Research Article

Treatment of refractory macular edema in retinal vascular diseases using intravitreal dexamethasone implant

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Abstract

Objective: To evaluate the safety and efficacy of intravitreal dexamethasone implant (Ozurdex) for treating refractory macular edema in retinal vascular diseases. **Methods:** This is a retrospective consecutive series of 10 eyes with refractory macular edema secondary to central retinal vein occlusion (5 eyes), branch retinal vein occlusion (3 eyes), and diabetic macular edema (2 eyes) treated with a single 0.7 mg dexamethasone implant. Data were collected on best-corrected visual acuity, intraocular pressure, and central macular thickness (CMT) preoperatively and at 1, 3, and 6 months postoperatively. **Results:** The mean baseline best-corrected visual acuity was 20/160 and improved statistically significantly to 20/80 and 20/60 at 1 months and 3 months, respectively (P, 0.05, both postoperative visits), and 20/125 at 6 months (P.0.05). The central macular thickness at baseline was 569.96±178.11µm, and it decreased statistically significantly to 305.81±155.94 µm, 386±210.79 µm, and 446.41±221.21 µm at 1, 3 and 6 months, respectively (P , 0.05, all visits compared with baseline). Two (20%) eyes developed high intraocular pressure after implantation and was successfully controlled with topical medications, and cataract progressed in 1 eye. **Conclusion:** The dexamethasone implant improved macular edema in refractory cases resulting in statistically significant improvements in best-corrected visual acuity and central macular thickness that remained stable to 3 months and 6 months, respectively.

Keywords: Branch retinal vein occlusion, Central retinal vein occlusion, Dexamethasone implant, Macular edema

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INTRODUCTION

Macular edema (ME) due to retinal vascular diseases such as diabetes and retinal vascular occlusion is considered a leading cause of mild to moderate vision loss. Disruption of blood-retinal barrier and microvascular damage results in vascular leakage and, eventually, ME. Dexamethasone, a potent corticosteroid with mainly glucocorticoid activity, is an antiinflammatory that is used to treat conditions in which water retention is undesirable, such as ME. In ME, dexamethasone suppresses vascular endothelial growth factor therefore inhibiting the growth of new blood vessels that often leak and reduce vision. Steroids are used for the treatment of edematous and proliferative diseases because the abnormal proliferation of cells is often associated with and trigged by inflammation. Additionally, intra-retinal accumulation of fluid is usually accompanied by blood–retinal barrier dysfunction that can be restored with steroid therapy. The principal effects of steroids are thought to be stabilization of the blood–retinal barrier (BRB), reduced exudation, and down-regulation of inflammatory stimuli.[8–10] The dexamethasone implant ([DEX implant], Ozurdex; Allergan Pharmaceuticals, Irvine, CA) is a biodegradable intraocular device that is a complete drug delivery system for intravitreal injection directly through the pars plana. The implant contains 700 µg of dexameth-asone, which is slowly and consistently released over a period of 6 months. The DEX implant is approved for the treatment of ME in branch and cen-tral retinal vein occlusion (CRVO), posterior noninfec-tious uveitis, and diabetic macular edema (DME) (pseudophakic patients or those

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who are scheduled for cataract surgery) by the United States Food and Drug Administration. Multiple studies have re-ported the safety and efficacy of the DEX implant for the treatment of persistent DME in vitrectomized and nonvitrectomized eyes. This study evaluated the efficacy and safety of the DEX implant for the treatment of refractory ME in retinal vascular diseases.

