Optical coherence tomography biomarkers in patients with macular edema secondary to retinal vein occlusion treated with dexamethasone implant

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Abstract

Purpose: To evaluate the impact of optical coherence tomography (OCT) biomarkers on intravitreal dexamethasone (DEX) implant clinical outcomes in patients with macular edema secondary to retinal vein occlusion (RVO-ME).

Methods: Retrospective study conducted on a cohort of patients with RVO-ME, either naïve or previously treated, who underwent treatment with DEX implant and had a follow-up of 6 months. Anatomic success was defined as a central retinal thickness (CRT) < 250 μm or a relative reduction of CRT ≥ 10% from baseline. The primary endpoint was the mean change in CRT from baseline to month-6. Secondary end-points included changes in BCVA, the impact of baseline OCT biomarkers on functional and anatomic outcomes; and the impact of treatment on the different OCT biomarkers. OCT biomarkers associated with functional and anatomic outcomes were estimated using a logistic regression model.

Results: Fifty-seven eyes were included in the study. Baseline CRT was significantly decreased from 567.6 ± 226.2 μm to 326.9 ± 141.0 μm at month-6 (p < 0.0001). 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. Baseline BCVA was significantly lower in eyes with > 20 hyperreflective foci (HRF) than in those with < 10 HRF (p = 0.0388). 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). 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 anatomic 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. No OCT-biomarkers were identified as predictors of clinical-outcomes. Additionally, presence of DRIL, presence of HRF (>20), or disrupted ELM were significantly associated with worse baseline BCVA.

Keywords: Macular edema, Central retinal vein occlusion, Branch retinal vein occlusion, Intravitreal dexamethasone implant, OCT
**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 has a better prognosis than CRVO [1, 2].

The introduction of intravitreal therapies has entailed a significant improvement in functional and anatomic outcomes among patients with macular edema secondary to RVO (RVO-ME) [3].

Corticosteroids, beside inhibiting the vascular endothelial growth factor (VEGF) pathway [4, 5], are able to downregulate other proinflammatory mediators [6].

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 [7, 8].

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 [9–14].

We have evidence suggesting that OCT biomarkers may help to predict treatment clinical outcomes. However, predictive value of OCT biomarkers varies among studies, likely because of differences in protocols, study populations, and treatment patterns. This issue may finally result in controversy regarding the validity of these findings [9–16].

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 associations between OCT biomarkers and 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 who underwent treatment with DEX implant. Additionally, we also evaluated the effectiveness of DEX implant on these features.

**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 (Protocol number: HGV-DEX-2020-01; Register 180/2020), which waived the need for informed consent for participating in the study.

**Patients**

Eligible patients had a clinical diagnosed of ME secondary to RVO, defined as a central retinal thickness (CRT) ≥ 250 μm measured with OCT, 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 > 24 mmHg) were excluded of the study.

Best corrected Visual acuity (BCVA) was measured using the ETDRS scale chart located at 4 m of the patient.

**OCT measurements**

All the patients underwent OCT imaging using the 3D-TopCon (3D OCT-2000 Spectral Domain OCT, Topcon Medical Systems, Inc., Oakland, USA). A three-dimensional scan protocols composed of 512 A-scans for each B-scans was used for macular measurements. Macular scans were performed with horizontal scanning protocols covering a 9 × 9 mm area centered on the fovea. Foveal thickness was defined as the average thickness in the central 1000-μm diameter of the Early Treatment Diabetic Retinopathy Study layout.

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

RVO-ME was classified, according to the Otani et al. classification [17], 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 biomarkers assessed on Spectral Domain OCT (SD-OCT) were: 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 and 1500 μ nasal (CTN) and temporally (CTT); and ELM continuity. The classification of the ELM disruption area is based on texture and morphologic features. Three different scenarios were arbitrarily considered, namely (1) Non-disrupted, whether discontinuity was less than 500 μm; (2) Partially disrupted, if
it was between 500 μm and 1000 μm; and (3) disrupted when discontinuity was greater than 1000 μm.

