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Prospective Evaluation of Morphological and Functional Changes after Repeated Intravitreal Dexamethasone Implant (Ozurdex®) for Retinal Vein Occlusion

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Key Words
Dexamethasone implant · Microperimetry · Optical coherence tomography · Ozurdex® · Retinal vein occlusion

Abstract
Aims: To evaluate changes in macular morphology and function after repeated intravitreal dexamethasone implant (Ozurdex®) for macular edema (ME) due to retinal vein occlusion (RVO). ***Methods:*** Consecutive treatment-naïve patients with ME secondary to RVO were treated with Ozurdex and followed up to 12 months to evaluate functional and morphological outcomes by means of best-corrected visual acuity (BCVA) and microperimetry and by enhanced depth imaging optical coherence tomography, respectively. ***Results:*** Thirty-five eyes of 35 patients were included for the analysis (26 central RVO, 9 branch RVO). During the 12-month study period, 8 of the 35 eyes (23%) underwent 1 intravitreal dexamethasone implant, 13 of the 35 eyes (37%) underwent 2, and 14 of the 35 eyes (40%) underwent 3 intravitreal dexamethasone implants. At 1 month from the 1st intravitreal dexamethasone implant, the mean BCVA, retinal sensitivity and central macular thickness (CMT) significantly improved compared to the baseline values. At 3 months, the mean BCVA improvement was no more significant, while retinal sensitivity further improved and CMT slightly worsened, remaining, however, significantly better than at baseline. At 12 months, those eyes that had undergone 2 retreatments showed a significant improvement of the mean BCVA, mean retinal sensitivity and CMT compared to the baseline values [0.61 ± 0.29 logarithm of the minimum angle of resolution (LogMAR) vs. 0.82 ± 0.33 LogMAR, p = 0.011; 12.94 ± 4.73 dB vs. 10.75 ± 3.27 dB, p = 0.043, and 321 ± 91 μm vs. 735 ± 169 μm, p = 0.001, respectively]. In those eyes that had undergone only 1 retreatment, a significant improvement was recorded only for the CMT (500 ± 224 μm vs. 695 ± 302 μm, p = 0.044). The mean retreatment interval between the 1st and the 2nd injection was 4.5 ± 1.1 months (range 3–7 months), and between the 2nd and the 3rd injection it was 4.1 ± 1 months (range 3–6 months). ***Conclusions:*** In eyes with ME secondary to RVO, Ozurdex produces functional benefits as early as 1 month after treatment/retreatment. Current optical coherence tomography and microperimetry findings confirm the concept that, in most cases, the optimum retreatment interval should be <6 months from the 1st injection.

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Introduction

Macular edema (ME) is the most common sight-threatening complication of both branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) [1]. Until recently, effective treatment options for retinal vein occlusion (RVO)-related ME were limited. Standard of care had been dictated by the Branch Retinal Vein Occlusion Study (BVOS) and Central Retinal Vein Occlusion Study (CVOS), which recommended grid laser photocoagulation for ME in perfused BRVO and observation for CRVO-associated ME [2, 3]. Over the past decade, advances in our understanding of the pathogenesis of ME led to new therapies, including antivascular endothelial growth factor agents and corticosteroids [4].

In 2009, a sustained-release intravitreal 0.7-mg dexamethasone delivery system, Ozurdex® (Allergan Inc., Irvine, Calif., USA), was approved for the treatment of ME secondary to RVO. Ozurdex, which contains the corticosteroid dexamethasone, has demonstrated efficacy and safety for the treatment of BRVO and CRVO when delivered to the vitreous cavity by a sustained-release intravitreal implant (DEX implant; Ozurdex, Allergan Inc.) [5, 6]. Dexamethasone is a potent water-soluble corticosteroid with an anti-inflammatory activity that is 6-fold greater than that of triamcinolone and 30-fold greater than that of cortisol.

Existing Ozurdex studies have not directly addressed the question of the optimum retreatment interval for the Ozurdex® implant 0.7 mg or safety after long-term repeated injections. Moreover, criteria for the retreatment of RVO-related ME have yet to be defined, and there are currently no established protocols for the long-term management of such patients. Despite phase II and III studies indicating that, in RVO, the effects of a 0.7-mg dexamethasone implant may last for 6 months [5–8], recent clinical studies [9–12], together with pharmacokinetics and pharmacodynamics analysis [13], have shown that the peak efficacy in terms of visual acuity (VA) and macular thickness is at the 1st to 2nd posttreatment month and have suggested that the optimum retreatment interval for intravitreal Ozurdex should be <6 months. However, it has been demonstrated that VA may show a poor degree of correlation with assessments of macular morphology [14]. VA reflects only foveal function, and measurement of VA alone may be not sufficient to evaluate visual function throughout the macular area in eyes undergoing treatment for ME secondary to RVO. Therefore, it is essential to establish another functional examination in order to better understand the functional impact of intravitreal Ozurdex and to gain insights on the optimum retreatment interval in patients who require a longer duration of treatment [15].

