

Intravitreal Injection of Ozurdex® Implant in Patients with Persistent Diabetic Macular Edema, with Six-Month Follow-Up

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ABSTRACT

AIM: To evaluate the efficacy of intravitreal dexamethasone injections in diabetic macular edema (DME).

METHODS: A 700 µg slow-release intravitreal dexamethasone implant (Ozurdex®) was placed in the vitreal cavity of 17 patients (19 eyes) affected with persistent DME. Best corrected visual acuity (BCVA) was assessed through Early Treatment Diabetic Retinopathy Study (ETDRS). Central macular thickness (CMT) was measured by spectral-domain optical coherence tomography. BCVA and CMT examinations were carried out at baseline (T0) and repeated after three days, one month (T1), three months (T3), four months (T4), and six months (T6) post injection.

RESULTS: Dexamethasone implant induced an improvement in ETDRS at T1, T3, T4, and T6 post injection. CMT was reduced at T1, T3, and T4, while at T6, CMT values were not statistically different from baseline. No complications were observed during the follow-up.

CONCLUSION: Our data suggest that dexamethasone implant is effective in reducing DME symptoms within a six-month frame.

KEYWORDS: macular edema, diabetes, intravitreal implant, dexamethasone

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Introduction

Diabetic macular edema (DME) is the leading cause for significant loss of visual acuity in patients with diabetic retinopathy (DR).¹ The treatment of DME remains problematic, with a high percentage of failures. In DR, the gold standard treatment of laser photocoagulation can indeed maintain and even improve the long-term condition of patients with baseline visual acuity, but in others, it is ineffective and leads to reduction of field of view, impaired color vision, and sensitivity to contrast.^{2–4}

The cause of DME is still under investigation, although it is believed that inflammation represents one of the leading events in disease development. It has been observed that the increased permeability of macular capillaries in the course of hypoxia leads to increased levels of vascular endothelial growth factor (VEGF) and release of inflammatory factors, including chemokines, cytokines such as interleukin (IL)-6 and IL-8, and prostaglandins.^{5,6} This, in turn, may cause the loss of endothelial cells and pericytes.⁷

According to this notion, intravitreal therapies with anti-VEGF have been considered as an efficient treatment strategy for patients affected by DME.^{8,9} Nevertheless, not all patients

respond to treatment, and the compliance to treatment is low because of the numerous injections required over time.^{10,11}

It has been demonstrated that intravitreal administration of corticosteroids reduces capillary permeability and the formation of secondary macular edema of various etiologies.^{12,13} Corticosteroids also restrict the migration of leukocytes and inhibit the formation of VEGF factor, prostaglandins, and other proinflammatory cytokines.^{14,15} It seems that the route of administration of steroid drugs is crucial for the effectiveness of their actions. The use of drugs administered directly into the vitreous body can achieve the appropriate concentration of the drug directly at the site of the disease, decreasing the systemic side effects.¹⁵

Dexamethasone is one of the most potent anti-inflammatory steroids. Its effect is six times stronger than intravitreal triamcinolone acetonide, which is widely used in the treatment of secondary macular edema, including DR,¹⁶ and 30 times more than cortisol.¹⁷ Triamcinolone acetonide is administered as lipophilic crystals deposited in the vitreous for several months. However, this form of triamcinolone acetonide deposit, administered at a dose of 1.2 and 4 mg in a single injection, does not provide a constant level of drug in the vitreous chamber,



even during the initial period of observation, and is associated with side effects such as increased intraocular pressure and steroid cataracts.^{18–20}

In 2009, treatment with dexamethasone 0.7 mg, in an intravitreal implant of poly(lactic-co-glycolic acid) (PLGA), was introduced.²¹

The progressive biodegradation of PLGA makes possible to obtain a constant daily release of dexamethasone in the vitreous chamber for at least four months after a single injection. With this method, the drug can produce enhanced therapeutic effects with reduced risk of adverse effects associated with multiple injections or high drug concentration immediately after injection.^{22,23}

In 2014, a sustained-release intravitreal 0.7 mg dexamethasone delivery system was approved by the Food and Drug Administration and Commission Européenne for the treatment of DME, based on the MEAD study results.¹⁷ However, data on its efficacy in the long term in patients affected by DME are still insufficient, and the results after six months are often contrasting, with studies showing either lasting or nonlasting therapeutic effects.