MATERIAL AND METHODS

This was a retrospective study of consecutive patients with refractory ME secondary to CRVO, branch retinal vein occlusion (BRVO), and DME treated with a single DEX implant of 0.7 mg at the Bhaskar Medical College and Hospital in Telangana, India. Institutional Review Board approval was obtained. This study adhered to the tenets of the Declaration of Helsinki. Follow-up visits were performed at 1 month, 3 months, and 6 months after injection of the DEX implant. Data were collected on Snellen best-corrected visual acuity (BCVA), intraocular pressure (IOP) measured with Goldmann applanation tonometry, and central macular thickness (CMT) measured with spectral domain optical coherence tomography (Carl Zeiss Cirrus 4000 HD-OCT; Germany). Patients were identified through medical records search for the study period from December 2014 to July 2015. Ten eyes of ten patients with refractory ME due to retinal vascular diseases were included: 3 eyes had BRVO, 5 eyes with CRVO, and 2 eyes with Moderate NPDR with DME (Fig 1). 6 eyes were pseudophakic and 4 eyes were phakic with early lenticular changes. In this study, refractory ME was defined as no improvement of 2 or more lines in Snellen BCVA and of the CMT on spectral domain optical coherence tomography that remained above 350 µm (normal CMT 250±50µm) despite monthly injections for at least 3 months of anti-vascular endothelial growth factor agents including bevacizumab (Avastin; Roche, India) and Ranibizumab (Lucentis; Genentech, Inc). Two cases underwent focal laser and one patient intravitreal triamcinolone acetonide (Aurocort, Aurolab, Madurai, India) during the 6 months. Patients received a DEX implant after a washout period of 3 months for anti-vascular endothelial growth factor injections and 3 months of washout for laser and intravitreal triamcinolone acetonide. Exclusion criteria were a history of glaucoma in the study eye, patients who were not compliant with follow-up appointments, laser treatment in the study eye within the previous 3 months, or patients who had any reason for visual acuity loss not related to ME secondary to retinal vascular diseases. All patients underwent a thorough informed consent procedure after a detailed explanation of all therapeutic alternatives and possible side effects of the DEX implant. The off-label use of the drug for patients with DME and its potential risks and benefits were discussed extensively. For statistical analysis, the difference between groups was assessed for statistical significance with the Wilcoxon signed-rank test and paired t-test. The BCVA was converted to logarithm of the minimal angle of resolution (logMAR) units for statistical analysis. Statistical analysis was performed with SPSS software version 17.0.1 for Windows. A P value less than 0.05 was considered statistically significant.

RESULTS

There were 8 (80%) eyes with ME due to retinal vein occlusion and 2 (20%) eyes with DME. Baseline patient characteristics are listed in Table 1. The mean age of the patients was 56 years (range, 52–65 years), and 70% of the patients were male (Fig 2). All patients were refractory to other modalities of treatment for ME before receiving the DEX implant (Table 2). The mean number of anti-vascular endothelial growth factor injections before DEX implant was 3.83 (range: 1–10 injections). One patient had intravitreal triamcinolone acetonide (Aurocort, Aurolab, Madurai, India) 9 months before DEX implant. In total, 26 (49%) eyes were pseudophakic. The mean duration of disease was 14.16 months (range: 4–43 months) for CRVO, 20 months (range: 17–23 months) for BRVO, and 18.25 months (range: 11–25 months) for DME. At the time of injection (baseline), mean BCVA was 0.97 ± 0.97 logMAR and improved statistically significantly to 0.61 ± 0.41 logMAR at the first month and 0.55 ± 0.46 logMAR at 3 months (P,0.001 and 0.01, respec-tively). Six months after the DEX implant, BCVA was 0.82 ± 0.44 logMAR, which was not statistically different from baseline (P = 0.758) The mean baseline CMT was 824.20 ± 221.01 µm (range, 510–1276 µm). The mean CMT decreased sta-tistically significantly to 244.30 ± 105.02 µm (range, 144–460 µm) at 1 month, 404.10 ± 129.98 µm (range, 220–686 µm) at 3 months, and 471.60 ± 139.87 µm (range, 283–740 µm) at 6 months (P, 0.001, all follow-up visits compared with baseline). The CMT decreased by 57% from baseline at 1 month, 42% at 3 months, and 35% at 6 months. There were no statistically significant differences between the anatomical and functional outcomes when the data were divided by diagnosis: retina vein occlusion vs. DME. Increased IOP (more than 21 mmHg) was seen in 2 (20%) eyes. However, it was controlled with a single topical anti-glaucoma medication. Cataract progression was noted in 1 eye. Subconjunctival hemorrhage was found in 7 eyes. There were no other ocular or systemic complications for the duration of this study.