Microperimetry is a valuable additional tool for macular diseases [16] which analyzes the function of a few central degrees and creates a functional map of the entire macula. In this way, microperimetry meets the fact that macular function is not fully characterized by VA alone but by the central visual field as well.

In this prospective study, we investigated the changes in macular morphology and function by means of spectral-domain optical coherence tomography (SD-OCT) and microperimetry in eyes undergoing repeated intravitreal dexamethasone implant (Ozurdex) for ME secondary to RVO over a 12-month period.

Methods

Study Participants

Treatment-naive patients with single-eye decreased VA, due to RVO-related ME, who consecutively presented at the Retina Service of the Department of Ophthalmology of the University Scientific Institute San Raffaele in Milan and the Fondazione G.B. Bietti, IRCCS, in Rome between October 2011 and September 2012, were enrolled in this prospective uncontrolled study. The study was performed in accordance with the ethical standards stated in the Declaration of Helsinki and was approved by the University Scientific Institute San Raffaele's Ethics Committee and by the Fondazione G.B. Bietti-IRCCS's Institutional Review Board. Each patient gave an informed consent before enrollment in the study. Criteria for inclusion were: (1) age >18 years old, (2) ME secondary to CRVO or BRVO with onset <1 year earlier, (3) a best-corrected visual acuity (BCVA) between 20/200 and 20/25 (Snellen equivalent) in the study eye at the baseline examination (to ensure proper execution of functional examination), and (4) a central macular thickness (CMT) of >300 μm, as measured by SD-OCT at the baseline examination. The exclusion criteria were: (1) any ocular surgery in the study eye in the last 6 months, (2) diabetic retinopathy, (3) previous laser photocoagulation, (4) previous intravitreal injection of corticosteroids or antivascular endothelial growth factor, (5) a history of ocular inflammation, (6) marked retinal hemorrhage (including macular bleeding involving the intrafoveal or subfoveal spaces), (7) any other ocular condition (such as ocular hypertension and glaucoma, significant media opacities or epiretinal membrane/vitreomacular traction) and (8) any uncontrolled systemic disease.

Study Protocol

At baseline, all patients underwent a complete ophthalmic evaluation, including an assessment of distance BCVA using Early Treatment Diabetic Retinopathy Study (ETDRS) charts, tonometry, slit-lamp biomicroscopy, indirect fundus ophthalmoscopy and SD-OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) with automated CMT measurements, generated by using a 19-horizontal line protocol (6 × 6-mm area), each consisting

of 1024 A scans per line. All patients were treated with a sustained-release dexamethasone 0.7-mg intravitreal implant (Ozurdex) within 3 ± 2 days from the baseline examination. Ozurdex was inserted into the vitreous cavity through the pars plana using a customized, single-use, 22-gauge applicator. All injections were performed in the operatory room. Patients were treated with a topical ophthalmic antibiotic during 7 days after the treatment.

All patients underwent a monthly complete ophthalmologic examination during the 12-month follow-up period (except at the 2nd month from the intravitreal injections for the patients enrolled at the University Scientific Institute San Raffaele). The complete ophthalmologic examination included distance BCVA, tonometry, slit-lamp biomicroscopy, indirect fundus ophthalmoscopy and SD-OCT. From month 3, in patients with a BCVA of <20/20 and recurrence/persistence of ME as documented by indirect fundus ophthalmoscopy and SD-OCT (i.e. intraretinal and/or subretinal fluid with a CMT of >300 μm), the treating physician was free to decide whether or not to readminister the intravitreal dexamethasone implant. If a rescue treatment for ME was deemed necessary by the treating physician, the patient exited the study.

As per study protocol, at baseline and at each follow-up examination, all patients also underwent microperimetry and customized high-resolution enhanced depth imaging (EDI) SD-OCT scans (to assess ultrastructural macular changes in the study eye).

Microperimetry Assessment

Microperimetry was performed with an MP-1 Microperimeter (Nidek Technologies, Padova, Italy) using an infrared fundus camera with a liquid crystal display controlled by special software. The MP-1 performs microperimetry with an automated eye-tracking system, which provides real-time compensation for eye movements and allows improved presentation of a stimulus at the predefined retinal location. Therefore, microperimetry can be performed while observing a target set on the fundus, so testing is quite reliable even in patients who do not have stable fixation. The retinal sensitivity can be measured easily because the level of stimulation changes automatically and progressively during microperimetry.

