• Clinical Research •

Intravitreal dexamethasone implant in naïve and previously treated patients with diabetic macular edema: a retrospective study

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Abstract

● **AIM:** To assess the effect of the intravitreal dexamethasone implant (DEX) Ozurdex on the best corrected visual acuity (BCVA) and central retinal thickness (CRT) in patients with diabetic macular edema (DME).

● **METHODS:** Totally 43 eyes (24 naïve and 19 previously treated) were included in the study. Retrospective and single-center study involved patients with a clinical diagnosed of DME, who received treatment with DEX implant and had a follow-up of at least 12mo. Primary endpoints included changes in BCVA and CRT.

● **RESULTS:** At month 12, mean improvement in BCVA from baseline was 20.4±20.8 letters and 6.8±6.9 letters in naïve and previously treated patients, respectively (*P*=0.0132). The naïve patients achieved the BCVA improvement significantly faster (2.4±1.5mo) than the previously treated ones (3.5±2.4mo, *P*=0.0298; Mann-Whitney test). The proportion of eyes gaining ≥15 letters was 54.2% and 21.1% in the non-previously treated and previously treated groups, respectively (*P*=0.0293). CRT was significantly reduced from 484.0±119.8 and 487.5±159.9 μm to 272.0±39.2 and 233.5±65.7 μm in the naïve and previously treated patients, respectively; *P*<0.0001 each, respectively. The presence of subretinal fluid was significantly associated with the proportion of patients achieving a BCVA improvement ≥5 letters [HR (95%CI), 1.23 (1.04 to 1.45), *P*=0.0145]; ≥10 letters [HR (95%CI), 1.75 (1.10 to 2.77), *P*=0.0182]; and ≥15 letters [HR (95% CI), 2.04 (1.03 to 4.02), *P*=0.0407]. Naïve patients received less DEX implants throughout the study than the previously treated ones (1.8±0.6 *vs* 2.3±0.6, *P*=0.0172, respectively). Totally 9 patients (20.9%) have developed ocular hypertension, which was successfully controlled with topical hypotensive drugs. Of the 23 phakic eyes at baseline, 5 eyes (21.7%) either had new onset lens opacity or progression of an existing opacity during the study follow-up. Four of them (2 in the naïve group and 2 in the previously treated one) required cataract surgery at months 4, 6, 6, and 6, respectively.

● **CONCLUSION:** The results obtained in this study may support the early use of DEX Ozurdex as first line therapy in naïve patients.

● **KEYWORDS:** diabetic macular edema; dexamethasone implant; Ozurdex; visual acuity; central retinal thickness; naïve patients

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INTRODUCTION

Diabetic macular edema (DME) represents a sight threating condition that may entail a negative impact on patient's life[1-2]. DME is a multifactorial disease, being inflammation an important factor of its pathophysiology[3-4]. Despite that DME is a prevalent cause of visual impairment among diabetic patients, it is easily accessible to treatment. Different approaches, including medical therapy, laser, and surgery have been used for the treatment of DME[5]. Intravitreal corticosteroids and vascular endothelial growth factor inhibitors (anti-VEGF) have currently become first-line treatment[5]. Since the identification of the role of inflammation, corticosteroids have taken an active role in the treatment of DME[6]. Corticosteroid therapy can inhibit many of the processes known to be involved in the progression of DME, through anti-inflammatory properties[7] and VEGF inhibition[8]. The efficacy and safety of Ozurdex® for the treatment of

DME have been recently evaluated in clinical and real-life studies[9-21]. The results of these studies clearly indicated that Ozurdex® significantly improved the functional (visual acuity) and anatomic (retinal thickness) outcomes, not only in the mid-term[9-10,16-17], but also in the long-term[11-18,20-21], in both naïve and previously treated DME patients, but naïve eyes consistently fared better[9-15,17-19,21].

