

RESEARCH

Open Access



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

Verónica Castro-Navarro*, Clara Monferrer-Adsuara, Catalina Navarro-Palop, Javier Montero-Hernández and Enrique Cervera-Taulet

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

*Correspondence: veronicacastronavarro@gmail.com
Ophthalmology Department, Consorci Hospital General Universitari de
Valencia, Avenida Tres Cruces s/n, 46016 Valencia, Spain



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 diagnosis of ME secondary to RVO, defined as a central retinal thickness (CRT) $\geq 250\mu\text{m}$ 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 $> 24\text{mmHg}$) 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 $9 \times 9\text{mm}$ area centered on the fovea. Foveal thickness was defined as the average thickness in the central $1000\text{-}\mu\text{m}$ 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 sub-retinal 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 $500\mu\text{m}$ and $1500\mu\text{m}$ 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 $500\mu\text{m}$; (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 $\geq 10\%$ 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 $> 50 \mu\text{m}$, 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 $p \leq 0.1$ 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.

For evaluating the differences between groups in the ANCOVA analysis, 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)				22 (71.0)	20 (76.9)	
Treatment status, n (%)							
Naïve	31 (54.4)	9 (60.0)	22 (52.4)	0.7647 ^a	N.A.	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		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 (%)							
SLRS	2 (3.5)	1 (6.7)	1 (2.4)	0.3056 ^b	2 (6.5)	0 (0.0)	0.1474 ^b
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)		23 (74.2)	12 (46.2)	
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	

Table 1 (continued)

Variable	Overall (n = 57)	CRVO (n = 15)	BRVO (n = 42)	P*	Naïve (n = 31)	Previously treated (n = 26)	P*
HRF, n (%)							
< 10	16 (28.1)	3 (20.0)	13 (31.0)	0.3247 ^b	8 (25.8)	8 (30.8)	0.5098 ^b
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 (%)							
< 100 μm	2 (3.6)	1 (6.7)	1 (2.4)	0.2838 ^b	1 (3.3)	1 (3.8)	0.4658 ^b
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)	0.2059 ^b	5 (16.1)	8 (30.8)	0.6727 ^b
Partially disrupted	24 (42.1)	6 (40.0)	18 (42.9)		16 (51.6)	8 (30.8)	
Disrupted	20 (35.1)	7 (46.7)	13 (31.0)		10 (32.39)	10 (38.5)	
SRF, n (%)							
Yes	35 (61.4)	11 (73.3)	24 (57.1)	0.3600 ^a	23 (74.2)	12 (46.2)	0.0548 ^a
No	22 (38.6)	4 (26.7)	18 (42.9)		8 (25.8)	14 (53.8)	
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	

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 μm, 1500 Ring of 1500 μm, CST Choroidal subfoveal thickness, HRF Hyperreflective foci, DRIL Disorganization of retinal inner layers, ELM External limiting membrane, SRF Serous retinal fluid

^a Fisher exact test

^b Chi-squared from trend test

* Mann-Whitney test

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

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 (Hodges-Lehmann median difference: 0.0; 95% CI: -10.0 to 10.0 , $p = 0.9934$).

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 than in those with less than 10 HRF ($p = 0.0388$, Kruskal-Wallis test).

Changes in BCVA

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 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

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

	Change in BCVA from baseline to month 6 ^c , n (%)				p ^a
	≥ 5	≥ 10	≥ 15	≤ 5	
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)	
ME duration ^d					
≤ 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 (%)					
< 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)	0.3391 ^b
Yes	17 (65.4)	16 (66.7)	15 (75.0)	10 (47.6)	
Cysts, n (%) ^e					
$< 100 \mu\text{m}$	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)	
$> 200 \mu\text{m}$	19 (73.1)	18 (75.0)	17 (5.5)	15 (75.0)	

Abbreviations: BCVA Best corrected visual acuity, CRVO Central retinal vein occlusion, BRVO Branch retinal vein occlusion, EM Macular edema, RVO-ME Macular edema secondary to retinal vein occlusion, 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

(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 $567.6 \pm 226.2 \mu\text{m}$ 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) (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 chorioidal 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 \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).

