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ORIGINAL RESEARCH

Systemic Effects of Repeated Intraocular Dexamethasone Intravitreal Implant in Diabetic Patients: A Retrospective Study

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ABSTRACT

Introduction: The objective of this study is to evaluate the influence of repeated intraocular dexamethasone implant (Ozurdex) injections on metabolic control in type 2 diabetic patients.
Methods: Retrospective study of 165 type 2 diabetic patients starting Ozurdex treatment who received no less than three consecutive injections. Glycated hemoglobin (HbA1c), serum creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TGs) were evaluated during 15 months of follow-up after Ozurdex treatment onset.
Results: Fifty-seven patients met inclusion criteria. Mean baseline values for HbA1c, creatinine, total cholesterol, HDL cholesterol, and TGs before treatment (7.1%, 1.3, 176.7, 51.1, and 125.6 mg/dl, respectively) were similar to mean values after Ozurdex onset (Wilcoxon test p values were 0.68, 0.41, 0.06, 0.87, and 0.33, respectively) and remained stable during the follow-up period. Mean LDL cholesterol levels increased slightly after Ozurdex treatment onset (90.1 vs 88.2 mg/dl, $p = 0.04$) but after 15 months of follow-up they had returned to baseline values. Transient increase in LDL cholesterol was remarkable in the group of 24 bilaterally treated patients (96.8 vs 88.4 mg/dl, $p = 0.03$). A third of these patients increased their baseline LDL values by more than 20%. Even with continuous injections of Ozurdex, LDL cholesterol levels also declined back to baseline by month 15.
Conclusion: Ozurdex injections had no influence on HbA1c or renal function. Lipid profile changes were mild and transient. However, a significant temporary increase has been found in LDL cholesterol levels in patients receiving simultaneous bilateral injections. Lipid levels should be monitored in patients starting with bilateral Ozurdex injections especially in those with recent history of acute myocardial infarction.

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INTRODUCTION

Diabetic macular edema (DME) is the leading cause of visual impairment in diabetic type 2 patients [1]. Two groups of intraocular drugs are currently used for the treatment of DME: anti-vascular endothelial growth factor (VEGF) agents [2] and corticosteroids [3]. Four of these drugs are approved for intraocular use: ranibizumab (Lucentis, Novartis, Basel, Switzerland), aflibercept (Eylea, Bayer Pharma, Berlin, Germany), fluocinolone acetonide implant (Iluvien, Alimera Sciences Inc., Alpharetta, GA, USA), and dexamethasone (DEX) implant (Ozurdex, Allergan Inc., Irvine, CA, USA).

The systemic safety profile is one of the main concerns about anti-VEGF drugs. Serious adverse events such as myocardial infarction, stroke, arteriothrombotic events, and serious hemorrhage have been described among others [4]. No systemic side effects have been reported related to Ozurdex implant injection so far [5], and safety parameter assessments tend to include local side effects exclusively, such as cataract development and intraocular pressure rise [3, 5–8].

Classic systemic effects of oral corticosteroids include increase in serum insulin and glucose levels, decrease in insulin-mediated glucose uptake [9, 10], and dyslipidemia, including increased serum levels of triglycerides (TGs), low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol [11]. These parameters are extremely important for cardiovascular risk of diabetic patients and have a deep impact on their medium and long-term survival [12, 13].

Ophthalmic local routes of corticosteroid administration, such as peribulbar injection, lead to significant systemic levels as demonstrated in previous studies [14–18]; for instance, 5 mg of dexamethasone administered peribulbarly is biologically equivalent to 50 mg of orally administered prednisone [14]. Ozurdex is a biodegradable sustained-release DEX implant, delivered in the vitreous body. However, with intravitreal 0.7-mg Ozurdex implant, dexamethasone can reach plasma concentrations of 1.11 ng/ml, and it can still be detected in the study subjects even 2 months after the intravitreal injection [19]. DME is a chronic entity and may need reinjections with an interval dosage regimen below 6 months. Whether or not repeated DEX-implant injections may alter metabolic control in diabetic patients has not been previously investigated.

The purpose of the present study was to assess the impact of repeated Ozurdex injections on systemic parameters of type 2 diabetic patients in real practice. This is, to our knowledge, the first study to address this issue.