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Dexamethasone Implant for Macular Edema

Table 1: Demographic and Baseline Characteristics, Functional and Anatomic Results, and Complications in Patients With Macular Edema and Retinal Vascular Diseases Treated With an Intravitreal Dexamethasone Implant

Patient No.	Age	Sex	Diagnosis	BCVA (logMAR)				CMT µm			Complications
				Baseline	Month 1	Month 3	Month 6	Baseline	Month 1	Month 3	Month 6	
1	60	F	CRVO	0.8	0.4	0.4	0.5	749	144	357	430	None
2	59	M	CRVO	1.1	0.7	0.6	0.8	1010	265	370	365	Increased IOP
3	63	F	DME	0.9	0.6	0.6	0.9	959	178	247	740	None
4	65	M	CRVO	0.8	0.7	0.6	0.7	841	401	516	511	None
5	53	M	CRVO	1.5	1.2	1.1	1.4	970	144	375	394	None
6	48	M	BRVO	0.7	0.6	0.6	0.6	647	215	350	377	None
7	45	M	DME	0.8	0.5	0.5	0.8	510	289	410	551	None
8	61	M	CRVO	1.0	0.6	0.6	0.9	697	147	686	383	Increased IOP
9	55	F	BRVO	0.6	0.2	0.1	0.4	583	200	220	283	None
10	52	M	BRVO	1.5	0.8	0.7	1.2	1276	460	510	682	None

logMAR, logarithm of the minimum angle of resolution.

Table 2: Treatment Modalities of Macular Edema Before

Treatment	Number of Patients (n = 10)	Percentage
Anti-VEGF	10	100
Focal laser	2	20
Intravitreal triamcinolone Acetonide	1	10

The Intravitreal Dexamethasone Implant. Three eyes received more than one treatment modality before intravitreal dexamethasone implant. Anti-VEGF, anti-vascular endothelial growth factor.

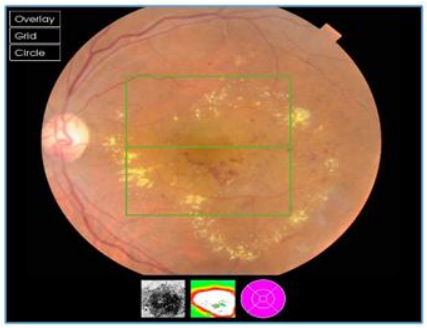

Figure 1: Baseline Fundus picture of Refractory DME

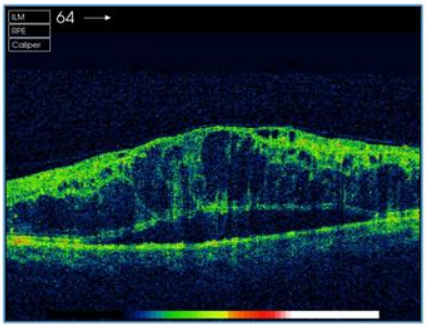

Figure 2: Baseline OCT - CMT 510µm

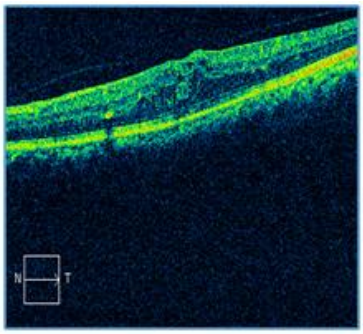

Figure 3: 1 Month post-injection CMT - 289µm

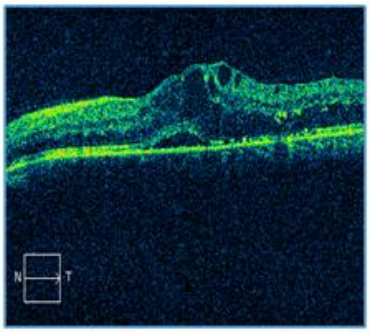

Figure 4: 3 Month post-injection CMT - 410µm

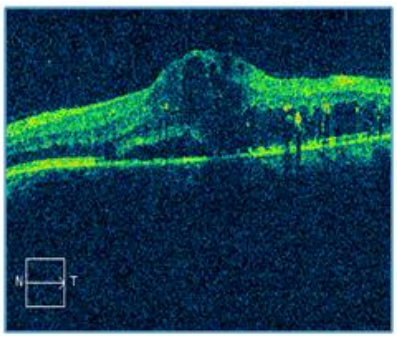

Figure 5: 6 Month post-injection CMT - 551µm

Fundus and OCT pictures of a case of refractory Diabetic Macular Edema before and after intravitreal dexamethasone (Ozurdex) implant injection.