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

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-naïve eyes and those previously treated

Variables	Overall (n = 57)		BRVO (n = 42)		Difference between treatment groups ^c	
	Mean difference (95% CI) from baseline	p ^b	Mean difference (95% CI) from baseline	p ^a	Median difference ^d (95% CI)	p ^b
BCVA	2.0 (−5.7 to 9.7)	0.6114	6.1 (−2.8 to 14.9)	0.1739	16.0 (0.0 to 35.0)	0.0798
CRT, μm	−240.7 (−318.4 to −162.9)	<0.0001	−257.3 (−351.9 to −162.6)	<0.0001	−45.5 (−227.0 to 127.0)	0.6311
CST, μm	1.7 (−17.8 to 21.3)	0.8594	−3.0 (−25.2 to 19.2)	0.7859	−16.0 (−68.0 to 30.0)	0.4967
NMCST500, μm	12.6 (−5.2 to 30.5)	0.1615	7.9 (−13.3 to 29.0)	0.4556	−11.0 (−54.0 to 30.0)	0.6768
NMCST1500, μm	1.8 (−18.5 to 22.2)	0.8581	−2.3 (−25.1 to 20.4)	0.8370	−6.5 (−61.0 to 39.0)	0.7788
TMCST500, μm	7.4 (−14.4 to 29.3)	0.4992	7.3 (−14.1 to 28.7)	0.4943	−11.5 (−55.0 to 31.0)	0.5259
TMCST1500, μm	12.6 (−8.0 to 33.2)	0.2257	10.3 (−10.8 to 31.3)	0.3302	−11.0 (−60.0 to 48.0)	0.5992
Cyst volume, μm ³	−195.8 (−255.5 to −136.1)	<0.0001	−216.2 (−285.5 to −146.8)	<0.0001	−68.0 (−207.0 to 85.0)	0.3323
SRF, μm	−114.3 (−159.8 to −68.7)	<0.0001	−139.9 (−200.5 to −79.4)	0.0001	−3.0 (−60.0 to −52.0)	0.6015
	CRVO (n = 15)		Previously treated (n = 26)		Difference between treatment groups ^c	
	Mean difference (95% CI) from baseline	p ^a	Mean difference (95% CI) from baseline	p ^a	Median difference (95% CI) ^d	p ^b
BCVA	−9.5 (−25.5 to 6.5)	0.2248	−8.8 (−19.2 to 1.6)	0.0928	−18.0 (−35.0 to −4.0)	0.0129
CRT, μm	−194.2 (−340.7 to 47.7)	0.0130	−205.9 (−286.9 to −124.9)	<0.0001	41.5 (−120.0 to 197.0)	0.6251
CST, μm	15.0 (−30.2 to 60.2)	0.4883	2.2 (−31.1 to 35.5)	0.8932	4.0 (−41.0 to 46.0)	0.8413
NMCST500, μm	25.9 (−10.6 to 62.5)	0.1502	12.3 (−18.8 to 43.5)	0.4218	−3.0 (−40.0 to 33.0)	0.8039
NMCST1500, μm	13.5 (−35.2 to 62.1)	0.5619	−0.8 (−35.4 to 33.8)	0.9620	−9.0 (−52.0 to 32.0)	0.6307
TMCST500, μm	7.7 (−56.2 to 71.7)	0.7990	7.2 (−26.2 to 40.6)	0.6630	0.0 (−36.0 to 43.0)	0.9872
TMCST1500, μm	19.1 (−38.2 to 76.4)	0.4856	2.2 (−31.7 to 36.1)	0.8951	−4.0 (−47.0 to 39.0)	0.8538
Cyst volume, μm ³	−140.1 (−267.5 to −12.7)	0.0335	−169.2 (−256.9 to −81.5)	0.0005	70.5 (−80.0 to 181.0)	0.3653
SRF, μm	−58.3 (−116.6 to 0.0)	0.0500	−92.3 (−133.9 to −50.7)	0.0004	0.0 (−64.0 to 48.0)	0.8969
	Naïve (n = 31)		Previously treated (n = 26)		Difference between treatment groups ^c	
	Mean difference (95% CI) from baseline	p ^a	Mean difference (95% CI) from baseline	p ^a	Median difference (95% CI) ^d	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