METHODS

Medical records from all patients starting Ozurdex treatment at the Ophthalmology Service, San Carlos University Hospital, between January 2013 and January 2015 were retrospectively reviewed. The following inclusion criteria were applied: type 2 diabetic patients diagnosed with macular edema treated with no less than three consecutive Ozurdex injections, interval between retreatments ranging from 4 to 6 months, and adequate systemic follow-up before and after Ozurdex (at least medical revisions every 6 months). Systemic parameters evaluated were glycated hemoglobin (HbA1c), serum creatinine, total cholesterol, HDL cholesterol, LDL cholesterol, and TGs. Patients with high HbA1c levels were not excluded from the study. To ensure representative basal values of these parameters, only those patients with at least three complete fasting blood tests available (18, 12, and 6 months) before Ozurdex were considered eligible. After initiation of Ozurdex treatments, blood tests performed at month 3, month 9, and month 15 were recorded (Fig. 1). Those blood tests performed during hospitalization were discarded to avoid acute-phase non-representative changes. Tendency graphs were created for every patient in search of predefined response patterns. Exclusion criteria were treatment with systemic corticosteroids, change in systemic treatment 2 years before

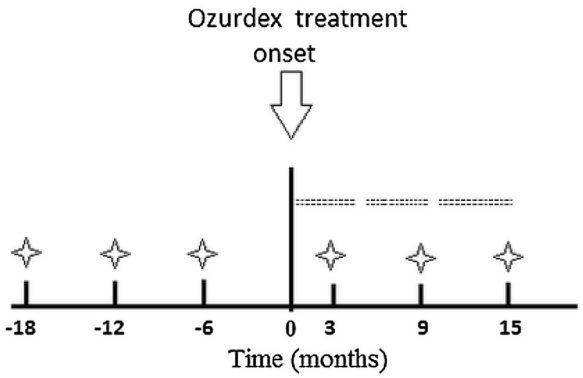

Fig. 1 Chronological scheme of Ozurdex injections (double line) and blood tests (stars) before and after treatment in this study. To minimize influence of possible variability in systemic parameters on baseline conditions three representative blood tests performed at 18, 12, and 6 months before the first Ozurdex implant were evaluated and mean values calculated for each recorded variable were considered as baseline values

Ozurdex, intravitreal anti-VEGF injections within 6 months prior to January 2013, and Ozurdex retreatment interval below 4 months. The metabolic statuses of patients were assessed on the basis of blood tests performed before starting Ozurdex treatment and those with remarkable oscillations in the evaluated systemic parameters were excluded.

The following data were extracted from the medical records of the patients: age (years), gender, systemic treatment, prior cataract surgery, affected eye (right, left, or both), basal best corrected visual acuity (measured with the Early Treatment Diabetic Retinopathy Study (ETDRS) method, an optotype with letters increasing in size from 1 to 100), and cause of macular edema (DME; retinal vein occlusion). Optic coherence tomography (Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany) was recorded at every visit.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was not obtained from patients because this is a retrospective study of records. The study protocol was approved by the institutional review board of our center (San Carlos Clinical Hospital, Madrid, Spain).

Statistical Analysis

Analyses were performed by using SPSS 20 (IBM SPSS, Chicago, IL, USA). Normally distributed data were expressed as mean and standard deviation (SD), and Student's paired *t* test was used to compare systemic parameters before and after DEX treatment. Skewed data are expressed as medians and quartiles, and Wilcoxon's test was used to compare values before and after treatment. Spearman correlation coefficient was calculated for the number of injections and change in systemic variables. To investigate if bilateral treatment had a greater impact on systemic variables compared to unilateral treatment, the Mann–Whitney test was used. The three blood tests used for every patient before Ozurdex treatment were considered as a mean value. The three blood tests performed during Ozurdex treatments were considered as a mean and also separately for comparison with baseline status, searching for transient changes that might go unnoticed because of a regression toward mean values. A p value less than 0.05 was considered statistically significant.