The number of HRF was arbitrarily 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.

Outcomes

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 ≥ 10% from baseline [14].

Patients received anti-VEGF as rescue therapy, unless there were contraindications, including heart problems in the last 6 months, bad or poor visit regimen compliance, or a previously failed anti-VEGF regime, in such cases patients received an additional DEX implant. Rescue therapy was administered on a pro re nata regime, according to specific retreatment criteria, including loss of 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 [18].

Outcomes

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

Secondary outcomes included mean change in 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 were determined for an alpha level of 0.05, the study sample size, and the effect size observed in the study [19].

Descriptive statistics number (percentage); mean and (SD); mean and 95% confidence interval (95% CI); median and interquartile range (IQR), 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 [20].

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. Factors associated with success in the univariate analysis at p ≤ 0.1 were included in the multivariate analysis. A backward strategy was adopted, with a statistically significant cut-off for variable screening of 0.05.

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.

Bonferroni corrected P-value was provided.

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

Baseline demographic and clinical characteristics

Fifty-seven eyes (29 treatment naïve and 28 previously treated) fulfilled the inclusion/exclusion criteria requirements. Fifteen (26.3%) eyes were diagnosed with CRVO and 42 (73.7%) ones with BRVO. In the overall study sample, mean age was 72.4 ± 9.3 years.
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 (%)               |                 |              |              |    |                |                             |     |
| CRVO                             | 15 (26.3)       | N.A.         | N.A.         | N.A. | 9 (21.0)       | 6 (23.1)                    | 0.7647 |
| BRVO                             | 42 (73.7)       |              |              |     |                |                             |     |
| Treatment status, n (%)          |                 |              |              |     |                |                             |     |
| Naïve                            | 31 (54.4)       | 9 (60.0)     | 22 (52.4)    | 0.7647 | N.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 |     |                |                             |     |
| 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)      |                             |     |
| NII                              |                 |              |              |    |                |                             |     |
| 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 (%)            |                 |              |              |    |                |                             |     |
| SLRS                             | 2 (3.5)         | 1 (6.7)      | 1 (2.4)      | 0.3056b | 2 (6.5)        | 0 (0.0)                     | 0.1474b |
| CME                              | 20 (35.1)       | 3 (20.0)     | 17 (40.5)    | 6 (19.4) | 14 (53.8)      |                             |     |
| SRD                              | 35 (61.4)       | 11 (73.3)    | 24 (57.1)    | 17 (54.8) | 15 (57.7)      |                             |     |
| 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 |
| TMCS500, 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 |
| TMCS1500, 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 |
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.

Median (IQR) duration of RVO-ME before treatment was 32.0 (8.0 to 83.0) days.

The Table 1 summarizes the main baseline clinical and demographic characteristics of the study population.

**Baseline best corrected visual acuity**

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 \( (0.0370) \).

The presence of SRF was not associated with worse BCVA at baseline \( (\text{Hodges-Lehmann median difference:} 0.0; 95\% \text{ CI:} −10.0 \text{ to } 10.0, p=0.9934) \).

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

**Changes in BCVA**

At month-6, 26 (45.6%); 24 (42.1%), and 20 (35.1%) eyes achieved a BCVA improvement \( \geq 5, \geq 10, \text{and} \geq 15 \)
letters respectively. However, 20 (35.1%) eyes experienced a BCVA worsening ≥5 letters. The Table 2 shows the proportion of eyes achieving certain change in BCVA according to different baseline characteristics.

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 3).

Once adjusted by different covariates, there was no significant improvement in BCVA at month-6 according to diagnosis, treatment status, or ELM status (Table 4).

**Changes in CRT and different anatomic outcomes**

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

In the overall study population, there was significant reduction in cyst volume, and height of SRF (p < 0.0001 each, respectively). However, there were no significant changes in nasal, temporal, or subfoveal choroidal thickness (Table 2).

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

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

The presence of the cysts was 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 anatomic 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 (Fig. 3).