Although there is evidence suggesting the efficacy and safety of anti-VEGF, many patients do not achieve significant improvements[22-25]. However, up to now, there are still doubts about the benefits of an early treatment change in patients with an insufficient therapeutic response to anti-VEGF[26-28].

To identify those factors able to predict treatment outcomes would facilitate the selection of the optimal treatment. The study of biomarkers in DME patients might provide a customized approach to patient treatment[29-30]. Castro-Navarro *et al*[17] reported better anatomical outcomes in patients with serous retinal detachment than in those with sponge-like diffuse retinal thickening. Several spectral domain optical coherence tomography (SD-OCT) image biomarkers, such as hyperreflective dots (HRDs)[31], subretinal fluid (SRF)[32], and disorganization of the retinal inner layers (DRILS)[33] have been suggested in DME.

Although there is evidence suggesting that the existence of HRDs have been associated with worse functional outcomes in DME patients[34-35], the presence of a greater number of HRDs at baseline was associated with good clinical outcomes[36]. Regarding SRF, patients with SRF at baseline obtained a greater treatment effect of the intravitreal dexamethasone (DEX) implant than those without SRF[37].

The purpose of this study was to evaluate the effectiveness of DEX implant on the best corrected visual acuity (BCVA) and central retinal thickness (CRT) in naïve and previously treated DME patients. Additionally, this study assessed the relationship between the presence of HRD, SRF, or DRILS at baseline and the functional outcomes. Finally, this study also evaluated the time elapsed from the device implant to the functional improvement.

SUBJECTS AND METHODS

Ethical Approval The study protocol was approved by the local ethics committee and adhered to the tenets of the Declaration of Helsinki. The local ethics committee waived the need for written informed consent of the participants.

Study Design This retrospective and single-center study involved consecutive DME patients, either naïve or previously treated with anti-VEGF agents, who received treatment with one or more Ozurdex® implant injections, between May 2015 and June 2018, and were followed-up for a minimum of 12mo.

Inclusion/Exclusion Criteria The study included patients with a diagnosis of diabetes mellitus (type 1 or type 2) and DME, either naïve or previously treated with anti-VEGF (three anti-VEGF injections); ≥18y of age; baseline BCVA ≥5 letters (ETDRS charts); glycosylated hemoglobin A1c (HbA1c) ≤10%; and that had at least a minimum post DEX implant follow-up period of 12mo. The exclusion criteria were macular edema due to any other condition; existence of macular ischemia (determined by fluorescein angiography or optical coherence tomography angiography), vitreomacular traction, foveal atrophy, or pigment abnormalities; history of vitrectomy; history of major ocular surgery within the previous 6mo; intraocular pressure (IOP) ≥25 mm Hg; history of uveitis; and loss of follow-up.

Study Parameters The following information was collected at baseline: age; sex; IOP; lens status; previous DME treatments; presence of HRD, SRF, and/or DRILS evaluated by means optical coherence tomography (OCT; Swept Source optical coherence tomography, DRI Triton. Topcon Medical Systems, Inc., Oakland, USA); BCVA using the ETDRS visual acuity; and CRT with OCT.

OCT images were evaluated. Quantitative analysis included CRT assessment (defined as the mean thickness within the central 1000-μm diameter area on the Early Treatment Diabetic Retinopathy Study map[38]). Qualitative analysis included the presence or absence of HRD the presence or absence of SRF, and the presence or absence of DRILS. HRD were defined as small discrete, well-circumscribed, dot-shaped, and highly reflective dots on OCT images[31]. Additionally, DRILS were defined as the presence of a region on the B-scan where the boundaries between the ganglion cell and inner plexiform layer complex, inner nuclear layer, and outer plexiform layer could not be separately identified[33]. BCVA, CRT, IOP, and treatment related complications were collected during the follow-up visits.

