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Intravitreal dexamethasone sustained release implant in refractory diabetic macular edema

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ABSTRACT

Purpose: Intravitreal therapies with anti-VEGF medications are regarded as effective treatment option. The biodegradable intravitreal implant, Ozurdex (Allergan, Irvine, CA, USA) depends on slow-release dexamethasone. The present study aimed to assess the effect on best corrected visual acuity and efficacy of intravitreal Ozurdex in patients with refractory DME. **Methods:** This prospective study included patient with refractory DME who received intravitreal Ozurdex. Baseline clinical evaluation, change in best corrected visual acuity BCVA and central retinal thickness CRT were analysed, intra ocular pressure, adverse effects were recorded. **Results:** The reported CRT measurements showed significant decrease in the first 3 months post injection, however at 6 months there was a slight increase in CRT. The reported BCV showing significant improvement from the baseline values, there was significant increase in IOP in the first month only which was controlled with medical treatment, no marked side effects were reported in the studied patients. **Conclusions:** For patients with refractory macular oedema, Ozurdex implant showed improvement in visual acuity and decreased macular thickness. Side effects such as increase of intraocular pressure, may require medical treatment.

Keywords: Dexamethasone, Refractory Diabetic Macular Edema, Macular Edema

1. INTRODUCTION

Diabetic retinopathy (DR) has been recognized as the most prevalent cause of vision loss in people aged 20-74 years in the developed world and 75% of this loss is due to Diabetic macular edema (DME) (Le et al., 2021). DME occur secondary to vascular leakage, local ischemia, chronic inflammatory conditions or vascular tissue degeneration and death (Gurreri and Pazzaglia,

2021). Multiple cytokines have been linked to this process including intercellular adhesion molecule-1 (ICAM-1), vascular endothelial growth factor (VEGF), tumor necrosis factor- α (TNF- α), interleukins 1 and interleukin-6 and fibroblastic growth factor-2 (FGF-2) (Kovoor et al., 2022; Honasoge et al., 2019).

Intravitreal anti-VEGF therapies are regarded as efficient treatment strategy for patients affected by DME. However, multiple injections are needed and its effect is usually transient in cases of resistant DME. Intravitreal corticosteroids use is associated with reduced capillary permeability and may result in secondary macular edema (Haller et al., 2009). Corticosteroids also reduce leukocytes migration of and down regulate VEGF, prostaglandins and other inflammatory mediators (Wang et al., 2008; Tamura et al., 2005).

Apparently, route of administration of steroids is essential for its effect. Systemic corticosteroids induce elevated blood glucose level in the diabetic patients, with intravitreal dexamethasone (DEX) implant, there was minimal systemic absorption (Agard et al., 2015). DEX is an effective anti-inflammatory steroid used in treatment of DME which surpasses the effect of intravitreal triamcinolone acetonide by six times and cortisol by thirty times (Martidis et al., 2002). Ozurdex is DEX-releasing intravitreal device with biodegradable capabilities. Upon administration, high intraocular concentration is reached with minimal concurrent systemic levels (Haller et al., 2010a). Its effects may last for 6 months with peak effect in the first two months (Chang-Lin et al., 2011). The present study aimed to evaluate the safety and efficacy of intravitreal Ozurdex in patients with refractory DME.

2. PATIENTS AND METHODS

This longitudinal research was performed at the retina clinic of Magrabi Eye Hospital, Cairo, Egypt, from 2019 to December 2022. The study plan was agreed by the Research Ethics Committee of Faculty of Medicine, Helwan University. Written informed and detained consent was given by all patients after sophisticated discussion of the procedure, treatment alternatives, follow-up schedule and expected benefits/risks.

