)	0.3193	1.69 (0.46 to 6.23)	0.4287
ME Subtype				
Ref: SLRS				
CME	2.33 (0.12 to 43.79)	0.5711	1.00 (0.98 to 1.02)	0.9981
SRD	2.50 (0.14 to 43.97)	0.5311	1.00 (0.98 to 1.02)	0.9981
Treatment status				
Ref: Naïve				
Previously treated	1.29 (0.41 to 4.07)	0.6613	0.36 (0.12 to 1.16)	0.0864
ELM status				
Ref: Non-disrupted				
Partially disrupted	0.73 (0.15 to 3.47)	0.6911	5.69 (0.62 to 52.34)	0.1248

Disrupted	0.56 (0.11 to 2.72)	0.4692	19.5 (2.11 to 179.91)	0.0088
DRIL				
Ref: No				
Yes	1.36 (0.39 to 4.74)	0.7280	2.84 (0.86 to 9.44)	0.0880
DRIL Location				
Ref: only INL/ONL				
Both affected	1.05 (0.33 to 3.33)	0.9340	0.36 (0.07 to 1.82)	0.2186
HRF				
Ref: < 10				
10-20	4.75 (1.11 to 20.39)	0.0361	0.96 (0.24 to 3.83)	0.9567
>20	2.60 (0.63 to 10.79)	0.1881	1.76 (0.43 to 7.19)	0.4313
HRF Location				
Ref: only INL/ONL				
Both affected	1.01 (0.31 to 3.32)	0.9830	0.72 (0.23 to 2.23)	0.5684
SRF				
Per μm thicker	1.00 (0.99 to 1.01)	0.4303	0.99 (0.99 to 1.01)	0.6753
SRF				
> 119 μm	2.97 (0.62 to 14.22)	0.1732	3.11(0.72 to 13.44)	0.1285
Cysts				
Ref: <100				
100-200	1.00 (0.05 to 19.96)	1.000	1.00 (0.98 to 1.02)	0.9981
>200	3.67 (0.21 to 64.55)	0.3746	0.99 (0.99 to 1.01)	0.9979
Change in Septum M6				
Ref: No				
Yes	13.93 (2.78 to 69.83)	0.0014	1.97 (0.65 to 5.959)	0.2300

*Reference group $\leq$ Median.

** In eyes with retinal vein occlusion related macular edema

Multivariate analysis:

- Anatomic success:

1. MD Duration > 60 days: OR: 0.34; 95% CI: 0.08 to 1.35; p= 0.1234
2. HRF 10-20: OR: 4.26; 95% CI: 0.88 to 25.60; p=0.0712
3. Change in Septum month 6: OR: 1.09; 95% CI: 0.31 to 3.83; p=0.8939

- BCVA gaining ≥ 15 letters:

1. Treatment status: OR: 0.41; 95% CI: 0.12 to 1.36; p=0.1441
2. ELM status (Disrupted): 1.31; 95% CI: 0.25 to 7.01; p=0.7511
3. DRIL: OR: 2.53; 95% CI: 0.73 to 8.85; p=0.1451

Age: OR: 2.96; 95% CI: 0.92 to 9.57; p=0.0695.

Duration of ME: OR: 2.65; 95% CI: 0.82 to 8.58; p=0.1036.

Abbreviations

OR= Odds ratio; CI= Confidence interval; ME: Macular edema; SLRS: Sponge-like retinal swelling; CME: Cystoid macular edema; SRD: Serous retinal detachment; DRIL: Disorganization of inner retinal layer; INL: Inner nuclear layer; ONL: Outer nuclear layer; HRF: Hyperreflective foci; SRF: Subretinal fluid; M: Month.

Figures

Figure 1

Mean central retinal thickness over the course of the study follow-up. The vertical bars represent the 95% confidence interval. Intra-group Statistical significance, at the different time point measured, was determined using the Repeated ANOVA test.

Figure 2

Mean change in central retinal thickness (CRT) from baseline. A. Comparison between eyes with central retinal vein (CRVO) and those with branch retinal vein (BRVO) occlusion. B. Comparison between treatment-naïve eyes those who received previous treatment. Statistical significance between groups was determined using the Mann–Whitney U test (statistical significance * $P<0.01$). Statistical significance intragroup was determined using the Repeated ANOVA test. CRT: Central retinal thickness; M: Month; CRVO: Central retinal vein occlusion; BRVO: Branch retinal vein occlusion; ns: Not significant.

Figure 3

Proportion of eyes classified as success according to diagnosis and treatment status.