The study protocol included a baseline visit and five follow-up visits at months 2, 4, and 6 (±2wk), and months 8 and 12 (±1mo). Previously treated patients had received a regime of three injections of anti-VEGF (bevacizumab, ranibizumab, or aflibercept) with lack of functional and/or anatomic response defined as a BCVA improvement <5 letters ETDRS and /or a CRT thickness reduction <10%. In the previously treated eyes, intravitreal DEX implant was implanted between 1 and 3mo after the last anti-VEGF injection. DEX implant was placed following standard indications[14]. Retreatment with DEX was performed if BCVA decreased and/or the presence of SRF/intraretinal fluid (IRF) were detected due to recurrence of DME during the follow-up.

Primary efficacy end-points were changes in BCVA and in CRT from baseline to the last follow-up visit and the percentage of patients achieving a BCVA improvement ≥15 letters in BCVA. Secondary outcome measures included the

percentage of patients achieving a BCVA improvement ≥10 letters; time elapse from the device implant to the functional improvement; number of DEX implants; assessment of lens status; and the impact of the presence of HRD, SRF, or DRILS on the proportion of eyes achieving a BCVA improvement ≥5, ≥10, and ≥15 letters.

Changes in IOP and incidence of ocular hypertension were assessed over the course of follow-up. According to Bahadorani *et al*[39], the degree of ocular hypertension was defined as IOP measurements of ≥23 (mild), ≥25 (moderate), or ≥30 (severe) mm Hg.

Statistical Approach Data were analyzed using the statistical analysis software MedCalc[40]. For detecting a mean difference of 10 letters in BCVA, with a standard deviation of 9 letters, with a type I and type II errors of 0.05 and 0.10, respectively, each group requires a target sample size of approximately 18 patients.

Data were evaluated in a masked fashion. Descriptive analysis included mean±standard deviation (SD), 95% confidence interval (CI), and percentages as appropriate. The test of D'Agostino-Pearson was used for testing the distribution of continuous variables. Changes in BCVA and CRT were evaluated by means repeated measures ANOVA or Friedman's two-way analysis test, as needed. Changes in BCVA, CRT, and time to improvement between naïve and previously treated eyes were assessed by using the Mann-Whitney *U* test. The χ^2 test was employed to test the differences in the proportion of patients gaining ≥10 letters and ≥15 letters in BCVA. Using the Cox proportional hazards model, with 95%CI, with patient intraclass correlation, Hazard ratios (HRs) were assessed by analyzing the eyes achieving an improvement ≥5, ≥10, and ≥15 letters in BCVA according to the presence of HRD, SRF, or DRILS at baseline. A backward strategy was adopted, with a statistically significant cut-off for variable screening of 0.05.

To evaluate the relationship between the change in BCVA and CRT (as dependent variables) and the length of diabetes and DME as independent variables, a linear regression analysis was performed. For linear regression analysis, the Pearson correlation coefficient (*r*) was used. A *P* value of less than 0.05 was considered significant.

RESULTS

Totally 43 (24 naïve and 19 previously treated) patients were included in the study. Table 1 shows the baseline characteristics of the study sample.

There were no significant differences in the majority of the baseline clinical and demographic characteristics (Table 1), with the exception of the age (naïve patients were younger); length of DME (significantly greater in the previously treated patients); and the presence of SRF (higher in naïve patients).