All patients underwent at least a 5-mm pupil dilation with tropicamide 1% and a 15-min mesopic adaptation before testing. In this way, the retinal sensitivity can be appropriately measured by the MP-1 with the following testing parameters: customized grid of 45 Goldmann III stimuli, covering the central 12° (centered on the fovea); time between stimuli equal to 1 s; stimulus size Goldmann III; white background at 4 apostilbs, and 4-2-1 double-staircase strategy. The stimulus intensity ranged from 0 to 20 dB (0 dB corresponded to the strongest signal intensity of 127 cd/m^2) in 1-dB steps, and the duration of each stimulus was 200 ms.

In each patient, microperimetry was performed twice within 1 week before baseline testing. Moreover, patients underwent a brief training at the beginning of each repeat microperimetry during follow-up.

High-Resolution EDI SD-OCT Assessment

The method of obtaining EDI OCT images has been reported previously [17]. The choroid was imaged by positioning the Spectralis SD-OCT close enough to the eye to obtain an inverted image. Two 9-mm high-resolution line scans through the fovea (1 horizontal and 1 vertical) were obtained for each eye. The line scans were saved for analysis after 100 frames were averaged, using the automatic averaging and eye-tracking features of the proprietary device. The resultant images were viewed and measured with the contained Heidelberg Eye Explorer software (version 1.7.0.0, Heidelberg Engineering) by two experienced retinal physicians, G.Q. and M.P. (fig. 1). The choroidal thickness was measured from the outer portion of the hyperreflective line corresponding to the retinal pigment epithelium (RPE) to the hyporeflective line or margin corresponding to the sclerochoroidal interface. These measurements were made of the subfoveal choroid and at 750-μm intervals from the fovea (750-μm nasal, 750-μm temporal, 750-μm superior and 750-μm inferior interval). Also, on the two 9-mm high-resolution line scans, we performed specific neurosensorial retinal evaluations and measurements that, at the center of the fovea, consisted of: presence and height of the serous retinal detachment, defined as the distance between the RPE and the bottom of the detached neurosensory retina just beneath the fovea; the sensory retinal thickness, calculated by subtracting the height of serous retinal detachment from the center point thickness (defined as the distance between the internal limiting membrane and the RPE); the diameter of the largest cyst; cone outer segment tip thickness, and inner and outer segment (IS/OS) junction status at the fovea (normal, disrupted/absent). At 750-μm intervals from the fovea, the specific neurosensorial retinal measurements consisted of: inner retinal thickness, defined as the distance between the internal limiting membrane and the outer plexiform layer, and outer retinal thickness, defined as the distance between the outer plexiform layer and the RPE. The values of the measurements were averaged for analysis.