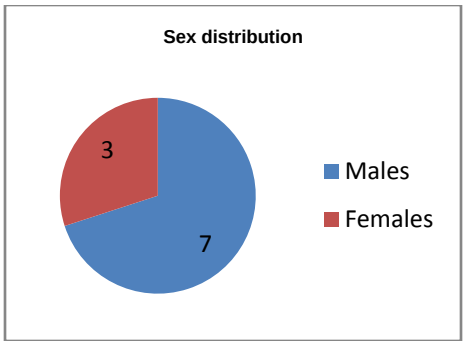

Figure 6

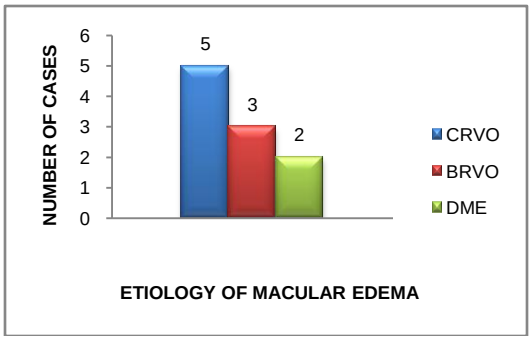

Figure 7

DISCUSSION

In our study, a single injection of the DEX implant led to improvement of ME which was resistant to other treatment modalities. It also improved visual acuity for the first 3 months. The mean CMT decreased significantly at 1 month post injection, and this reduction remained statistically significant throughout the 6 months of follow-up (P, 0.001, all follow-up visits compared with baseline). There was statistically significant improvement in BCVA at 1 month and 3 months after baseline (P, 0.001 and 0.01, respectively). However, the effectiveness of the DEX implant decreased by 6 months in terms of functional outcomes, and BCVA was not statistically different from baseline (P. 0.05). The reduction in CMT was greatest (46%) at 1 month after the injection. The BCVA was highest at 3 months at 0.5 logMAR (20/63). Our results were comparable to previous studies. For example, Haller *et al*,[15] in their evaluation of a 0.7 mg dexamethasone implant for DME, reported improvements in BCVA and CMT compared with an observa-tion group. However, they noticed that BCVA was not significantly better after 3 months. A randomized sham-controlled trial in patients with retinal vein occlusion reported that the group that received the 0.7 mg DEX implant had a significant reduction in ME with a significant improvement of BCVA with the best results observed at Month 3.[14] At 6 months, the differences in BCVA were not sig-nificant.[14] Ocular hypertension was observed in 4% of eyes and cataract progression in 7.3% of eyes.[14] Boyer *et al*[22] reported that rates of cataract-related adverse events in phakic eyes were 67.9%, 64.1%, and 20.4% in the 0.7 mg DEX implant, 0.35 mg DEX implant, and sham groups, respectively. They found that increases in IOP were usually controlled with medication or no therapy, and only 2 patients (0.6%) in the 0.7 mg DEX implant group and 1 (0.3%) in the 0.35 mg DEX implant group required trabeculectomy. The mean number of treat-ments received over 3 years was 4.1, 4.4, and 3.3 with the 0.7 mg DEX implant, 0.35 mg DEX implant, and sham group, respectively. In our study, a transient increase in IOP was seen in 20% of eyes. However, IOP did not exceed 25 mmHg in any eye. All cases were managed successfully with a single topical antiglaucoma medication. Cataract progressed in 1 (10%) eye in our series throughout the 6-month study. Subconjunctival hemorrhage was seen in 7 eyes. Limitations of our study include that it is a retrospective, nonrandomized study. Additionally, it is a single-injection study reporting only 6 months of follow-up, which precludes any estimation of the long-term efficacy or safety of the dexamethasone implant, and need for reinjections. Our low rate of progression cataract may be related to our short follow-up and that a single-injection was given per eye during our study. In summary, in this study, the DEX implant improved ME in cases that were resistant to other treatment modalities. An improvement in CMT was seen from the first month after the injection and remained statistically significantly decreased com-pared with baseline for 6 months of follow-up. An improvement in BCVA was seen from the first month after the injection and remained statistically significant for 3 months of follow-up. High IOP was observed after implantation in 2 (20%) eyes, but it was controlled with topical antiglaucoma medications.

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