Table 1 Baseline demographic and clinical characteristics

Parameters	Naïve (*n*=24)	Previously treated (*n*=19)	*P*[a]
Age, y			0.0113
Mean±SD	63.7±11.5	71.8±9.9	
95%CI	58.8 to 68.6	67.0 to 76.6	
Sex, *n* (%)			0.8655[b]
Male	12 (50.0)	9 (47.4)	
Female	12 (50.0)	10 (52.6)	
HbA1c (%)			0.1388
Mean±SD	8.2±1.1	7.5±1.1	
95%CI	7.5 to 8.9	6.8 to 8.0	
Lens status, *n* (%)			0.9211[b]
Phaquic	13 (54.2)	10 (52.6)	
Pseudophaquic	11 (45.8)	9 (47.4)	
Length of diabetes, y			0.8151
Mean±SD	14.2±6.9	13.3±4.5	
95%CI	11.3 to 17.1	11.1 to 15.4	
Length of DME, mo			0.0001
Mean±SD	4.8±5.0	7.7±1.9	
95%CI	2.7 to 6.9	6.6 to 8.4	
Previous treatment, *n* (%)			NA
Bevacizumab	NA	3 (15.8)	
Ranibizumab		6 (31.6)	
Aflibercept		10 (52.6)	
HRD, *n* (%)			0.0823[b]
Yes	16 (66.7)	17 (89.5)	
No	8 (33.3)	2 (10.5)	
SRF, *n* (%)			0.0466[b]
Yes	9 (37.5)	2 (10.5)	
No	15 (62.5)	17 (89.5)	
DRILS, *n* (%)			0.5197[b]
Yes	15 (62.5)	10 (52.6)	
No	9 (37.5)	9 (47.4)	
IOP, mm Hg			0.2237
Mean±SD	15.3±3.0	16.5±2.8	
95%CI	14.1 to 16.6	15.2 to 17.8	
BCVA, letters[c,d]			0.3646
Mean±SD	46.9±25.7	40.5±21.1	
95%CI	36.o to 57.8	30.4 to 50.7	
BCVA, letters[c,e]			NA
Mean±SD	NA	45.0±20.3	
95%CI		35.2 to 54.8	
CRT, μm[d]			0.9805
Mean±SD	484.0±119.8	487.5±159.9	
95%CI	433.4 to 534.5	410.5 to 564.6	
CRT, μm[e]			NA
Mean±SD	NA	451.3±103.1	
95%CI		401.6 to 500.9	

[a]Mann-Whitney *U* test (between naïve and non-naïve patients); [b]Chi-square test; [c]Letters in the Early Treatment Diabetic Retinopathy Study (ETDRS) charts; [d]Before to administer the dexamethasone intravitreal implant; [e]Prior to the first vascular endothelial growth factor inhibitor injection. SD: Standard deviation; CI: Confidence interval; DME: Diabetic macular edema; HRD: High reflective dots; SRF: Subretinal fluid; DRILS: Internal limiting membrane disruption; BCVA: Best corrected visual acuity; CRT: Central retinal thickness; NA: Not applicable.

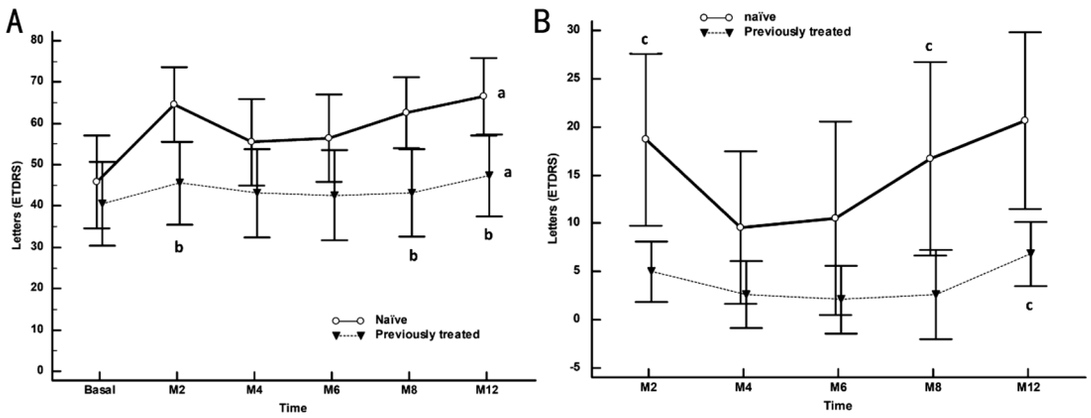

Figure 1 Overview of the BCVA over the course of the study A: Comparison of BCVA throughout the study between naïve and previously treated patients; B: Mean change in BCVA (letters ETDRS) in naïve and previously treated patients. [a]*P*<0.0001 (Intra-group statistical significance; Friedman test). [b]*P*<0.01 (Between groups statistical significance; Mann-Whitney *U* test); [c]*P*<0.05 (Mann-Whitney *U* test). The vertical bars represent the 95%CI. BCVA: Best corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study.