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		<i>P</i>	
	CRVO (n = 15)	BRVO (n = 42)		
BCVA ^a				
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 ^b , 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 ^c , 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 ^{*d} , 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 ^e , 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)	<i>P</i>	
BCVA ^a				
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 ^b , 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 ^c , 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 ^{*d} , 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 ^e , 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	
BCVA ^a			<i>p</i>	
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 ^b , 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 ^c , 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 ^{*d} , 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	

Table 4 (continued)

Cyst volume ^e , 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	

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

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

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),

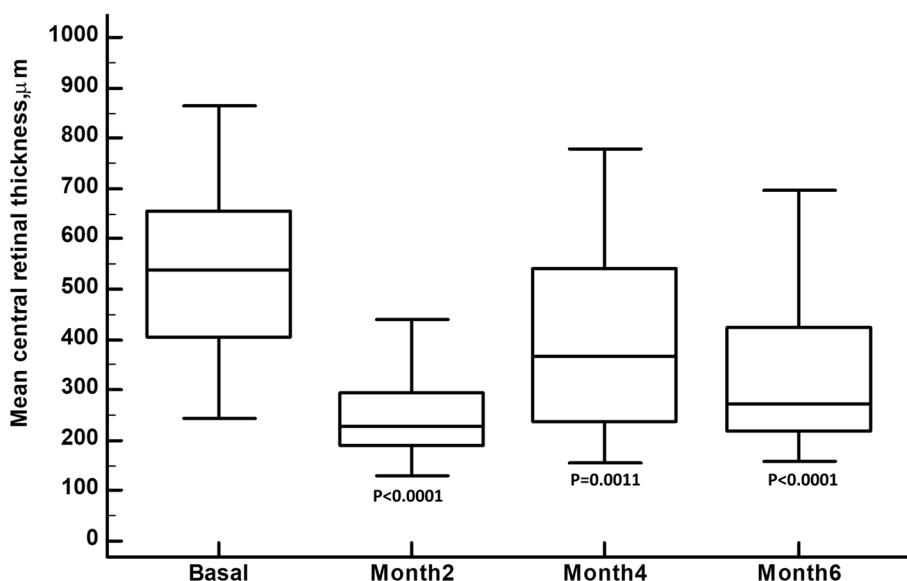
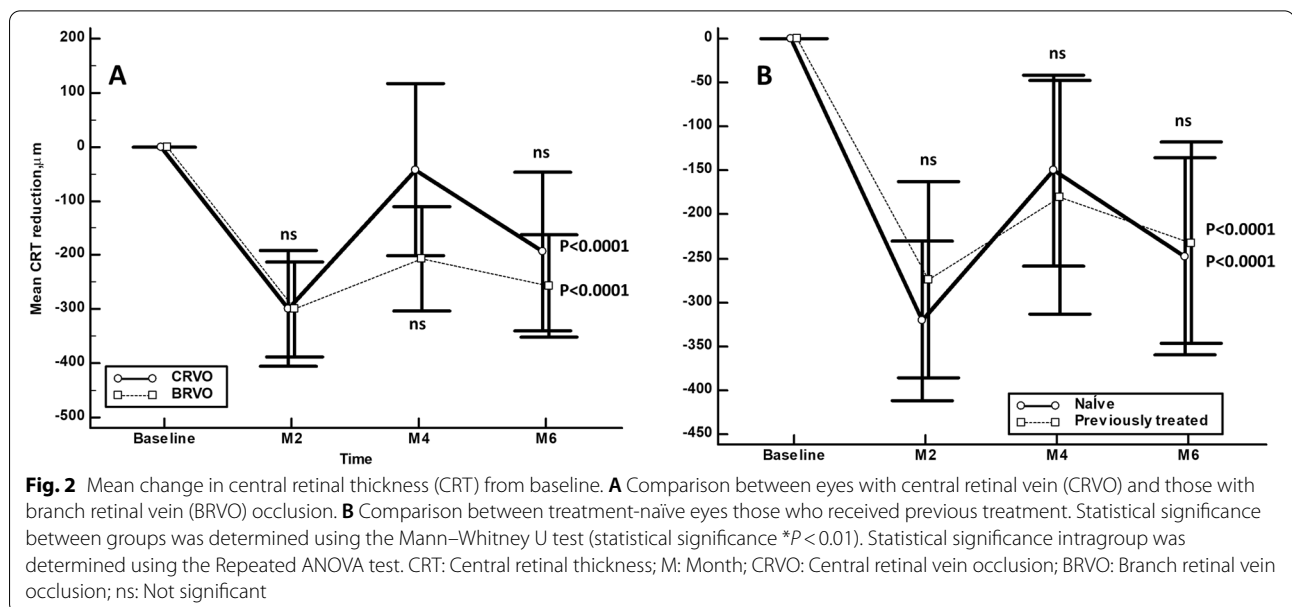