Statistical Analysis

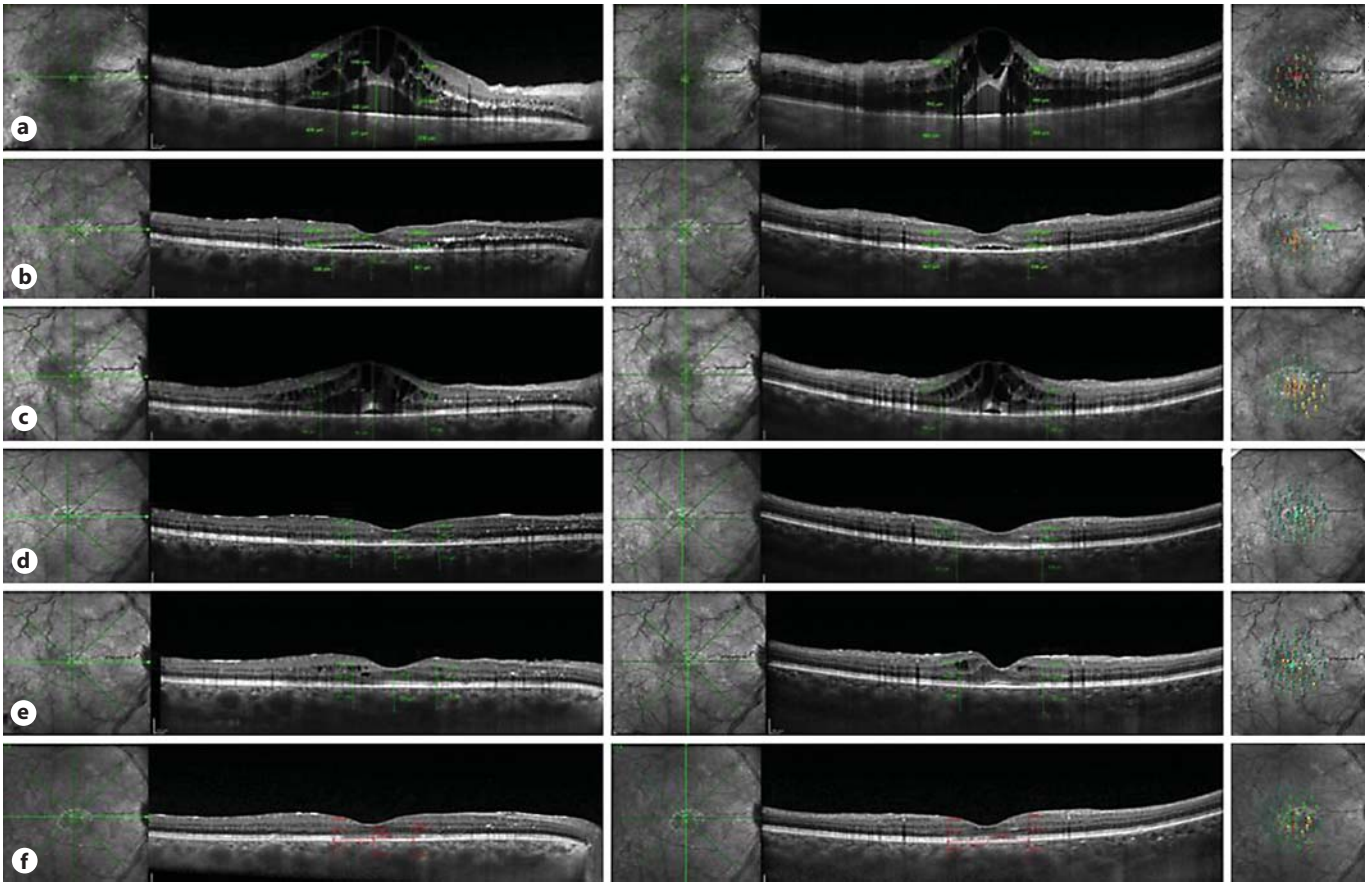
Statistical calculations were performed using the Statistical Package for Social Sciences (version 17.0, SPSS Inc., Chicago, Ill., USA). Comparisons of the mean BCVA, converted to the logarithm of the minimum angle of resolution (LogMAR), the sensitivity on microperimetry, CMT and optical coherence tomography parameters between baseline and follow-up at each month for the overall RVO population (CRVO + BRVO) and for different groups of patients (BRVO, CRVO, never retreated, once retreated, twice retreated) were performed using the Student's t test with Bonferroni correction. Pearson correlation analyses were performed between the LogMAR BCVA, retinal sensitivity as measured by microperimetry (MP) and optical coherence tomography parameters. The chosen level of statistical significance was $p < 0.05$.

Results

Patient Demographics and Outcome Measures after First Intravitreal Dexamethasone Implant

Thirty-five eyes (26 CRVO eyes, 9 BRVO eyes) of 35 patients (25 males; mean age 63 ± 13 years) met the inclusion criteria and were included for analysis. The mean duration of the RVO was 3.4 ± 1.2 months (median 2.9 months; range 1–12 months). Twenty-six of 35 patients (74%) had an ME onset of <3 months.

At 1 month (35 eyes) from the 1st intravitreal dexamethasone implant, 26 out of 35 patients showed a func-



Color version available online

Fig. 1. Horizontal (left panels) and vertical (central panels) EDI OCT scans (9-mm high-quality lines, 100 averaged frames) through the fovea and MP1 microperimetry (right panels) from a 30-year-old patient affected by CRVO in his right eye, acquired at the baseline visit (**a**), 1 month (**b**) and 4 months (**c**) after the 1st Ozurdex injection, at 1 month (**d**) and 4 months (**e**) after the 2nd Ozurdex injection and at 4 months (**f**) after the 3rd Ozurdex injection.

tional improvement (at least 1 ETRDS line). The mean BCVA significantly improved from 0.71 ± 0.4 LogMAR (baseline) to 0.53 ± 0.36 LogMAR (p = 0.001). At 3 months (35 eyes), the mean BCVA improvement was no more significant (0.61 ± 0.37 LogMAR; p = 0.114).

Similarly to the BCVA, the mean MP significantly improved at 1 month from 10.04 ± 4.31 dB (baseline) to 11.74 ± 4.55 dB (p = 0.014). Interestingly, at 3 months, the mean retinal sensitivity further improved to 12.09 ± 5.21 dB (still significantly as compared to baseline; p = 0.004).