When comparing BCVA and CRT at the time of anti-VEGF administration (previously treated eyes), there were no significant differences in CRT (*P*=0.4633). However, the BCVA was significantly greater at the time of anti-VEGF administration than at the time of DEX implant (*P*=0.0172), which clearly suggested that in those eyes anti-VEGF treatment was not effective. A significantly greater proportion of patients achieved a BCVA improvement ≥15 letters in the naïve group (54.2%) than in the previously treated one (21.1%, *P*=0.0293). Although the proportion of patients achieving a BCVA improvement ≥10 letters was greater in the naïve group, such difference was not significant (66.7% *vs* 42.1%, respectively; *P*=0.1114). Nevertheless, the naïve patients achieved the BCVA improvement significantly faster (2.4±1.5mo) than the previously treated ones (3.5±2.4mo, *P*=0.0298, Mann-Whitney *U* test). The time elapsed to reach the ≥15 letters improvement was lower in the no previously treated patients than in the previously treated ones (2.9±2.3 *vs* 5.0±3.5, respectively, *P*=0.2892; Mann-Whitney *U* test), although the difference was not significant due to the limited sample.

The mean BCVA significantly increased in the naïve patients from 46.9±25.7 letters at baseline to 65.2±20.7, 56.7±24.3, 57.6±24.6, 62.6±20.0 and 67.3±21.6 letters at months 2, 4, 6, 8 and 12, respectively (*P*<0.0001; Figure 1A).

Similarly, BCVA significantly increased throughout the study in the previously treated patients (*P*<0.0001, Friedman rank sum test; Figure 1A). At month 12, mean improvement in BCVA from baseline was 20.4±20.8 letters and 6.8±6.9 letters in naïve and previously treated patients, respectively (*P*=0.0132, Mann-Whitney *U* test; Figure 1B).

CRT significantly decreased from 484.0±119.8 and 487.5±159.9 μm to 272.0±39.2 and 233.5±65.7 μm in the naïve and previously treated patients, respectively; *P*<0.0001 each, respectively, Friedman rank sum test (Figure 2).

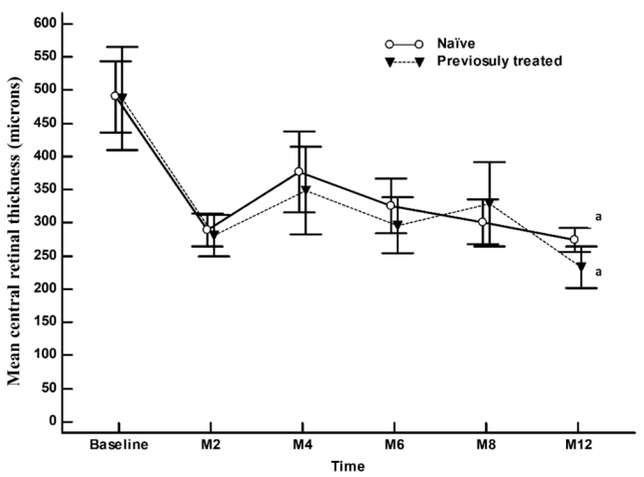

Figure 2 Comparison of mean central retinal thickness among the study groups The vertical bars represent the 95%CI. Intra-group statistical significance, at the different time point measurements, was determined using the Friedman rank sum test. Statistical significance between groups was determined using the Mann-Whitney *U* test. [a]*P*<0.0001. No significant differences were found at any of the time point visits between groups.

There were no significant differences in CRT reduction between naïve and previously treated patients throughout the study follow-up (Table 2).