Thus, in this study, we evaluated the efficacy and safety of intravitreal injection of dexamethasone (Ozurdex® implant) in 17 patients affected by persistent DME resistant to anti-VEGF therapy, within a follow-up of six months.

Materials and Methods

Patient selection. This was a retrospective study of consecutive patients affected by type 2 diabetes mellitus and DME.

The subjects were recruited at the Department of Sense Organs, Faculty of Medicine and Dentistry, Sapienza University of Rome, Italy. The study included 17 patients (19 eyes), 14 males and 3 females. The mean age was 68 ± 9 years, and the mean duration of diabetes was 19.9 ± 5.29 years. The mean duration of DME was 45.4 ± 16.5 months (Table 1). In these patients, macular edema persisted for more than six months, despite treatments with grid macular photocoagulation and anti-VEGF ranibizumab 0.5 mg intravitreal injections. The last injection of ranibizumab 0.5 mg was performed at least three months before starting the treatment with dexamethasone implant. After that, the anti-VEGF effect had completely worn off. Informed consent was obtained from all patients. The study was exempt from the requirement to obtain ethics committee approval, because it is a retrospective study of records.

The study adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

Inclusion criteria. Criteria for inclusion were as follows: (1) age > 18 years old, (2) DME refractory to anti-VEGF therapy, (3) best-corrected visual acuity (BCVA) between

Table 1. Demographic and clinical features of subjects with persistent DME included in the study.

PATIENT NO.	SEX	AGE (YEARS)	DURATION OF DME (MONTHS)	I.V. ANTI-VEGF	PREVIOUS PRP	SECOND DEXAMETHASONE INJECTION	CMT	ETDRS
1	M	79	28	Yes	Yes	No	736	4
2	M	74	28	Yes	Yes	No	624	28
3	F	74	28	Yes	No	No	325	3
4	F	88	30	Yes	Yes	Yes	309	17
5	M	56	26 (left eye)	Yes	No	No	720	28
			27 (right eye)	No	No	No	541	12
6	M	61	40	Yes	Yes	No	487	18
7	M	55	40	Yes	Yes	No	464	22
8	M	70	38	Yes	Yes	No	357	12
9	M	70	50	Yes	Yes	No	639	27
10	M	57	60 (left eye)	Yes	No	No	539	12
			65 (right eye)	No	No	No	326	11
11	M	68	75 (left eye)	No	No	No	729	23
			74 (right eye)	Yes	No	No	678	41
12	M	70	68	Yes	No	No	654	24
13	M	69	52	Yes	Yes	No	366	34
14	M	72	85	Yes	Yes	Yes	352	13
15	F	73	34	Yes	No	No	688	16
16	M	64	38	Yes	Yes	No	520	4
17	M	59	40	Yes	No	No	301	4

Abbreviations: M, male; F, female; DME, diabetic macular edema; IV, intravitreal; VEGF, vascular endothelial growth factor; PRP, panretinal photocoagulation.

5 and 40 letters in the study eye at baseline examination (to ensure proper execution of functional examination), and (4) central macular thickness (CMT) $>270 \mu\text{m}$.

Exclusion criteria. The exclusion criteria were as follows: (1) structural damage (including atrophy of the retinal pigment epithelium, subretinal fibrosis, laser scars, epiretinal membrane involving fovea, or organized hard exudative plaques) within a 0.5 disc diameter of the center of the macula in the studied eye precluding improvement in visual acuity following the resolution of macular edema; (2) ocular surgery in the study eye in the last six months; (3) a history of ocular inflammation or (4) glaucoma; and (5) ocular hypertension in response to steroid treatment.