RESULTS

A total of 165 type 2 diabetic patients started Ozurdex treatment during the study period. Fifty-seven (34.5%) patients met study criteria. The main exclusion criterion was lack of periodic complete blood tests performed. Demographic data are shown in Table 1. Mean age was 72.4 years (SD 10.4). Thirty-three patients were male (58%). Thirty-nine subjects (68.4%) were followed by an endocrinologist. Twenty-nine (50.8%) patients were on insulin therapy and the remaining (49.2%) were taking oral antidiabetic drugs. At the end of the follow-up, these percentages were stable but three patients in the DME group had their oral antidiabetic medication changed (from metformin to metformin in association with sitagliptin in order to better control their HbA1c). The cause of the

Table 1 Characteristics of the patients in the study

Parameter	All patients, $N = 57$	Diabetic macular edema, $N = 36$	Macular edema secondary to retinal vein occlusion, $N = 21$	p value[†]
Age (years), mean (median; SD; range)	72.4 (73.0; 10.4; 46–95)	69.9 (72; 9; 54–84)	76.8 (79; 11.2; 46–95)	0.01
Gender				
Female	24 (42.1%)	14 (59%)	10 (44%)	0.35
Male	33 (57.9%)	22 (41%)	11 (55%)	
Visual acuity at presentation (ETDRS letters)	46.1 (50; 20.3; 1–75)	49.4 (50; 19.5; 1–75)	40.6 (50; 20.8; 1–70)	0.12
Number of injections per subject	5.3 (5; 2.4; 3–10)	6.0 (5; 2.5; 3–10)	4.14 (4; 1.6; 3–10)	0.001
Bilateral treatment	24 (42.1%)	22 (61.1%)	2 (9.5%)	0.001

[†] Mann–Whitney test; p values refer to comparisons between the two subgroups of patients

macular edema was retinal vein occlusion (RVO) in 21 of our diabetic patients (36.8%) and DME in 36 patients (63.2%). Twenty-four patients (42.1%) received bilateral Ozurdex injections. During the study period, a mean of 5.3 injections (SD 2.4) were used per patient. Mean visual acuity was 46.1 ETDRS letters (SD 20.3) before treatment and 57.6 (SD 14.9) during the peak effect after treatment. No patient lost more than 15 letters during study time and 26 patients (45.6%) gained more than 15 letters. Increased intraocular pressure after treatment was reported in 12 patients (21%).

Metabolic status before and after Ozurdex treatment onset was compared. To reduce variability of baseline conditions, the mean value of each recorded variable was calculated from the blood tests performed at months 18, 12, and 6 before the first Ozurdex injection and considered as baseline value for every parameter. Table 2 shows HbA1c, creatinine, total cholesterol, HDL cholesterol, LDL cholesterol, and TG levels before and after Ozurdex treatment. Values of systemic parameters are displayed for the whole group of diabetic patients and also for both subgroups of patients with DME or RVO. In the entire cohort, mean baseline HbA1c was 7.1% (SD 1.2, range 5.3–11.2). In the first blood test recorded for the study after Ozurdex treatment onset, mean HbA1c value was 7.2% (SD 1.3, range 5.2–11.3). Wilcoxon tests showed no significant differences compared to baseline ($p = 0.68$). Thirty-three patients (57.8%) had increased HbA1c levels with a mean change of 0.4% (SD 0.4). Maximum change was 2% (one patient). Lower HbA1c levels were found in 31.6% of patients while 10.5% remained unchanged with respect to basal values. The second blood test showed a mean HbA1c of 7.1% (SD 1.3, range 5.5–12.5) and the third one showed a mean of 7.1% (SD 1.1, range 5.2–9.7). Corresponding Wilcoxon tests showed no differences between baseline and the periods assessed (p values 0.43 and 0.74, respectively). Patients receiving more than five injections in our study were also assessed separately. Again, no differences were found in HbA1c before and after Ozurdex treatment. Likewise, DME and RVO subgroups showed no significant differences in HbA1c levels at any time in the follow-up as compared to their respective baseline values (all p values above 0.05).

Overall, no significant changes were found in the whole study group for creatinine, total cholesterol, HDL cholesterol, or TGs at any period of the follow-up. LDL cholesterol levels increased slightly after Ozurdex treatment onset, but this effect was no longer detectable at the end of the follow-up period. Although statistically significant, variations in this

Table 2 Systemic parameters of diabetic patients before and after Ozurdex treatment onset