Thirty-three out of 35 patients showed a morphological improvement (a CMT decrease of at least 50 μm). In 18 eyes, we found a complete regression of ME. At 1 month, the mean CMT significantly decreased from 710 ± 237 μm (baseline) to 355 ± 143 μm (p < 0.001). At 3 months, the mean CMT slightly worsened to 431 ± 186 μm (even though still significantly decreased as compared to the baseline; p = 0.002).

On the two 9-mm high-resolution line scans through the fovea, all the specific neurosensorial retinal measurements, except the cone outer segment tip, for both the center of the fovea and the 750-μm intervals from the fovea (average values from the combination of the 750-μm nasal, 750-μm temporal, 750-μm superior and 750-μm inferior intervals from the center of the fovea) showed an improvement at 1 month, 2 months and 3 months after intravitreal Ozurdex (table 1). The subfoveal choroid as well as the choroid at 750-μm intervals from the fovea did not show significant changes during the study period (table 1).

We also separately analyzed the morphological and functional changes of the CRVO (26 eyes) and BRVO patients (9 eyes). At 1 month and 3 months, for each differ-

Table 1. Mean neurosensorial retinal measurements and choroidal thickness in the center of the fovea and at 750 μm from the fovea at baseline and at 1, 2 and 3 months after each injection

	Baseline (n = 35)	1 Month (n = 35)	2 Months (n = 16)	3 Months (n = 35)
Cyst (central)	357±207	122±188	157±255	220±208
p value		0.001	0.003	0.007
COST (central)	114±73	106±78	87±69	90±73
p value		0.657	0.135	0.171
Sensory retinal thickness	587±221	302±190	327±264	387±217
p value		0.002	0.003	0.004
Serous retinal detachment	151±188	18±42	16±40	17±40
p value		0.003	0.001	0.001
Inner retinal thickness	299±79	225±66	214±82	243±74
p value		0.001	0.001	0.003
Outer retinal thickness	334±173	175±97	186±65	199±116
p value		0.002	0.002	0.002
Choroid (central)	236±91	227±68	231±89	211±66
p value		0.642	0.754	0.198
Choroid (750-μm average value)	228±79	218±61	223±96	207±58
p value		0.588	0.632	0.211
Choroid (750-μm nasal interval)	224±88	214±60	219±100	207±65
p value		0.429	0.588	0.197
Choroid (750-μm temporal interval)	222±89	224±65	217±92	211±72
p value		0.89	0.612	0.478
Choroid (750-μm superior interval)	238±82	219±71	228±97	210±62
p value		0.127	0.485	0.039
Choroid (750-μm inferior interval)	226±81	217±71	227±103	199±57
p value		0.441	0.873	0.031

Sensory retinal thickness was calculated by subtracting the height of the serous retinal detachment from the center point thickness; serous retinal detachment is the height of the serous retinal detachment, defined as the distance between the RPE and the bottom of the detached neurosensory retina; inner retinal thickness is the distance between internal limiting membrane and outer plexiform layer; outer retinal thickness is the distance between outer nuclear layer and the IS/OS; choroid is the choroidal thickness in the subfoveal area (central) and at 750-μm intervals from the fovea. Cyst = Diameter of the largest cyst; COST = cone outer segment tip thickness.

ent group, the mean BCVA (except for the BCVA at 3 months in the CRVO group), retinal sensitivity and CMT had a significant improvement compared to baseline values (table 2).

We also compared the morphological and functional changes between the CRVO (26 eyes) and the BRVO group (9 eyes; table 3).

One month and 3 months after the 1st intravitreal dexamethasone implant, those eyes characterized by an absence of serous retinal detachment showed a better mean MP than those eyes presenting serous retinal detachment (12.01 ± 4.19 dB vs. 10.64 ± 6.04 dB, p = 0.484 at 1 month; 13.08 ± 4.84 dB vs. 8.11 ± 5.06 dB, p = 0.022 at 3 months). Similarly, 1 month and 3 months after the 1st intravitreal dexamethasone implant, those eyes presenting a normal IS/OS junction showed a better mean retinal sensitivity than those eyes presenting a disrupted/absent IS/OS junction (13.17 ± 4.78 dB vs. 11.31 ± 4.48 dB, p = 0.317, and 14.8 ± 2.67 dB vs. 11.53 ± 5.46 dB, p = 0.044, respectively).

At any time point, we found that CMT had a significant negative correlation with the MP.

Per study protocol, starting from month 3 in patients with a BCVA of <20/20 and recurrence/persistence of ME (as documented by indirect fundus ophthalmoscopy and SD-OCT), the treating physicians were free to decide whether or not to readminister the intravitreal dexamethasone implant.