DME diagnostic criteria and evaluations. Baseline evaluation of vision was carried out before therapy (T0). Fluorangiography (FAG) was performed to evaluate the presence of macular ischemia, while BCVA was assessed through Early Treatment Diabetic Retinopathy Study (ETDRS) tables ($62 \times 64 \text{ cm}$) placed at a distance of 4 m following the protocol described in previous reports,^{8,9,23} by slit lamp biomicroscopy, ocular tonometry (using a Goldmann applanation tonometer), fundus biomicroscopy, optical coherence tomography (OCT; for measurement of macular thickness and morphology using a Spectralis HRA-OCT produced by Heidelberg Engineering with a volumetric 512×49 -scan) and color fundus photography. CMT was measured by spectral-domain OCT.

BCVA and CMT examinations were carried out at baseline (T0) and repeated after three days, one month (T1), three months (T3), four months (T4), and six months (T6) post injection.

All patients underwent a blood test for glycosylated hemoglobin (HbA1c).

Efficacy criteria.

- Primary outcome measures included mean BCVA and CMT values at baseline and at all follow-up visits. The implant was considered efficient when a mean improvement of BCVA ≥ 10 letters (two-line ETDRS) was observed.
- Secondary outcomes included the analysis of the retinal layer structure using OCT. The outcomes expected were a reduced mean CMT $\geq 250 \mu\text{m}$. Evaluations of the integrity of the external membrane and of the inner and outer segments of the photoreceptor interface were carried out at baseline (T0) and repeated after three days (day 3), one month (T1), three months (T3), four months (T4), and six months (T6) post injection.

Safety criteria. The appearance of undesired side effects correlated with the drug, such as inflammation of the anterior chamber, lens opacity, ocular pain, keratitis, or vitreous opacity was monitored.

The side effects correlated with the surgical intervention, such as endophthalmitis, perforation of the eye, conjunctival hemorrhage, and systemic effects related to the drug, were also monitored.

Intraoperative procedure of intravitreal dexamethasone implant. All implants were performed under sterile conditions, after preparation of the conjunctiva using 5% povidone–iodine solution, topical anesthetic with ropivacaine, and positioning of the blepharostat. A $700 \mu\text{g}$ slow-release intravitreal dexamethasone implant (Ozurdex®) was placed in the vitreal cavity, behind the crystalline lens within 3 ± 2 days from baseline examination. All injections were performed in an operating room. The dexamethasone implant was inserted into the vitreous cavity through the pars plana using a customized, single-use 22-gauge applicator. Patients were treated with a topical ophthalmic antibiotic (netilmicin sulphate) for seven days after treatment.

Re-injection criteria. Starting from month 3, in patients with a loss of five letters in BCVA and recurrence/persistence of ME as documented by indirect fundus ophthalmoscopy and spectral-domain OCT, the treating physicians were free to decide whether to readminister an intravitreal dexamethasone implant.

Statistical analysis. Data were analyzed by ANOVA with repeated measures followed by Fisher's Protected Least Significant Difference (PLSD) post hoc test. A P -value < 0.05 was considered statistically significant. Statistical analysis was performed using the Statview software from SAS Institute.

Results

Baseline values of clinical measurements. Before injection of the intravitreal dexamethasone implant, all the 17 eyes included in the study had a significant edema of the retina. The average thickness of the retina at baseline was $508.8 \pm 164.05 \mu\text{m}$, the medial BCVA was 19.16 ± 10.97 , and average corrected intraocular pressure was 13.7 mmHg .

Visual acuity measured with Early Treatment Diabetic Retinopathy Scale after intravitreal dexamethasone implant. The BVCA was measured using the Early Treatment Diabetic Retinopathy Scale (ETDRS). Repeated measures ANOVA showed a significant effect of the treatment on ETDRS ($P < 0.001$; Fig. 1). Post hoc analyses showed that ETDRS values were significantly increased at T1, T3, and T4 ($P < 0.001$) as compared with baseline value (T0). At six months, we found that ETDRS values were still statistically higher as compared with baseline although to a lower significance level ($P < 0.001$; Fig. 1).