	HbA1c (%)	$p^{\dagger}$	Creatinine[a]	$p^{\dagger}$	Cholesterol[a]	$p^{\dagger}$	HDL[a]	$p^{\dagger}$	LDL[a]	$p^{\dagger}$	TG[a]	$p^{\dagger}$
Basal	7.1		1.3		176.7		51.1		88.2		125.6	
Mean (SD; range)	(1.2; 5.3–11.2)		(1.1; 0.6–8.3)		(54.6; 107–480)		(12.9; 27–84)		(32.1; 20–167)		(52.6; 48–353)	
DME/RVO	7.5/6.6		1.4/1.1		158.2/178.4		48.8/54.2		81.1/89.5		134.3/121.1	
Post Ozurdex[b]	7.2	0.81	1.3	0.58	165.7	0.09	50.8	0.77	89.7	0.14	125.7	0.88
Mean (SD; range)	(1.3; 5.6–10.9)		(1.1; 0.6–8.3)		(35.4; 89–280)		(13.5; 25–89)		(31.9; 17–189)		(59.4; 51–373)	
DME/RVO	7.3/7.1		1.4/1.1		178.3/182.4		49.6/56.4		90.6/92.7		136.4/112.7	
- **First test**	7.2	0.68	1.3	0.41	195.1	0.06	50.8	0.87	90.1	0.04	128	0.33
Mean (SD; range)	(1.3; 5.2–11.3)		(1.2; 0.6–8.7)		(150; 106–1222)		(14.6; 25–89)		(33.5; 20–165)		(64.9; 50–340)	
DME/RVO	7.4/7.2		1.4/1.1		189.7/182.5		49.9/57.5		92.4/89.9		141.6/110.3	
- **Second test**	7.1	0.43	1.3	0.44	170.7	0.12	52.3	0.36	90.2	0.01	120.6	0.23
Mean (SD; range)	(1.3; 5.5–12.5)		(1.3; 0.6–9.4)		(35.6; 107–277)		(14.3; 30–93)		(33.8; 13–186)		(56.5; 39–368)	
DME/RVO	7.1/7.5		1.4/1.1		166.2/187.7		50.1/60.6		91.8/88.8		132.4/107.8	
- **Third test**	7.1	0.74	1.3	0.05	164.3	0.92	49.5	0.05	84.8	0.89	128.2	0.38
Mean (SD; range)	(1.1; 5.2–9.7)		(1.3; 0.5–9.4)		(41.6; 97–276)		(13.3; 24–75)		(35.4; 20–184)		(55.2; 49–351)	
DME/RVO	7.3/7		1.4/1.1		159.4/185.4		48.1/55.5		85.3/82.8		136.7/119.3	

Mean values of parameters for the entire group of patients (first line in the cells) and for each of the two subgroups (diabetic macular edema, DME, and macular edema secondary to retinal vein occlusion, RVO) are shown. Standard deviation and range are indicated between parenthesis for the whole group; for DME and RVO subgroups only mean values are shown for simplicity

† Wilcoxon test, mean basal is reference. *p* values shown refer to the entire group of diabetic patients

[a] Units mg/dl

[b] Mean of the three measurements post Ozurdex injection onset

parameter are quantitatively low. The increase in LDL cholesterol levels was pronounced in the DME subgroup (92.4 vs 81.1 mg/dl; $p = 0.03$) whereas no changes were apparent in the RVO patients.

Table 3 shows further subset analysis of systemic parameters in bilaterally treated patients (24 subjects of the total cohort). Mean basal HbA1c was 7.6% (SD 1.1, range 6.1–9.8). Mean post treatment was 7.3% (SD 1.3, range 5.3–11.2). There was no effect on this parameter after Ozurdex treatment (Wilcoxon $p = 0.45$) or in the whole follow-up ($p = 0.56$, $p = 0.17$, and $p = 0.21$). Again, no significant changes were detected for creatinine, total cholesterol, HDL cholesterol, or TGs levels at any time of the follow-up (all p values above 0.05). However, remarkable changes were observed in LDL cholesterol. Overall, mean baseline values were 88.4 mg/dl (SD 26.5, range 17–129) whereas 3 months after DEX implant, levels increased to 96.8 mg/dl (SD 33.6, range 24–165). The difference is significant ($p = 0.03$) and corresponds to a 9.5% mean increase. Thirty-four percent of the bilaterally treated patients increased their LDL cholesterol levels more than 20% and half of these were by more than 40% compared to baseline values. This effect was transient because in the third blood test after Ozurdex treatment, LDL cholesterol values had returned to basal levels (Fig. 2).

DISCUSSION

Our study shows that repeated Ozurdex injections had no influence on serum levels of HbA1c or creatinine, nor on serum lipid profile in type 2 diabetic patients. However, bilateral simultaneous injections induced a transient increase in LDL cholesterol levels.