There were no significant differences in CTR reduction or in mean change in BCVA between eyes with a RVO-ME duration ≤ median (−253.4 ± 267.4 μm and 0.9 ± 29.5 letters, respectively) and those with a RVO-ME duration > median (−227.5 ± 321.8 μm and 3.0 ± 29.0 letters, respectively), p = 0.5494 and p = 0.8730, respectively (Mann-Whitney U test).

**Factors associated with functional and anatomic outcomes**

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 month-6) were

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Table 2: Change in best corrected visual acuity (BCVA) according to different baseline characteristics

| Change in BCVA from baseline to month 6^c, n (%) | ≥ 5 | ≥ 10 | ≥ 15 | ≤ 5 | p^a |
|-----------------------------------------------|----|-----|-----|-----|-----|

| Diagnosis | CRVO | 5 (19.2) | 5 (20.8) | 5 (25.0) | 9 (42.9) | 0.0728b |
|----------|------|-----------|-----------|-----------|-----------|-----------|
| BRVO | 21 (80.8) | 19 (79.2) | 15 (75.0) | 12 (57.1) | 0.0690b |

| Treatment status | Naïve | 18 (69.2) | 18 (75.0) | 14 (70.0) | 9 (42.9) | 0.0690b |
|-----------------|------|-----------|-----------|-----------|-----------|
| Previously treated | 8 (30.8) | 6 (25.0) | 6 (30.0) | 12 (57.1) |

| ME duration^d | ≤ 32 days | 10 (38.5) | 9 (37.5) | 9 (45.0) | 13 (61.9) | 0.1010b |
|---------------|-----------|-----------|-----------|-----------|
| > 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 (%) | < 10 | 5 (19.2) | 4 (16.7) | 5 (25.0) | 6 (28.6) | 0.7126 |
|------------|------|-----------|-----------|-----------|
| 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 (%) | Non-disrupted | 6 (23.1) | 6 (25.0) | 3 (15.0) | 4 (19.0) | 0.3960 |
|------------|-------------|----------|-----------|---------|---------|
| 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) | 0.3391b |
|-----------|----|---------|----------|---------|
| Yes | 17 (65.4) | 16 (66.7) | 15 (75.0) | 10 (47.6) |

| Cysts, n (%) | ≤ 100 μm | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (10.0) | 0.2014 |
|-------------|----------|---------|----------|---------|
| 100–200 μm | 7 (26.9) | 6 (25.0) | 3 (15.0) | 3 (15.0) |
| > 200 μm | 19 (73.1) | 18 (75.0) | 17 (55.0) | 15 (75.0) |

Abbreviations: BCVA Best corrected visual acuity, CRVO Central retinal vein occlusion, BRVO Branch retinal vein occlusion, ELM External limiting membrane, DRIL Disorganization of the retinal inner layers, SLRS Sponge-like retinal swelling, CME Cystoid macular edema, SRD Serous retinal detachment, HRF Hyperreflective foci, ELM External limiting membrane, DRIL Disorganization of the retinal inner layers.

^a Chi-squared test
^b Chi-squared for trend test
^c Letters in the Early Treatment Diabetic Retinopathy Study (ETDRS) charts
^d Median split
^e Fifty-six eyes
Table 3 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-naive eyes and those previously treated