At the end of the study follow-up, mean HbA1c is 7.8%±1.0% and 8.2%±1.2% in the naïve and nonnaïve patients (*P*=0.2399), with no significant differences as compared to baseline measurements (*P*=0.1940 and *P*=0.1743, respectively).

The presence of SRF was significantly associated with the proportion of patients achieving a BCVA improvement ≥5 letters [HR (95%CI), 1.23 (1.04 to 1.45), *P*=0.0145]; ≥10 letters [HR (95%CI), 1.75 (1.10 to 2.77), *P*=0.0182]; and ≥15 letters [HR (95%CI), 2.04 (1.03 to 4.02), *P*=0.0407; Table 3]. However, neither the presence of HRD or DRILS were predictors of the functional outcome (Table 3).

Table 2 Mean changes in central retinal thickness in naïve and previously treated mean (SD), μm

Parameters	Naïve	Non-naïve	*P*
MCCRTM2			0.9512
Mean (SD)	196.8 (126.2)	206.8 (152.8)	
95%CI	143.5 to 250.1	133.2 to 280.5	
MCCRTM4			0.3833
Mean	107.4 (123.7)[a]	138.4 (132.7)	
95%CI	53.9 to 160.9	74.4 to 202.3	
MCCRTM6			0.6776
Mean	155.6 (147.8)	191.2 (188.4)	
95%CI	93.2 to 218.1	100.4 to 282.0	
MCCRTM8			0.2885
Mean	187.5 (147.6)	159.3 (155.4)	
95%CI	123.6 to 251.3	84.4 to 234.2	
MCCRTM12			0.7413
Mean	212.0 (103.5)	254.1 (198.9)	
95%CI	168.3 to 255.7	158.2 to 349.9	
Significance[b]	0.009	0.0021	

[a]Significant differences between months 4 and 12 (Bonferroni corrected, *P*=0.0181); [b]Repeated measures ANOVA. MCCRTM: Mean change in central retinal thickness at month; SD: Standard deviation; CI: Confidence interval. *P*<0.05 was considered as statistically significant (Mann-Whitney *U* test).

Table 3 Prediction capacity of HRD, SRF and/or DRILS for achieving a BCVA improvement ≥5 letters, ≥10 letters, and ≥15 letters

Parameters	≥5 letters		≥10 letters		≥15 letters	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
HRD	1.30 (0.85 to 1.98)	0.2224	0.91 (0.50 to 1.65)	0.7532	0.73 (0.34 to 1.57)	0.4156
SRF	1.23 (1.04 to 1.45)	0.0145	1.75 (1.10 to 2.77)	0.0182	2.04 (1.03 to 4.02)	0.0407
DRILS	1.04 (0.81 to 1.33)	0.7606	1.58 (0.87 to 2.88)	0.1323	1.13 (0.53 to 2.41)	0.7495

HRD: High reflective dots; SRF: Subretinal fluid; DRILS: Disorganization of the retinel inner layers.

There was no significant relationship between age, length of diabetes, or length of DME and the improvement in BCVA (*r*=-0.12, *P*=0.4302; *r*=-0.12, *P*=0.4297; *r*=-0.23, *P*=0.1320; respectively) or the reduction in CRT (*r*=0.11, *P*=0.4867; *r*=-0.09, *P*=0.5545; *r*=0.04, *P*=0.7695, respectively).

The mean number of DEX implants received during the study was significantly lower in the naïve than in the previously treated patients (1.8±0.6 *vs* 2.3±0.6, *P*=0.0172, respectively). In the naïve patients, 6 (25.0%) patients received one DEX implant, 16 (66.7%) two implants, and 2 (8.3%) three DEX implants; whereas, in the previously treated patients 1 (5.2%) patients received one DEX implant, 12 (63.2%) two implants, and 6 (31.6%) three DEX implants (*P*=0.0247). The median (interquartile range) duration of the first DEX implant was 6 (4.0 to 9.0) and 6.0 (4.0 to 6.0) months in naïve and previously treated patients, respectively (*P*=0.1983).