CMT after intravitreal dexamethasone implant. As for ETDRS values, repeated measures ANOVA also showed a significant effect of intravitreal dexamethasone implant ($P < 0.0001$; Fig. 2). CMT significantly decreased at T1 and T3 ($P < 0.001$). At T4, CMT was still significantly lower than T0 ($P < 0.05$), while at T6, CMT values were not statistically different from baseline (Figs. 2 and 3).

Efficacy. The efficacy of the treatment, as demonstrated by CMT and ETDRS values reported in Table 2, had an effective rate of 100%.

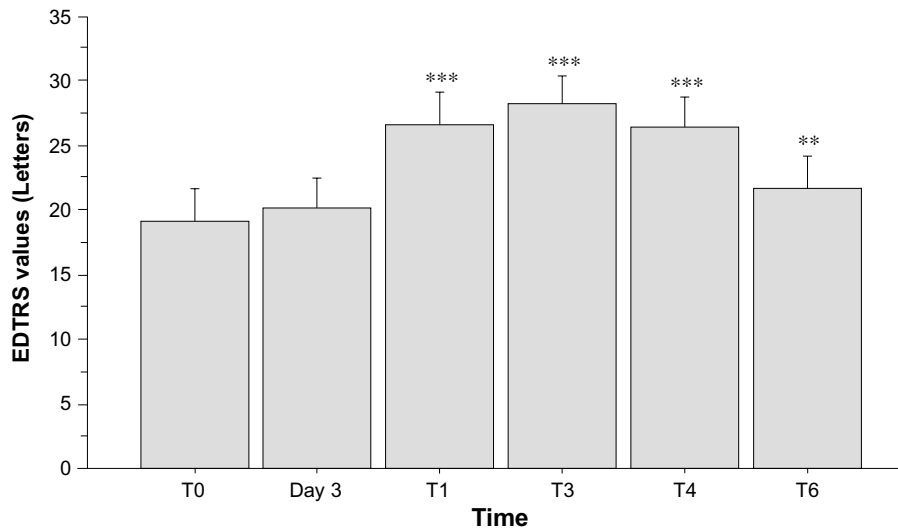


Figure 1. Early Treatment Diabetic Retinopathy Study (ETDRS) in 17 patients affected by persistent DME and treated with intravitreal dexamethasone implant (Ozurdex®) over six months.

Notes: Data are the mean ± SEM. Data are expressed in letters (ETDRS values). Asterisk (*) indicates significant difference versus baseline. ***P* < 0.01; ****P* < 0.001.

Abbreviations: T0, baseline; Day 3, three days; T1, one month; T3, three months; T4, four months; T6, six months post injection.

Safety of intravitreal dexamethasone implant. The side effects correlated with intravitreal dexamethasone implant were monitored during the follow-up. No particular complications caused by either the implant or the drug itself were found. In addition, none of the eyes showed an increase in intraocular pressure requiring medical treatment.

Retreatment. Two patients underwent a second injection at the end of the fourth month. In these patients, the HbA1c value was constantly over 8% as compared with the remaining patients where HbA1c value ranged from 6.5% to 7%.

Discussion

This study was performed to evaluate the efficacy of intravitreal dexamethasone implant (Ozurdex), in patients affected by DME resistant to treatment with anti-VEGF. In particular, we evaluated the visual acuity and CMT during six months of follow-up. The results showed that dexamethasone implant induced an improvement of visual acuity, as measured by ETDRS, after one, three, four, and six months from implants. In addition, we observed a reduction of CMT after one, three, and four months from implants, while at T6, CMT values were not statistically different from baseline.