| Variables | Overall (n = 57) | BRVO (n = 42) | Difference between treatment groups\(a\) | \(p^b\) |
|-----------|----------------|-------------|---------------------------------|-------|
| BCVA      | 20.0 (–5.7 to 9.7) | 6.1 (–2.8 to 14.9) | 16.0 (0.0 to 35.0) | 0.0798 |
| CRT, μm   | –240.7 (–318.4 to –162.9) | –257.3 (–351.9 to –162.6) | –45.5 (–227.0 to 127.0) | <0.0001 |
| CST, μm   | 1.7 (–17.8 to 21.3) | –3.0 (–25.2 to 19.2) | –16.0 (–68.0 to 30.0) | 0.4967 |
| NMCST500, μm | 12.6 (–5.2 to 30.5) | 7.3 (–14.1 to 28.7) | –11.5 (–55.0 to 31.0) | 0.5259 |
| NMCST1500, μm | 1.8 (–18.5 to 22.2) | 10.3 (–10.8 to 31.3) | –11.0 (–60.0 to 48.0) | 0.5992 |
| TM CST1500, μm | 7.4 (–14.4 to 29.3) | 7.3 (–14.1 to 28.7) | –11.5 (–55.0 to 31.0) | 0.5259 |
| TM CST1500, μm | 12.6 (–8.0 to 33.2) | 10.3 (–10.8 to 31.3) | –11.0 (–60.0 to 48.0) | 0.5992 |
| Cyst volume, μm\(^3\) | –195.8 (–255.5 to –136.1) | –216.2 (–285.5 to –146.8) | –68.0 (–207.0 to 85.0) | <0.0001 |
| SRF, μm   | –114.3 (–159.8 to –68.7) | –139.9 (–200.5 to –79.4) | –3.0 (–60.0 to 52.0) | 0.6015 |

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 μm, 1500 Ring of 1500 μm, TRT Temporal retinal thickness, SRF Subretinal fluid

\(a\) Two-way analysis of variance (ANOVA) test

\(b\) Mann–Whitney U test

\(c\) First column versus (VS) the second one

\(d\) Hodges–Lehmann median difference (95% Confidence interval)

predictors of anatomic success in the univariate analysis; while baseline disrupted ELM and Baseline BCVA were predictors of achieving a BCVA ≥15 letters at month 6. However, in the multivariate analysis only the baseline BCVA was significantly associated with functional success; while none factor was predictor of anatomic success (Table 6).

The mean number of DEX implant administered throughout the study was 1.46 ± 0.50. Twenty-one (36.8%) eyes underwent only one DEX implant during
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)

| Diagnosis | CRVO (n = 15) | BRVO (n = 42) | p  |
|-----------|---------------|---------------|----|
| **BCVA**<sup>a</sup> | Mean (SEM) | 4.0 (3.6) | 3.8 (6.3) | 0.2930 |
| 95% CI | -3.3 to 11.4 | -16.4 to 8.8 | |
| **CRT**<sup>b</sup>, μm | Mean (SEM) | -255.1 (43.1) | 200.2 (74.1) | 0.5338 |
| 95% CI | -341.7 to -168.5 | -349.1 to -51.3 | |
| **CST**<sup>c</sup>, mm<sup>3</sup> | Mean (SEM) | 0.4 (11.2) | 5.5 (19.3) | 0.8218 |
| 95% CI | -22.2 to 23.0 | -33.3 to 44.4 | |
| **SRF**<sup>d</sup>, μ | Mean (SEM) | 49.2 (24.2) | 46.6 (42.3) | 0.9583 |
| 95% CI | 98.8 to 0.32 | 133.3 to 40.2 | |
| **Cyst volume**<sup>e</sup>, μm<sup>3</sup> | Mean (SEM) | 291.3 to -107.3 | -71.0 (78.7) | 0.1771 |
| 95% CI | -155.3 to 24.7 | -30.8 to 90.1 | |
| **Treatment Status** | | | | |
| **Naïve (n = 31)** | | | | |
| **BCVA**<sup>a</sup> | Mean (SEM) | -1.0 (4.9) | 4.4 (4.5) | 0.4522 |
| 95% CI | -10.9 to 9.0 | -4.6 to 13.4 | |
| **CRT**<sup>b</sup>, μm | Mean (SEM) | 165.5 (57.7) | 308.4 (58.3) | 0.0983 |
| 95% CI | -49.2 to 24.2 | -199.3 to 261 | |
| **CST**<sup>c</sup>, mm<sup>3</sup> | Mean (SEM) | 281.3 to -49.5 | 8.6 (21.0) | 0.6974 |
| 95% CI | -396.8 to -158.1 | -30.8 to 26.1 | |
| **SRF**<sup>d</sup>, μ | Mean (SEM) | 87.3 (33.2) | 22.7 (26.9) | 0.1498 |
| 95% CI | 155.3 to 24.7 | -77.9 to 32.3 | |
| **Cyst volume**<sup>e</sup>, μm<sup>3</sup> | Mean (SEM) | 136.8 (61.7) | 186.0 (50.0) | 0.5482 |
| 95% CI | 263.2 to -10.4 | -288.3 to -83.6 | |
| **ELM status** | | | | |
| **Non-disrupted** | | | | |
| **BCVA**<sup>a</sup> | Mean (SEM) | 2.3 (5.6) | -3.5 (6.8) | 0.2651 |
| 95% CI | -8.9 to 13.5 | -17.2 to 10.1 | |
| **CRT**<sup>b</sup>, μm | Mean (SEM) | 175.3 (66.1) | -273.6 (80.6) | 0.2783 |
| 95% CI | -308.2 to -42.3 | -435.6 to -111.7 | |
| **CST**<sup>c</sup>, μm | Mean (SEM) | 8.0 (17.2) | 8.6 (21.0) | 0.5796 |
| 95% CI | -266.2 to 42.7 | -33.5 to 50.9 | |
| **SRF**<sup>d</sup>, μ | Mean (SEM) | 57.7 (41.9) | -19.0 (48.7) | 0.6068 |
| 95% CI | -143.7 to 28.4 | -119.0 to 80.9 | |
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), with a median time interval of 109 (95% CI: 72 to 148) days.