At baseline, 3 people were taking antiglaucoma medication with an IOP of 12, 22, and 22 mm Hg, respectively. Nine (20.9%) patients (7 previously treated and 2 naïve patients) developed ocular hypertension throughout the study, 1 (2.3%) mild, 5 (11.6%) moderate and 3 (7.0%) severe ocular hypertension. Nevertheless, in all the cases the IOP was successfully controlled with topical hypotensive medication.

Of the 23 phakic eyes at baseline, 5 eyes (21.7%) either had new onset lens opacity or progression of an existing opacity during the study follow-up. Four of them (2 in the naïve group and 2 in the previously treated one) required cataract surgery at months 4, 6, 6, and 6, respectively. During the study, other treatment related adverse events have not been observed.

DISCUSSION

The results of this study showed that in patients with DME, both the BCVA and the CRT significantly improved after the treatment with the DEX implant Ozurdex®. Moreover, the proportion of patients achieving a BCVA improvement ≥15 letters was significantly greater in the naïve patients than in the previously treated ones (54.2% and 21.1%, respectively).

Although the improvement in BCVA was observed in both naïve and previously treated patients, the improvement in BCVA at months 2, 8, and 10 were significantly greater in the naïve patients. These results might support the early use of the

dexamethasone implant Ozurdex® as first line therapy in naïve patients.

As regards clinical outcomes, the results of our study were in line with the published evidence[9-21]. It was recently published a systematic review search evaluating the pharmacological management of DME in real-life observational studies[41]. The mean visual acuity improvement observed in our study in the previously treated patients (6.8 letters) was in line with that published by Kodjikian *et al*[41] (8.6 letters). Nevertheless, in the naïve patient's group, the current study found a mean BCVA improvement slightly greater (20.4 letters) than that reported by Kodjikian *et al*[41] (12 letters).

Additionally, the final mean BCVA in naïve patients was almost 10 letters greater than that presented in the Kodjikian *et al*[41] study (67.3 *vs* 57.9 letters, respectively), while the final mean BCVA in the previously treated patients was almost the same (47.4 *vs* 48.7, respectively)[41].

The time to initial gain ≥10 letters in the naïve patients (2.4±1.5mo) was significantly shorter than that observed in the previously treated patients (3.5±2.4mo). Additionally, the time to initial gain ≥15 letters was lower in the naïve patients (2.9±2.3mo) than in the previously treated ones (5.0±3.5mo), although that difference was not significant. The time observed in the naïve patient is in line with the previous data[42]. Nevertheless, in previously treated patients, the time to initial gain either ≥10 letters or ≥15 letters, found in our study, was slightly greater than that reported by Singer *et al*[42].

According to the results of the current study, visual outcomes were not significantly associated with the presence of either HRD and/or DRILS. These results dissent from those studies which suggested that the presence of HRD[34,43] and/or DRILS[43] was significantly associated with final visual acuity. Moreover, it was also reported that the absence of HRD and integrity of the inner segment-outer segment layer were all predictive of better visual outcome after treatment with DEX implants[44].

These findings disagreed with those studies suggesting that the presence of HRDs was associated with the functional and/or anatomic outcomes[34-36,45-46]. The lack of agreement between our results and the published evidence may be due to differences in study population or an insufficient sample size.

This study identified the presence of SRF at baseline as a predictor for achieving a BCVA improvement. This finding agrees with that reported by Zur *et al*[47], who found that the presence of SRF was predictive of better visual outcome after treatment with DEX implants. Additionally, a post hoc analysis of 2 randomized controlled trials found better functional outcomes in eyes with SRF at baseline than in those without SRF[47]. These findings were also observed in patients treated with anti-VEGF, where eyes with SRF at baseline had greater visual improvements[32,48].

However, the results of the current study disagree with those reported by Lee *et al*[44] who found that an improvement in BCVA≥0.2 was significantly correlated with absence of SRF. This study did not observe any significant difference in the reduction in CRT between naïve and previously treated patients at the different time points. These results agree with previous papers[9-21,41].