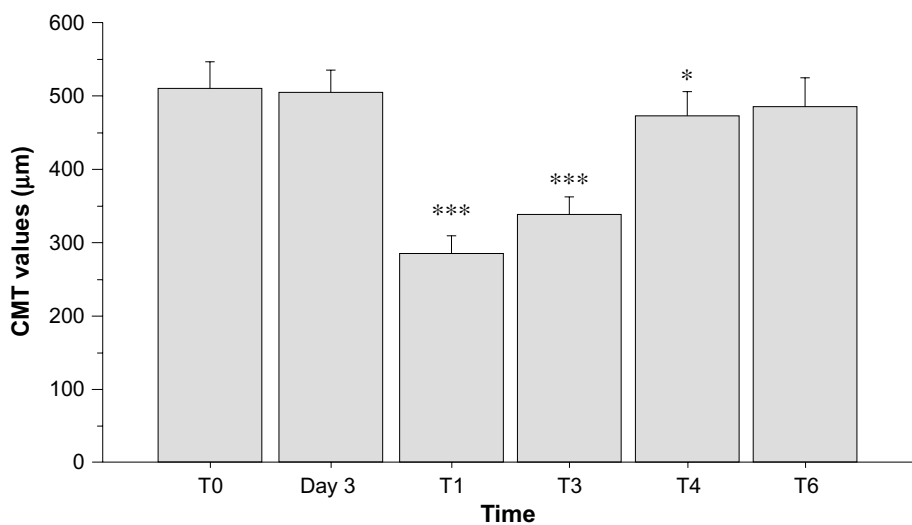


Figure 2. CMT in 17 patients affected by persistent DME and treated with intravitreal dexamethasone implant (Ozurdex®) over six months.

Notes: Data are the mean ± SEM. Values are expressed in µm. Asterisk (*) indicates significant difference versus baseline. **P* < 0.05; ****P* < 0.001.

Abbreviations: T0, baseline; Day 3, three days; T1, one month; T3, three months; T4, four months; T6, six months post injection.

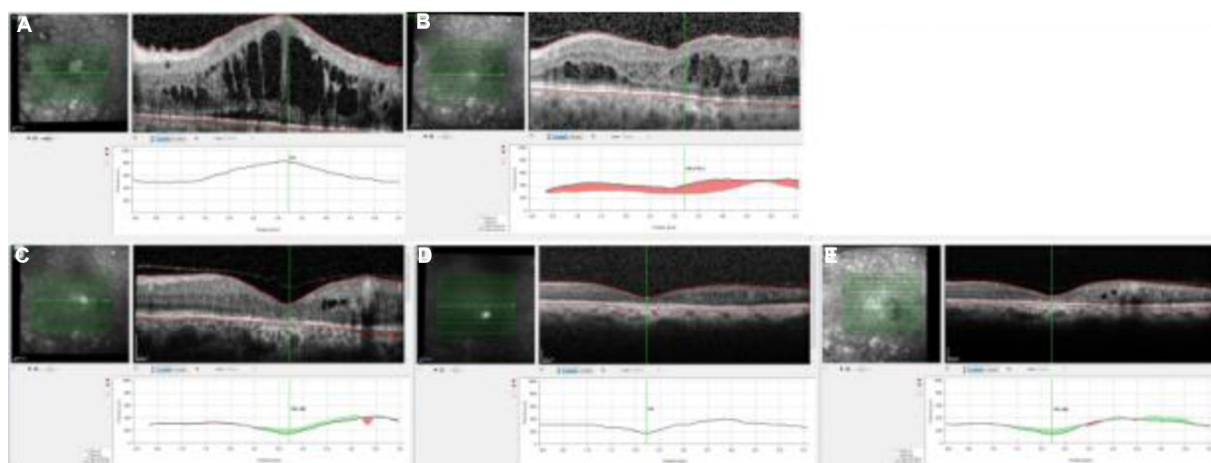


Figure 3. OCT images of a patient with persistent diabetic macular edema. Left eye, CMT: (A) baseline; (B) three days; (C) one month; (D) three months; and (E) six months after treatment.