The study included consecutive 30 eyes (30 patients) with diabetic macular edema diagnosed by spectral-domain optical coherence tomography (SD-OCT) and visual acuity assessment who did not respond to three consecutive doses of anti-VEGF. Patients were excluded from the study if they had corneal opacity, cataract, ischemic maculopathy, vitreomacular traction, proliferative diabetic retinopathy (PDR) needing additional interventions (laser or surgery), previous laser therapy, glaucoma or conditions that can affect HbA1c levels (e.g., kidney or liver diseases, hemoglobinopathies or hemolytic anemia). Sample size was calculated using G Power (Kiel University, Germany) with a study power of 80.0% and alpha error of probability of 5.0%.

Preoperative assessment

Preoperatively, all patients were subjected to careful history taking, thorough ophthalmological examination (intra-ocular pressure, best-corrected visual acuity (BCVA), slit-lamp bio-microscopy, detailed fundus examination and SD-OCT) and assessment of glycemic control (HbA1c).

Operative procedure

All procedure was performed under standard sterile precautions after conjunctival preparation using povidone-iodine 5% solution. Local anesthetic with benoxinate hydrochloride 0.4% was applied. Then, Ozurdex insertion into the vitreous cavity was achieved through the pars plana via a single-use 22-gauge application device. All patients received topical ophthalmic antibiotic (Gatifloxacin) for one week postoperatively.

Postoperative assessment

Postoperatively, patients were subjected to thorough ophthalmological examination and glycemic control assessment at 1, 2, 3 and 6 months. Patients were also observed for possible side effects (cataract formation, increased intraocular pressure, RD, vitreous hemorrhage and endophthalmitis).

Study outcome

The primary outcome endpoint of this study was the effect of treatment on central retinal thickness (CRT) measured by SD-OCT. Secondary outcomes included assessment of BCVA, assessment of glycemic control (HbA1c) and adverse effects.

Statistical analysis

Data retrieved from the current study were expressed as number and percent, mean and standard deviation or median and range. Obtained results over follow up intervals were compared using repeated measures ANOVA or Friedman's test as appropriate. All statistical procedures were computed using SPSS-25 (IBM, USA) with p-value <0.05 considered statistically significant.

3. RESULTS

The present included 30 eyes (30 patients) with an age of 57.5 ± 8.2 years. They comprised 26 males (86.7%) and 4 females (13.3%). Duration of DM was 15.69 ± 8.73 years. Affected eyes were the right in 18 patients (60.0%) and the left in 12 patients (40.0%). The reported CRT measurements at baseline, 1 month, 2 months and 3 months were $480.5 \pm 103.0 \mu\text{m}$, $333.2 \pm 97.1 \mu\text{m}$ and $303.6 \pm 71.5 \mu\text{m}$ respectively with a statistically significant difference from the baseline measurements. However, at 6 months, there was a slight increase in CRT ($315.8 \pm 72.3 \mu\text{m}$) (Figure 1).

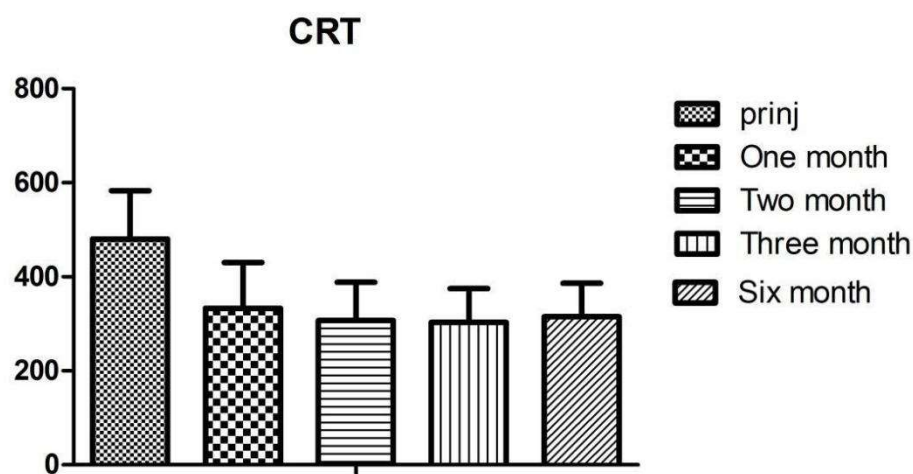


Figure 1 CRT in the studied patients

The reported BCVA measurements at baseline, 1 month, 2 months, 3 months and 6 months were: (Median (Interquartile range): 0.16 (0.1-0.4), 0.25 (0.1-0.6), 0.25 (0.1-0.6), 0.35 (0.2-0.6) and 0.30 (0.18-0.5)) respectively showing significant improvement from the baseline values (Figure 2).