Fig. 1 Mean central retinal thickness over the course of the study follow-up. The vertical bars represent the maximum and the minimum values. Intra-group Statistical significance, at the different time point measured, was determined using the Repeated ANOVA test



with no differences between CRVO/BRVO (mean difference 4.7%, $p = 0.7350$) and between naïve/previously treated (men 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 SRE, higher percentage of DRIL, and percentage of ELM disruption

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)	48 (26.7)	
Cyst, n (%)					
No Cysts	0 (0.0)	9 (60.0)	2 (15.4)	5 (33.3)	0.0016
< 100 μm ³	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 (%)					
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 (31.0)	
> 20	17 (40.5)	10 (23.8)	9 (23.1)	14 (33.3)	

Table 5 (continued)

Cyst, n (%)					
No Cysts	0 (0.0)	22 (52.4)	8 (20.5)	15 (35.7)	<0.0001
< 100 μm ³	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 (%)					
Non-disrupted	11 (26.2)	7 (16.7)	6 (15.4)	12 (29.3)	0.6724
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

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).

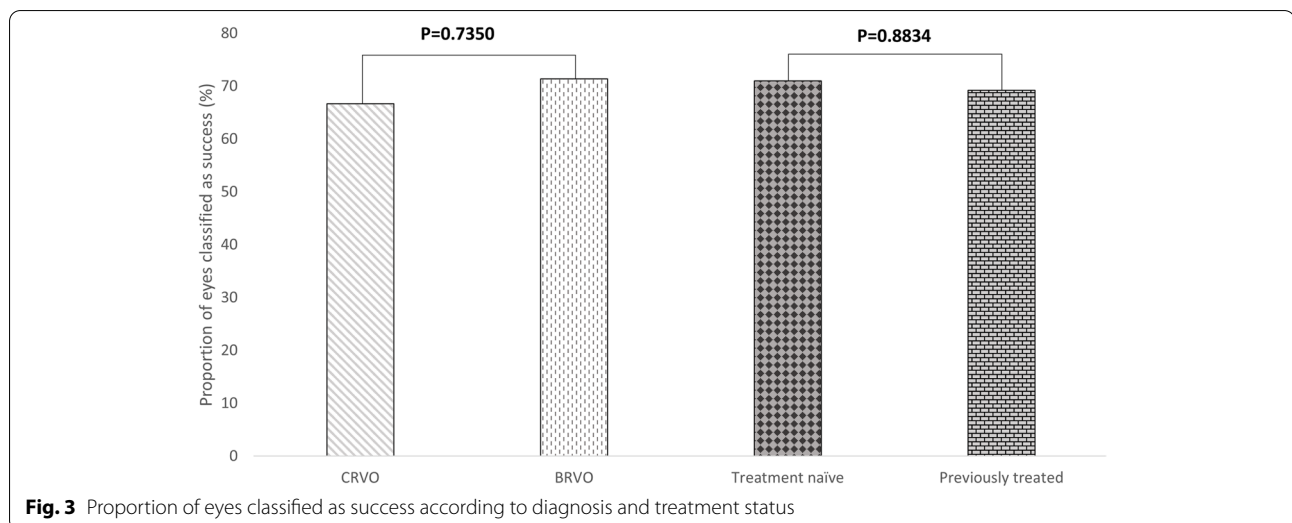


Fig. 3 Proportion of eyes classified as success according to diagnosis and treatment status