Twelve-Month Study Period Analysis

Overall, during the 12-month study period, 8 of 35 eyes (23%) underwent 1 intravitreal dexamethasone im-

Table 2. Mean BCVA, retinal sensitivity and CTM evaluated at baseline and at 1, 2 and 3 months from each intravitreal dexamethasone implant in BRVO and CRVO eyes

	BRVO				CRVO			
	baseline (n = 9)	1 month (n = 9)	2 months (n = 3)	3 months (n = 9)	baseline (n = 26)	1 month (n = 26)	2 months (n = 13)	3 months (n = 26)
BCVA, LogMAR	0.61±0.36	0.37±0.25	0.48±0.03	0.34±0.19	0.74±0.41	0.59±0.38	0.74±0.37	0.7±0.37
p value		0.008	0.046	0.005		0.014	0.78	0.61
MP, dB	10.92±3.19	12.9±4.15	14.83±5.47	14.12±3.8	9.74±4.65	11.34±4.69	12.13±4.54	11.39±5.51
p value		0.05	0.048	0.006		0.046	0.004	0.045
CMT, μm	503±163	353±107	325±76	371±134	782±217	355±151	379±235	452±199
p value		0.044	0.007	0.049		0.001	0.003	0.001

Table 3. Comparison between the BRVO and CRVO group of the mean BCVA, retinal sensitivity and CMT evaluated at each time point from intravitreal dexamethasone implant

	Baseline		1 Month		2 Months		3 Months	
	BRVO (n = 9)	CRVO (n = 26)	BRVO (n = 9)	CRVO (n = 26)	BRVO (n = 3)	CRVO (n = 13)	BRVO (n = 9)	CRVO (n = 26)
BCVA, LogMAR	0.61±0.36	0.74±0.41	0.37±0.25	0.59±0.38	0.48±0.03	0.74±0.37	0.34±0.19	0.7±0.37
p value		0.399		0.106		0.034		0.009
MP, dB	10.92±3.19	9.74±4.65	12.9±4.15	11.34±4.69	14.83±5.47	12.13±4.54	14.12±3.8	11.39±5.51
p value		0.372		0.288		0.383		0.18
CMT, μm	503±163	782±217	353±107	355±151	325±76	379±235	371±134	452±199
p value		0.001		0.966		0.71		0.187

plant, 13 of 35 eyes (37%) underwent 2 intravitreal dexamethasone implants, and 14 of 35 eyes (40%) underwent 3 intravitreal dexamethasone implants.

At 12 months, those eyes that had undergone 2 retreatments showed a significant improvement of the mean BCVA, retinal sensitivity and CMT compared with the baseline values (table 4). In those eyes that had undergone only 1 retreatment, a similar significant improvement was recorded only for the CMT (table 4).

Moreover, the 8 eyes (7 CRVO and 1 BRVO) that had not undergone a retreatment during the 12-month study period showed a better mean retinal sensitivity at baseline compared with the 27 eyes (19 CRVO and 8 BRVO) that had undergone retreatment at <12 months (11.32 ± 3.92 dB vs. 9.66 ± 4.4 dB, p = 0.048). On the other hand, the mean BCVA and CMT were similar between the 2 different groups (0.69 ± 0.36 LogMAR vs. 0.71 ± 0.41 LogMAR, p = 0.857, and 690 ± 249 μm vs. 716 ± 238 μm, p = 0.793, respectively).

The mean retreatment interval between the 1st and the 2nd Ozurdex injection was 4.5 ± 1.1 months (range 3–7 months) and between the 2nd and the 3rd injection 4.1 ± 1 months (range 3–6 months).

During the 12-month follow-up, 14 patients also benefited from laser photocoagulation: 9 of 14 eyes (9 CRVO) underwent panretinal photocoagulation, 2 of 14 eyes (2 BRVO) underwent macular grid associated to peripheral laser photocoagulation (these 2 eyes exited the study at 2 months and 6 months, respectively), and 3 of 14 eyes (3 BRVO) underwent peripheral laser photocoagulation alone.

Posterior or anterior segment neovascularization did not develop during follow-up in any patient of the study population. No serious ocular and systemic adverse events were observed in eyes undergoing repeated Ozurdex treatment. Nine eyes developed a transient intraocular pressure increase (mean 24.9 ± 1.6 mmHg), which was successfully managed with topical intraocular pres-

Table 4. Change of the mean BCVA, retinal sensitivity and CMT in patients who underwent 1 or 2 retreatments

	1 retreatment (n = 13)		2 retreatments (n = 14)	
	baseline	12 months	baseline	12 months
BCVA, LogMAR	0.6±0.47	0.81±0.52	0.82±0.33	0.61±0.29
p value		0.209		0.011
MP, dB	8.49±5.26	8.99±4.47	10.75±3.27	12.94±4.73
p value		0.631		0.043
CMT, μm	695±302	500±224	735±169	321±91
p value		0.044		0.001