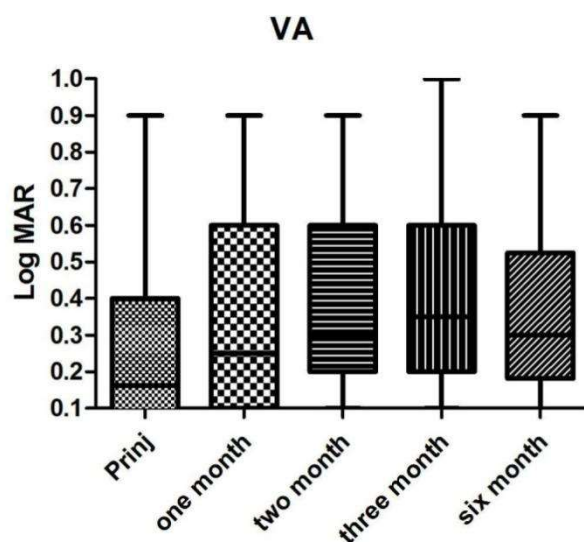


Figure 2 VA in the studied patients

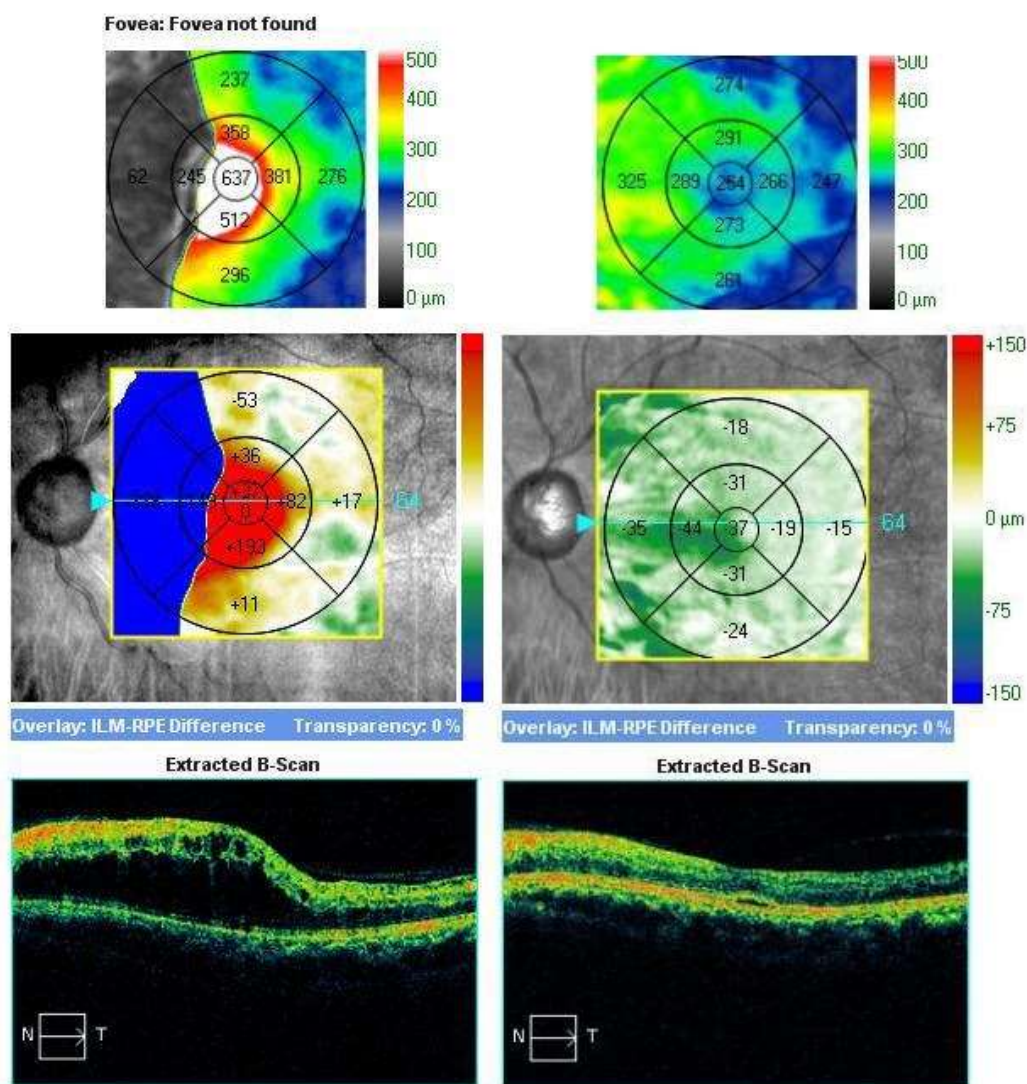


Figure 3 Compares findings of one patient at baseline (left) and 6 months postoperative

The reported HbA1c levels at baseline, 3 months and 6 months were $10.4 \pm 1.4\%$, $10.4 \pm 1.4\%$ and $10.5 \pm 1.5\%$ respectively with no statistically significant differences. No marked side effects were reported in the studied patients. Only three eyes (10.0%) experienced transient IOP elevation to between 25 and 28 mmHg at 1 month postoperative and was controlled using dorzolamide 2%/timolol 0.5%. Figure 3 illustrates the progress of ophthalmological findings in one patient after 6 months postoperative in comparison to the baseline.

4. DISCUSSION

In the present study, Ozurdex implantation resulted in improvement of visual acuity and decrease in CRT with minimal side effects. These findings are in line with multiple previous studies. In the study of Boyer et al., (2014), patients experienced decreased CRT and improved visual acuity. The reported side effects included intravitreal hemorrhage and endophthalmitis. In another study by Zucchiatti et al., (2012), BCVA improved after one month and continued for four months. Similar findings were reported by the study of Scaramuzzi et al., (2015).

In comparison, Dutra-Medeiros et al., (2014) found that previously non-responsive DME patients had the maximum treatment effect on CMT and BCVA in the third months following a single Ozurdex injection. In one randomized controlled trial (RCT), Haller et al., (2010b) reported that the frequency of DME eyes with improved BCVA after intravitreal DEX was comparable to the total study patients.

However, Rishi et al., (2012), noted that Ozurdex effect continued for a shorter duration in cases with refractory DME in comparison to those with macular oedema related to retinal vein occlusion dependent (4 versus 6 months respectively). In the

current study, the reported time between treatment before and after Ozurdex was 1.7 ± 0.9 months ranging from 1 to 4 months. This indicates that early period after switching from other anti-VEGF therapies to Ozurdex is affected by previous anti-VEGF treatment.

5. CONCLUSION

Conclusively, for patients with refractory macular oedema, Ozurdex implantation proved to be effective and safe; its use was associated with increased visual acuity and decreased macular oedema. However, conclusions of the present study may be limited by lack of control group and the relatively small sample size. Subsequent studies with larger sample size and multicentric design are strongly advocated to confirm conclusions of the present study.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Compliance with Ethics Guidelines

The study protocol was approved by the Research Ethics Committee of Faculty of Medicine, Helwan University (Ref. No. 39-2019).

Authors' Designation and Contribution

Manuscript Preparation: All authors; Manuscript Editing: All authors; Design: All authors; Literature Search: All authors; Data Analysis: All authors; Statistical Analysis: All authors; Manuscript Review: All authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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