There are no published studies on the pharmacokinetics of Ozurdex implants in the human eye. Systemic exposure was measured during the two pivotal phase III studies [20]. In 5% of the subjects treated with 0.35-mg Ozurdex implant, plasma dexamethasone levels were above the limit of quantitation of the test used for measurement (0.05 ng/ml). For subjects treated with 0.7-mg implant (unilateral injection), this percentage rose to 13.7% [21]. Bilateral implant injection is routinely performed as DME is often a bilateral condition; thus, it is reasonable to think that systemic exposure would be higher in these cases. In a study performed on monkeys [19] with 0.7-mg Ozurdex implants, a biphasic release pattern was observed in treated eyes with peak levels of the drug over the 2 months after administration and continued releasing activity at decreasing doses for 6 months. Mean maximum concentration of dexamethasone in plasma was 1.11 ng/ml (range 0.99–1.22), and levels were detectable up to 60 days. This concentration could be clinically relevant, as maximum suppression of the hypothalamic–pituitary–adrenal axis occurs in humans at plasma concentrations of 5 ng/ml and above [22].

Experimental administration of glucocorticoids increases plasma free fatty acid (FFA) availability in the systemic circulation [23–25]. Increased plasma FFA availability can lead to ectopic fat deposition in the liver and skeletal muscle, attenuation of hepatic and skeletal muscle insulin action (resulting in hyperglycemia and hyperinsulinemia), and stimulation of hepatic very low-density lipoprotein (VLDL) secretion and hypertriglyceridemia [23]. Hyperinsulinemia induces cardiac hypertrophy and hyperglycemia mediates cardiac injury through the generation of reactive oxygen species [13]. This is especially relevant considering the target population for Ozurdex treatment in our study, diabetic patients, already at risk for cardiovascular events.

Biological effects of dexamethasone can be achieved regardless of the route of administration used. Thus, it has been shown that topical administration of 0.1% dexamethasone (50 µl) to male rats three times daily for 4 weeks increased plasma total cholesterol threefold and significantly reduced creatinine levels when compared to sham-treated rats [26].

In the 3-year, randomized trial of Ozurdex in DME (MEAD study) systemic safety issues were mentioned [3]. HbA1c appeared to increase progressively, and mean glomerular filtration rates decreased during the study, but mean values, standard deviations, or comparative statistics were not presented. Our study was

Table 3 Bilaterally treated patients ($n = 24$). Systemic parameters before and after Ozurdex treatment onset

	HbA1c (%)	$p^{\dagger}$	Creatinine[a]	$p^{\dagger}$	Cholesterol[a]	$p^{\dagger}$	HDL[a]	$p^{\dagger}$	LDL[a]	$p^{\dagger}$	TG[a]	$p^{\dagger}$
Basal	7.6		1.4		162.5		48.9		88.4		127.2	
Mean (SD; range)	(1.1; 6.1–9.8)		(1.6; 0.4–8.3)		(34.5; 89–213)		(13.8; 25–89)		(26.5; 17–129)		(56.6; 43–286)	
Post Ozurdex[b]	7.3	0.45	1.5	0.45	167.3	0.25	51.1	0.37	95.0	0.1	133.5	0.47
Mean (SD; range)	(1.3; 5.3–11.2)		(1.8; 0.7–9.2)		(33.4; 107–230)		(13.1; 27–84)		(24.8; 44–148)		(59.5; 76–353)	
First test	7.4	0.56	1.5	0.23	171.5	0.50	51.6	0.26	96.8	0.03	140.8	0.65
Mean (SD; range)	(1.4; 5.2–11.3)		(1.7; 0.6–8.7)		(42.4; 106–257)		(14.1; 26–86)		(33.6; 24–165)		(82.6; 65–340)	
Second test	7.4	0.17	1.5	0.68	169.5	0.74	51.7	0.48	95.1	0.06	130.4	0.48
Mean (SD; range)	(1.4; 5.5–12.5)		(1.8; 0.7–9.4)		(32.7; 107–237)		(14.1; 30–93)		(23.2; 46–138)		(72.9; 39–368)	
Third test	7.1	0.21	1.5	0.84	161.1	0.95	49.9	0.83	88.9	0.73	129.4	0.33
Mean (SD; range)	(1.1; 5.2–9.7)		(1.9; 0.7–9.4)		(34.7; 101–235)		(13.2; 24–72)		(26.2; 35–149)		(61.6; 68–351)	