Table 5. Mean BCVA, retinal sensitivity and CMT evaluated before the 1st and 2nd retreatment and 1, 2 and 3 months after the 1st and 2nd retreatment

	Retreated eyes				Retreated eyes			
	before 1st retreatment (n = 27)	1 month after retreatment (n = 27)	2 months after retreatment (n = 11)	3 months after retreatment (n = 27)	before 2nd retreatment (n = 14)	1 month after retreatment (n = 14)	2 months after retreatment (n = 7)	3 months after retreatment (n = 14)
BCVA, LogMAR	0.84±0.4	0.65±0.41	0.66±0.34	0.67±0.44	0.62±0.3	0.61±0.31	0.58±0.31	0.56±0.37
p value		0.001	0.001	0.001		0.95	0.756	0.67
MP, dB	10.29±4.29	11.81±4.47	13.98±5.45	12.31±5.23	12.67±5.58	13.02±4.95	13.73±4.34	13±4.49
p value		0.001	0.009	0.003		0.86	0.89	0.95
CMT, μm	679±188	462±213	303±94	453±220	625±148	470±120	418±136	324±85
p value		0.001	0.001	0.002		0.005	0.001	0.001

sure-lowering medication. No cataract progression was observed during the study period. All the eyes were phakic.

Outcome Measures after Repeated Administrations of Intravitreal Dexamethasone Implant

One month after the 1st retreatment (27 eyes), the mean BCVA, retinal sensitivity, and CMT improved compared with preretreatment values (table 5). Three months after the 1st retreatment (27 eyes), the mean BCVA was similar to values measured 1 month after retreatment, while retinal sensitivity and CMT showed a further improvement (table 5). One month after the second retreatment (14 eyes), the mean CMT significantly improved compared with the preretreatment values, while the mean BCVA and retinal sensitivity were similar to the preretreatment values (table 5). A similar trend was recorded 3 months after the 2nd retreatment (table 5).

Discussion

In this prospective study, we investigated, over a 12-month follow-up period, the changes in macular morphology and function in eyes undergoing an intravitreal dexamethasone implant (Ozurdex) for ME secondary to both CRVO and BRVO. Overall, we found that intravitreal Ozurdex produced an improvement in the BCVA and macular sensitivity (microperimetry) as early as 1 month after treatment administration. At 3 months, while BCVA regressed to baseline values, macular sensitivity still showed a significant improvement. CMT showed a similar trend by also significantly improving at the 1-month and 3-month follow-up visit.

Starting from month 3, the treating physicians were free to decide whether or not to readminister the intravitreal dexamethasone implant on the basis of the combined functional and morphological findings.

During the 12-month study period, 27 out of 35 patients benefited from at least 1 retreatment after the 1st intravitreal dexamethasone implant, and 14 of these 27

patients underwent 2 retreatments. Interestingly, at 12 months, these 14 eyes showed a significant improvement of the mean BCVA, retinal sensitivity and CMT compared with the baseline values.

On the other hand, the 13 eyes that had undergone only 1 retreatment showed at 12 months a significant improvement of the morphological but not of the functional parameters. Particularly, the fact that at 12 months the CMT was abnormally thickened (albeit significantly reduced as compared to baseline) and that the BCVA and retinal sensitivity were abnormally reduced suggest that these 13 eyes should probably have been receiving a 2nd retreatment earlier. It is noteworthy that after the 2nd retreatment (14 eyes), while the CMT significantly improved at both 1 month and 3 months, the BCVA and MP did not improve. This is probably due to a ceiling effect of the functional parameters: at the time of the 2nd retreatment, while the CMT regressed to values similar to baseline, i.e. 735 ± 169 μm (baseline) versus 625 ± 148 μm (before the 2nd retreatment), the BCVA and MP showed better values than at baseline, i.e. 0.82 ± 0.33 LogMAR (baseline) versus 0.62 ± 0.3 LogMAR (before the 2nd retreatment) and 10.75 ± 3.27 dB (baseline) versus 12.67 ± 5.58 dB (before the second retreatment), and consequently presented less room for improvement.

Overall, 8 eyes (7 CRVO and 1 BRVO) did not undergo retreatment during the 12-month study period. Interestingly, these eyes showed a better mean retinal sensitivity at baseline compared with eyes that had undergone retreatment at <12 months. On the other hand, the mean BCVA and CMT were similar between the 2 different groups.

These findings suggest that while in most cases retreatment with intravitreal Ozurdex should be considered largely before 6 months (in the GENEVA study [5, 6], as per protocol schedule, retreatment was allowed at 6 months from the 1st treatment); in cases showing a better macular sensitivity at baseline, the retreatment interval could be notably longer.