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		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
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
Baseline BCVA^a				
> 60	0.66 (0.21 to 2.06)	0.4702	0.03 (0.00 to 0.21)	0.0007
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

Table 6 (continued)

Factor	Anatomic success		BCVA gaining \geq 15 letters	
	Univariate		Univariate	
	OR (95% CI)	P	OR (95% CI)	P
SRF				
> 119 μ m	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

Multivariate analysis:

• Anatomic success:

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

• BCVA gaining \geq 15 letters:

- Baseline BCVA: OR: 0.04; 95% CI: 0.00 to 0.39; $p = 0.0057$
- Treatment status: OR: 0.46; 95% CI: 0.19 to 1.96; $p = 0.3003$
- ELM status (Disrupted): 5.78; 95% CI: 0.48 to 69.77; $p = 0.1670$
- DRIL: OR: 1.29; 95% CI: 0.26 to 6.54; $p = 0.7571$

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

^a Reference group \leq Median

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 \geq 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 \geq 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; 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.

Acknowledgements

Medical writing and Editorial assistant services have been provided by Antonio Martínez (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

References

- Rogers S, McIntosh RL, Cheung N, Lim L, Wang JJ, Mitchell P, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmology*. 2010;117(2):313–9 e1.
- Ponto KA, Elbaz H, Peto T, Laubert-Reh D, Binder H, Wild PS, et al. Prevalence and risk factors of retinal vein occlusion: the Gutenberg health study. *J Thromb Haemost*. 2015;13(7):1254–63.
- Maggio E, Mete M, Maraone G, Attanasio M, Guerriero M, Pertile G. Intravitreal injections for macular edema secondary to retinal vein occlusion: long-term functional and anatomic outcomes. *J Ophthalmol*. 2020;2020:7817542. <https://doi.org/10.1155/2020/7817542>.
- Shim SH, Hah JH, Hwang SY, Heo DS, Sung MW. Dexamethasone treatment inhibits VEGF production via suppression of STAT3 in a head and neck cancer cell line. *Oncol Rep*. 2010;23(4):1139–43.
- Greenberger S, Boscolo E, Adini I, Mulliken JB, Bischoff J. Corticosteroid suppression of VEGF-A in infantile hemangioma-derived stem cells. *N Engl J Med*. 2010;362(11):1005–13.
- Saraiya NV, Goldstein DA. Dexamethasone for ocular inflammation. *Expert Opin Pharmacother*. 2011;12(7):1127–31.
- Haller JA, Bandello F, Belfort R Jr, Blumenkranz MS, Gillies M, Heier J, et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology*. 2010;117(6):1134–46 e3.
- Haller JA, Bandello F, Belfort R Jr, Blumenkranz MS, Gillies M, Heier J, et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. *Ophthalmology*. 2011;118(12):2453–60.
- Mo B, Zhou HY, Jiao X, Zhang F. Evaluation of hyperreflective foci as a prognostic factor of visual outcome in retinal vein occlusion. *Int J Ophthalmol*. 2017;10(4):605–12.
- Jonas JB, Monés J, Glacet-Bernard A, Coscas G. Retinal vein occlusions. *Dev Ophthalmol*. 2017;58:139–67.
- Moon BG, Cho AR, Kim YN, Kim JG. Predictors of refractory macular edema after branch retinal vein occlusion following Intravitreal bevacizumab. *Retina*. 2018;38(6):1166–74.
- Banaee T, Singh RP, Champ K, Conti FF, Wai K, Bena J, et al. Ellipsoid zone mapping parameters in retinal venous occlusive disease with associated macular edema. *Ophthalmol Retina*. 2018;2(8):836–41.
- Babiuch AS, Han M, Conti FF, Wai K, Silva FQ, Singh RP. Association of Disorganization of retinal inner layers with visual acuity response to anti-vascular endothelial growth factor therapy for macular edema secondary to retinal vein occlusion. *JAMA Ophthalmol*. 2019;137(1):38–46.
- Castro-Navarro V, Monferrer-Adsuara C, Navarro-Palop C, Montero-Hernández J, Cervera-Taulet E. Effect of dexamethasone Intravitreal implant on visual acuity and Foveal photoreceptor integrity in macular edema secondary to retinal vascular disease. *Ophthalmologica*. 2021;244(1):83–92.
- Călugăru D, Călugăru M. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with macular edema secondary to vein occlusion. *Am J Ophthalmol*. 2017;184:190–1.
- Schmidt-Erfurth U, Michl M. Disorganization of retinal inner layers and the importance of setting boundaries. *JAMA Ophthalmol*. 2019;137(1):46–7.
- Otani T, Kishi S, Maruyama Y. Patterns of diabetic macular edema with optical coherence tomography. *Am J Ophthalmol*. 1999;127(6):688–93.
- Castro-Navarro V, Cervera-Taulet E, Navarro-Palop C, Monferrer-Adsuara C, Hernández-Bel L, Montero-Hernández J. Intravitreal dexamethasone implant Ozurdex® in naïve and refractory patients with different subtypes of diabetic macular edema. *BMC Ophthalmol*. 2019;19(1):15.
- Yuan K-H, Maxwell S. On the post hoc power in testing mean differences. *J Educ Behav Stat*. 2005;30(2):141–67.
- Lang KM, Little TD. Principled missing data treatments. *Prev Sci*. 2018;19:284–94.
- Kuppermann BD, Haller JA, Bandello F, Loewenstein A, Jiao J, Li XY, et al. Onset and duration of visual acuity improvement after dexamethasone intravitreal implant in eyes with macular edema due to retinal vein occlusion. *Retina*. 2014;34(9):1743–9.