These data demonstrate that the greatest efficacy of dexamethasone is obtained within the first three months. After that, its therapeutic efficacy slowly decreases, although this effect is more pronounced in CMT than in BCVA measurements. These findings are in line with other reports showing that the anti-inflammatory action of dexamethasone is rapid and may produce beneficial effects within the first week of treatment.^{12,21,24–29} This effect might be attributable to the strong anti-inflammatory and antiedema properties of the dexamethasone. As stated in the introduction, it has been demonstrated that steroid administration may reduce VEGF expression, attenuate leukostasis, and vascular leakage and decrease the production of proinflammatory cytokines.^{14,15} The fact that dexamethasone is able to improve DME symptoms in patients refractory to anti-VEGF suggests that in these cases inflammatory mediators may have a more important role than VEGF in disease development. However, this hypothesis needs to be further investigated.

Our findings are in line with other reports where the efficacy of dexamethasone lasted at least six months.¹² Indeed, we found that only BCVA improvements were persistent at

the end of the follow-up. The reason for these discrepancies among the effects of dexamethasone may be attributable to differences in individual response.

In our cohort, we found that only two patients necessitated a second slow-release intravitreal dexamethasone implant after six months since ETDRS and CMT values were worse than those recorded at baseline. These patients were characterized by high HbA1c levels (above 7%) presumably caused by inadequate monitoring of glycemic levels. This finding suggests that differences in other factors related to disease development, such as an inadequate therapeutic approach to diabetes, may cause a reduced response to dexamethasone in DME. Thus, the need for retreatment may not only be necessarily due to a decrease in dexamethasone concentration in the vitreous but also due to a worsening of patient metabolic state caused by chronic diabetes.

Regarding dexamethasone safety profile, no particular complications resulting from either the implant or the drug itself were found, a result in accordance with other reports.^{8,12,21} During the follow-up, none of the eyes showed increase in intraocular pressure requiring medical treatment. This finding has some relevance in clinical practice. In cases where prolonged duration of DME is associated with a reduced response to intravitreal anti-VEGF injection, the risk of complications due to repeated injection may significantly increase.^{9–11} Dexamethasone implants, having a duration of efficacy for at least three months, would extend the interval between injections and provide a better compliance for such patients. In addition, in the recent years, it has been proposed that the association of dexamethasone with other therapeutic strategies may produce significant structural retinal improvements in these patients.^{30–32}

Although our findings further provide evidence for the use of Ozurdex in DME, there are some limitations to our data interpretations. First, the number of eyes examined is relatively low with a short follow-up period, and hence, it is difficult to

Table 2. ETDRS and CMT values at baseline and in the successive follow-up points.

TIME POINTS	VISUAL ACUITY (NUMBER OF LETTERS ETDRS)	CMT (μM)
Baseline (T0)	19.16 ± 10.97	508.88 ± 164.05
3 days (Day 3)	21.23 ± 8.56	503.18 ± 124.06
1 month (T1)	26.56 ± 10.76	284.22 ± 113.13
3 months (T3)	28.16 ± 9.90	338.16 ± 109.78
4 months (T4)	26.38 ± 10.32	470.77 ± 154.28
6 months (T6)	21.66 ± 11.24	484.77 ± 167.43

Note: Data are the mean ± standard deviation.



reach definitive conclusions. Second, we acknowledge that a control group is missing. Further studies with greater cohorts of subjects and longer follow-up are required to characterize the pharmacokinetics and therapeutic efficacy of dexamethasone implant in DME.

Conclusion

In conclusion, our study demonstrates the efficacy and safety profile of the intravitreal dexamethasone implant within the six-month time frame. Our findings also suggest that chronic DME patients who do not respond to consecutive anti-VEGF treatment may benefit from switching the therapy to dexamethasone implant, although individual response and metabolic state of the patient should be strictly monitored.

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Author Contributions

Conceived and designed the experiments: EP, FP, AFF, PT. Analyzed the data: EP, FP. Wrote the first draft of the manuscript: EP, FP, AFF. Contributed to the writing of the manuscript: PT, TL, RG, AB, VF. Agreed with manuscript results and conclusions: EP, FP, AFF, PT, TL, RG, AB, VF, MRR. Jointly developed the structure and arguments for the paper: EP, FP, AFF, PT. Made critical revisions and approved the final version: EP, FP, AFF, PT, TL, RG, AB, VF, MRR. All the authors reviewed and approved the final manuscript.

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