In the overall study population, the mean number of DEX throughout the study follow-up was 2.0±0.6, with most patients receiving two DEX implants throughout the study. In the previously treated patients, the mean number of DEX implants per patient (2.3 in 12mo) was slightly greater than that reported by Pareja-Rios *et al*[14] and by Kodjikian *et al*[41], but in line with that published by the BEVORDEX study (2.7 implants)[49]. This may reflect that in our study the criteria for retreatment were strict and BCVA values were no allowed to decline too much before retreatment. Additionally, this intensive and customized therapeutic regimen might explain the greater BCVA improvement achieved in naïve patients when compared to other studies, such as Kodjikian *et al*[41].

The mean number of implants administered in the naïve patient's (1.8) was really very similar than that expound by Kodjikian *et al*[41] (1.9). Interestingly, Kodjikian *et al*[41] reported fewer implants in the previously treated eyes than in the naïve eyes (1.4 *vs* 1.9), while in our study we observed the opposite one, more implants in the previously treated eyes than in the naïve ones (2.3 *vs* 1.8). Nevertheless, it should be pointed out, that our results are in line with previously published studies that suggested the need of a greater number of DEX implants in previously treated eyes than in the naïve ones[50].

Regarding the adverse events, 9 (20.9%) eyes developed ocular hypertension (IOP≥23 mm Hg) over the course of the study. In all cases, ocular hypertension was successfully controlled with topical hypotensive drugs or observation; none required surgery. These results are in agreement with previously published studies[10-15,39,51].

Similar to the study published by Early Treatment Diabetic Retinopathy Study Research Group[38], in our study repeated Ozurdex® implants did not affect the frequency and degree of ocular hypertension.

Four (17.4%) of the phakic eyes underwent cataract surgery during the study. There were no cases of serious local or systemic adverse events. However, the low number of implants administered in this study and the fact that steroids cause cataract after one to two years of treatment might justified the low incidence of cataract surgery found in our study.

Finally, some considerations about OCT should be done. The OCT plays an important role in both diagnosing and managing DME[52]. From its inception, OCT images were

acquired in a time domain fashion[53]. Spectral-domain (SD-) and swept-source (SS-) OCT instruments have been developed to overcome the limitations of time domain OCT. Both instruments use Fourier domain detection techniques, which allows faster imaging acquisition, denser scan patterns, and better images of the deep retinal structures[54-57].

However, due to they use different image processing algorithms and different segmentation strategies, normal values for SD-OCT and SS-OCT differ, which makes their findings non-interchangeable across instruments made by different companies[55-56,58].

The main limitations of this study were its retrospective nature and the relatively small size of the single center studies. Regarding the retrospective design, the strict inclusion/exclusion criteria applied in our study were such to minimize this potential bias. Although this was a single center study with a limited number of patients, the sample size was calculated prior the study. Another limitation is the fact that the difference in the functional outcomes between naïve and previously treated eyes might be due to the differences in some of the baseline parameters, namely the age (naïve patients were younger); length of DME (significantly greater in the previously treated patients), and the presence of SRF (higher in naïve patients). Nevertheless, our results did not significantly differ from those of the currently available scientific evidence[9-21,32,37,41,47-48]. Despite these limitations, the results of this study suggested that the DEX intravitreal implant Ozurdex®, either in naïve or in previously treated patients, improved BCVA and CRT. The time to initial gain ≥10 or ≥15 letters in the naïve patients was shorter than that observed in the previously treated patients, although only the time to gain ≥10 letters was statistically significant. The results obtained in this study might support the early use of the DEX implant Ozurdex® as first line therapy in naïve patients and as a second-line therapy in the previously treated ones.

Finally, our study found that the presence of SRF at baseline was predictive of a better functional outcome. Further studies are needed to elucidate predictive factors associated with positive functional and structural outcomes as well as the time elapsed to reach the best functional improvement.

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