† Wilcoxon test, mean basal is reference

[a] Units mg/dl

[b] Mean of the three measurements post Ozurdex injection onset

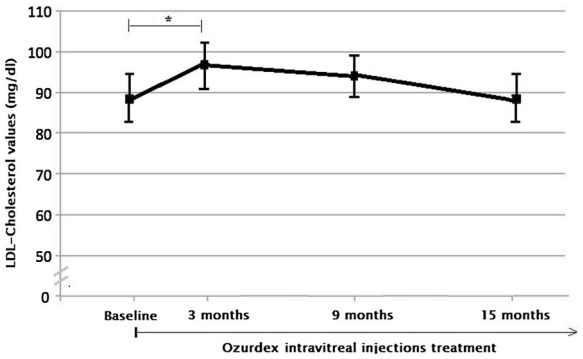

Fig. 2 Serum LDL cholesterol levels in patients treated with bilateral Ozurdex injections. Mean values and standard error are represented. *Significantly different from baseline value, $p = 0.03$

carefully designed to be able to detect changes in systemic parameters. To avoid influence of variability in HbA1c in pretreatment status, three representative (and not overlapped) values from 18 months before Ozurdex treatment were used. Only blood tests performed after 3 months from injection onset were considered, because of red blood cell turnover (average 120 days [27]). Careful selection of blood tests was applied, discarding those performed during hospitalization. Three values during follow-up were recorded to be able to detect transient changes that might be regulated by compensatory mechanisms and camouflaged in average analysis. As an example of this, in Table 2, LDL cholesterol values increase during the first and second blood tests after Ozurdex injections were started (p values less than 0.05); however, in the third blood test they are decreased. As a result, comparison between pre- and post-treatment finds no significant changes, because of regression towards the mean value.

Although no specific study has addressed the different systemic profile of diabetic patients with DME and RVO, we found that RVO patients tended to be older and their glycemic control better than DME patients. Interestingly, no significant differences between both groups were found in baseline total cholesterol ($p = 0.06$), HDL cholesterol ($p = 0.16$), LDL cholesterol ($p = 0.35$), TGs ($p = 0.15$), or creatinine ($p = 0.6$), but Ozurdex treatment seemed to induce changes of LDL cholesterol levels in the DME group and not in the RVO patients. Reasonably, the number of injections tended to be higher in DME patients because RVO was unilateral in almost all the cases included. Thus, bilaterally treated patients were also considered separately.

In patients receiving simultaneous bilateral injections, LDL cholesterol values increased significantly during short-term follow-up (88.4 vs 96.8 mg/dl , $p = 0.03$). Recommended LDL cholesterol values for diabetic patients are less than 100 mg/dl and less than 70 mg/dl if history of myocardial infarction is present [28]. After acute infarction, LDL cholesterol is also a marker of systemic inflammation and has been related to further destabilization of vascular plaques [29]. Controlled levels of LDL cholesterol are advisable, especially in the first 6 months after acute infarction, to prevent recurrences and comorbidities [30]. Therefore, and even when the systemic safety profile would make Ozurdex preferable above anti-VEGF drugs in this scenario, it would be advisable to monitor lipid levels after onset of bilateral Ozurdex injections, especially in the first 6 months after acute myocardial infarction and in those patients with pre-existing altered LDL cholesterol levels.

A limitation of this study is the modest sample size. Because of its retrospective nature, the systemic parameters analyzed were restricted to those reported on medical charts of the patients included for analysis. Also, as certain periods were selected for follow-up, we detected a transient increase, but it is not possible to know the real maximum level of LDL cholesterol, and when that maximum is reached. On the other hand, our population showed an appropriate baseline metabolic control on average as a result of the high percentage of patients under monitoring by endocrinologists (68.4%). This may represent a potential bias and thus caution is necessary when extrapolating these results to a broader population. The increase in LDL cholesterol found in our study might be exacerbated in a diabetic population with poorer metabolic control. Future studies with shorter interval between blood tests, increased population size studied, and wider range of diabetes management are needed to further investigate these issues.

CONCLUSIONS

Systemic effects of repeated intravitreal Ozurdex injections assessed in this study are slight and transient. However, caution must be exercised in patients receiving bilateral Ozurdex injections if LDL cholesterol levels are not controlled in advance.

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Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was not obtained from patients because this is a retrospective study of records. The study protocol was approved by the institutional review board of our center (San Carlos Clinical Hospital, Madrid, Spain).

Data Availability. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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