Several studies have suggested that retreatment should be performed before 6 months. Mathew et al. [18] analyzed the morphological and functional changes following intravitreal Ozurdex injections in 30 patients with ME secondary to retinal vascular diseases. The authors evaluated the BCVA, contrast sensitivity, microperimetry, chromatic sensitivity, macular thickness and morphology using SD-OCT and fluorescein angiography at baseline and monitored monthly with BCVA and SD-OCT assessments up to 36 weeks. They found that based on functional and structural outcomes and known side effects of Ozurdex treatment, the ideal retreatment time point should be at 20 weeks.

Querques et al. [9] evaluated the effects of a repeated intravitreal dexamethasone implant, administrated on an 'as-needed' basis, in 33 patients with ME due to RVO. The outcome measures were changes in the BCVA, CMT, retreatment interval and incidence of side effects. Both the BCVA and the CMT significantly improved after each reinjection, with a peak efficacy at 1.4 ± 0.7 months from the 1st retreatment and at 1.8 ± 0.8 months from the 2nd retreatment. Similarly to our series, retreatment was judged necessary after 4.7 ± 1.1 months from the 2st injection and after 5.1 ± 1.5 months from the 2nd injection. The authors concluded that repeated intravitreal Ozurdex on an 'as-needed' basis, with a retreatment interval of <6 months, may produce long-term clinically meaningful benefits in the treatment of ME due to RVO, without other significant side effects than those expected after an intraocular corticosteroid treatment.

Joshi et al. [19] reported the 12-month outcomes of the dexamethasone intravitreal implant in RVO, using an as-needed repeat injection protocol. They analyzed 51 eyes of 49 patients with ME due to RVO: 70% of the patients responded to the dexamethasone implant injection with an improvement in VA and ME within 3 months from the injection, even if only 30% of the eyes gained ≥15 letters. 56% of the patients recurred, with the median time to recurrence being 17 weeks for patients with BRVO and 18 weeks for patients with CRVO. The authors suggested that an intravitreal dexamethasone implant does not last the 6 months (retreatment protocol adopted in the GENEVA [5, 6] trial) and that improved results can be achieved with an as-needed retreatment protocol, particularly in CRVO.

The design of the current study also allowed analyzing, in treatment-naïve eyes with ME secondary to RVO, the relation between morphological and functional parameters. Our data suggest that, early after the development of ME secondary to RVO (the mean disease duration was 3.4 ± 1.2 months, and 26 of 35 patients had an ME onset of <3 months), a thicker macula might be responsible for a reduced photoreceptor function (CMT was negatively related to macular sensitivity already at baseline and at any time point). Also, an absence of serous retinal detachment at the 1-month and 3-month follow-up visit was associated to a better MP. In the same way, eyes characterized by a normal IS/OS junction had a better retinal sensitivity than eyes presenting a disrupted or absent IS/OS junction.

All these findings suggest that microperimetry is a very useful tool to characterize macular function in the presence of ME secondary to RVO and to assess the effects of treatment. Several studies investigated the functional and morphological effects of intravitreal injection of corticosteroids in patients with ME secondary to BRVO and CRVO.

Senturk et al. [15], using microperimetry, evaluated the effect of an intravitreal injection of triamcinolone acetonide on macular function in 12 patients with ME secondary to CRVO. The authors showed an increase in retinal sensitivity 1, 3 and 6 months after the triamcinolone acetonide injection. These functional changes were accompanied by a significant reduction in the foveal thickness.

Recently, Parravano et al. [20] reported that a DEX implant determined a significant improvement of retinal sensitivity and VA associated with a reduction of retinal thickness in patients with ME due to RVO at 6 months.

Similarly, in our series, we found a significant increase in retinal sensitivity and decrease in CMT as early as 1 month after the intravitreal dexamethasone implant, which, in a subset of eyes, lasted up to 12 months (8 eyes characterized by better macular sensitivity at baseline).

Our study has several limitations. The series presented here is relatively small and the follow-up was relatively short (12 months). Moreover, since this study is uncontrolled, there is a possibility that the changes seen after intravitreal Ozurdex would have occurred even if the treatment had not been applied.

In conclusion, we showed that in eyes with ME secondary to RVO, an intravitreal dexamethasone implant provides meaningful functional benefits as early as 1 month after treatment/retreatment. Current findings relying on optical coherence tomography and microperimetry changes further confirmed the concept that, in most cases, the optimum retreatment interval should be earlier than 6 months from the 1st intravitreal Ozurdex.

Disclosure Statement

The authors have no proprietary interest in the materials used in this study.

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