22. Capone A Jr, Singer MA, Dodwell DG, Dreyer RF, Oh KT, Roth DB, et al. Efficacy and safety of two or more dexamethasone intravitreal implant injections for treatment of macular edema related to retinal vein occlusion (Shasta study). *Retina*. 2014;34(2):342–51.
23. Li X, Wang N, Liang X, Xu G, Li XY, Jiao J, et al. Safety and efficacy of dexamethasone intravitreal implant for treatment of macular edema secondary to retinal vein occlusion in Chinese patients: randomized, sham-controlled, multicenter study. *Graefes Arch Clin Exp Ophthalmol*. 2018;256(1):59–69.
24. Mishra SK, Gupta A, Patyal S, Kumar S, Raji K, Singh A, et al. Intravitreal dexamethasone implant versus triamcinolone acetonide for macular oedema of central retinal vein occlusion: quantifying efficacy and safety. *Int J Retina Vitreous*. 2018;4:13.
25. Simsek M, Citirik M, Ozates S, Ozkoyuncu D. The efficacy of intravitreal dexamethasone implant as the first-line treatment for retinal vein occlusion-related macular edema in a real-life scenario. *Indian J Ophthalmol*. 2018;66(6):831–6.
26. Kang JW, Lee H, Chung H, Kim HC. Correlation between optical coherence tomographic hyperreflective foci and visual outcomes after intravitreal bevacizumab for macular edema in branch retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol*. 2014;252(9):1413–21.
27. Yiu G, Welch RJ, Wang Y, Wang Z, Wang PW, Haskova Z. Spectral-domain OCT predictors of visual outcomes after Ranibizumab treatment for macular edema resulting from retinal vein occlusion. *Ophthalmol Retina*. 2020;4(1):67–76.
28. Korobelnik JF, Kodjikian L, Delcourt C, Gualino V, Leaback R, Pinchinat S, et al. Two-year, prospective, multicenter study of the use of dexamethasone intravitreal implant for treatment of macular edema secondary to retinal vein occlusion in the clinical setting in France. *Graefes Arch Clin Exp Ophthalmol*. 2016;254(12):2307–18.
29. Rajesh B, Zarranz-Ventura J, Fung AT, Busch C, Sahoo NK, Rodriguez-Valdes PJ, et al. Safety of 6000 intravitreal dexamethasone implants. *Br J Ophthalmol*. 2020;104(1):39–46.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