Safety
No patient experienced a significant increase (≥5 mmHg) in IOP.

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 anatomic success at month-6 (CRT ≤250 μm or CRT reduction >10%, at the end of the follow-up period),

Table 4 (continued)

| Cyst volumea, μm³ | Mean (SEM) | 95% CI | 95% CI | 95% CI | 95% CI | 95% CI |
|------------------|------------|--------|--------|--------|--------|--------|
|                  | −173.5 (90.6) | −156.4 (54.4) | −181.6 (78.0) | 0.8661 |

Bonferroni correction was applied to the pairwise comparisons

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

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

a Also adjusted by baseline BCVA
b Also adjusted by baseline CRT
c Also adjusted by baseline CST
d Also adjusted by baseline SRF
e Also adjusted by baseline volume cysts
f In the yes with serous retinal detachment (35 eyes). This variable was not adjusted by type of edema

Fig. 1 Mean central retinal thickness over the course of the study follow-up. The vertical bars represent the maximum and the minimum values. Intra-group Statistical significance, at the different time point measured, was determined using the Repeated ANOVA test.
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 [7, 8, 21–25].

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) [14]. 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 [14] 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 the current study, we found significant differences in baseline BCVA depending on ELM status. 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).

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. In our study a significant association between HRF and final BCVA 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 [26].

The relationship between SRF and visual function is controversial.

Larger intraretinal cysts, greater amount of SRF, higher percentage of DRIL, and percentage of ELM disruption

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**Fig. 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.
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)                                                                 | CRVO (n = 15)                                                                 | BRVO (n = 42)                                                                 |
|----------------|---------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|
|                | Baseline  | Month 2   | Month 4   | Month 6   | p                      | Baseline  | Month 2   | Month 4   | Month 6   | p                      | 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 μm³      | 2 (3.6)   | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   |                        |           |           |           |           |                        |           |           |           |           |                        |
| 100–200 μm³    | 12 (21.4) | 7 (12.3)  | 4 (7.7)   | 4 (7.0)    |                        |           |           |           |           |                        |           |           |           |           |                        |
| > 200 μm³      | 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) | 4826.7 |                        |
| Cyst, n (%)    |           |           |           |           |                        |
| No Cysts       | 0 (0.0)   | 9 (60.0)  | 2 (15.4)  | 5 (33.3)  | 0.0016                 |
| < 100 μm³      | 1 (6.7)   | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   |                        |
| 100–200 μm³    | 5 (33.3)  | 0 (0.0)   | 0 (0.0)   | 1 (6.7)   |                        |
| > 200 μm³      | 9 (60.0)  | 6840.0    | 11 (84.6) | 9 (60.0)  |                        |
| ELM status, n (%) |       |           |           |           |                        |
| Non-disrupted  | 2 (13.3)  | 3 (21.4)  | 2 (15.4)  | 3 (20.0)  | 0.9950                 |
| 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 (%)     |           |           |           |           |                        |
| < 10           | 13 (31.0) | 23 (54.8) | 20 (51.3) | 15 (35.7) | 0.2755                 |
| 10–20          | 12 (28.6) | 9 (21.4)  | 10 (25.6) | 13,831.0 |                        |
| > 20           | 17 (40.5) | 10 (23.8) | 9 (23.1)  | 14 (33.3) |                        |
have been associated with worse baseline BCVA in patients with RVO-ME. However, only percentage of ELM disruption independently impacted baseline BCVA [27].

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 [14].

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

Moreover, patients with good initial VA were more likely to achieve a BCVA improvement ≥15 letters. This finding demonstrates superior visual outcomes in those eyes with good initial vision, suggesting that initiating treatment as soon as BCVA begins to decline is of utmost importance in the treatment of RVO-ME.

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 [28]. 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 ± 261.6 μm and 7.0 ± 27.6 letters, respectively) than in those with ME duration <90 days (263.5 ± 300.6 μm 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).

![Fig. 3](image-url) Proportion of eyes classified as success according to diagnosis and treatment status
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.

| Factor          | Anatomic success | BCVA gaining ≥ 15 letters |
|-----------------|------------------|---------------------------|
|                 | Univariate       |                           |
|                 | 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$^a$         |                  |                           |
| > 73 years      | 2.2 (0.69 to 7.25) | 0.1779 | 0.57 (0.19 to 1.71) | 0.3132 |
| ME duration$^a$ |                  |                           |
| > 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 |
| RVO             |                  |                           |
| Ref: CRVO       | 1.88 (0.54 to 6.50) | 0.3193 | 1.69 (0.46 to 6.23) | 0.4287 |
| BRVO            |                  |                           |
| 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 |
| Baseline BCVA$^a$ |                  |                           |
| > 60            | 0.66 (0.21 to 2.06) | 0.4702 | 0.03 (0.00 to 0.21) | 0.0007 |
| SRF             |                  |                           |
| Per μm thicker  | 1.00 (0.99 to 1.01) | 0.4303 | 0.99 (0.99 to 1.01) | 0.6753 |
Although in patients with RVO-ME the DEX implant has been associated with an elevation of IOP [7, 8, 28], in the current study none eye has experienced an IOP increased ≥ 5 mmHg.

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.

Although of the total amount of follow-up measurements there were only 4% of missing values and that they were allocated using an algorithm of multiple imputation, it should be taken into consideration when interpreting the results.

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 [29].

**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. We did not find any relationship between the OCT biomarkers and the clinical outcomes, although those eyes with good initial VA were more likely to achieve a BCVA improvement ≥ letters.
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.

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; IFR: Infrared 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; SLSR: Sponge-like retinal swelling; SRD: Serous retinal detachment; SRF: Subretinal fluid; VA: Visual acuity; VEGF: Vascular endothelial growth factor.

Acknowledgements
Medical writing and Editorial assistant services have been provided by Antonio Martinez (MD) of Ciencia y Deporte S.L.

Authors’ contributions
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. The author(s) read and approved the final manuscript.

Funding
Dr. Verónica Castro-Navarro has received a Grant from Allergan during the conduct of the study.

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

Declarations
Ethics approval and consent to participate
“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.

Competing interests
The authors have no conflicts of interest to disclose.

Received: 4 July 2021 Accepted: 20 April 2022
Published online: 26 April 2022

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