The Open Ophthalmology Journal

Content list available at: https://openophthalmologyjournal.com

RESEARCH ARTICLE

Safety and Effectiveness of Intravitreal Dexamethasone Implant (Ozurdex®) for the Treatment of Refractory Cystoid Macular Oedema (CMO) in Galway University Hospital

Bobby Tang[1,*], Casserene E. Shen Yeow[2], Fiona Harney[2] and Deirdre Townley[2]

[1]*Royal Victoria Eye & Ear Hospital, Adelaide Road, Dublin, Ireland*
[2]*University College Hospital Galway, Newcastle Road, Galway, Ireland*

Abstract:

Aim:

The aim of this study is to assess the real-life effectiveness and safety of intravitreal Ozurdex in an Irish setting.

Background:

Ozurdex is an intravitreal dexamethasone implant that is used for the treatment of macular oedema secondary to retinal vein occlusion and diabetic macular oedema.

Methods:

This was a retrospective observational study of adult patients in University Hospital Galway who received an intravitreal dexamethasone implant (Ozurdex) for the treatment of cystoid macular oedema secondary to diabetic eye disease or retinal vein occlusion. The main outcome was the mean change in best-corrected visual acuity 3-6 months after the treatment.

Results and Discussion:

36 patients were included in the study. Overall, there was a 1.66 mean letter gain (SD 11.8) 3-6 months post-treatment. The proportion of patients who gained >10 letters was 15.6%. The mean reduction in CST was 110.6um (SD 255.7), and in the linear regression analysis, no variables were found to be significantly associated with a change in visual acuity. In terms of adverse events, 14.3% of patients had significant cataract progression and 20.6% of patients had a significant rise in IOP following intravitreal Ozurdex implant.

Conclusion:

Intravitreal Ozurdex was found to be safe and effective, supporting it as an appropriate second-line treatment in patients with refractory macular oedema secondary to diabetic eye disease and retinal vein occlusion. Further studies should be carried out to evaluate the possible predictors of visual acuity outcome.

Keywords: Diabetic, Eye disease, Retinal vein occlusion, Cystoid macular oedema, Diabetic macular oedema, Treatment.

Article History	Received: April 12, 2022	Revised: August 29, 2022	Accepted: September 29, 2022

1. INTRODUCTION

Diabetic eye disease has long been considered an inflammatory process [1], with mediators, such as VEGF and ICAM-1, shown to have a strong association with vascular permeability and the severity of diabetic macular oedema (DMO) [2]. Similarly, inflammatory mediators, such as VEGF, ICAM-1, and IL-6, have been implicated in the pathogenesis of retinal vein occlusions (RVO), leading to a recent interest in the use of intravitreal steroid preparations in the management of these conditions [3].

Ozurdex, an implant containing 700 micrograms of dexamethasone, was approved in 2010 for the management of macular oedema secondary to retinal vein occlusions, diabetic eye disease as well as non-infectious uveitis [4]. Its efficacy in diabetic macular oedema (DMO) has been evidenced by

* Address correspondence to this author at the Royal Victoria Eye & Ear Hospital, Adelaide Road, Dublin; E-mails: btang02@qub.ac.uk, tangb@tcd.ie

previous studies showing an 83% increase in the proportion of patients achieving ≥15 letter gain compared to sham [5] and non-inferiority compared to anti-VEGF agents in achieving the same outcome [6]. In these studies, the rate of adverse events was higher in the Ozurdex treatment arm, with 30-40% having a significant IOP rise and 40–70% showing the progression of cataracts. On subgroup analysis, outcomes of Ozurdex compared to anti-VEGF were more favourable in pseudophakic eyes, leading to recommendations from the National Institute for Health and Care Excellence (NICE) to consider Ozurdex as a second-line agent in selected patients [7].

Similar efficacy has been shown in the management of macular oedema secondary to retinal vein occlusions (RVO). In a recent systematic review, intravitreal injection of Ozurdex showed similar efficacy to anti-VEGF agents, with effects lasting 3-5 months. However, up to 20% of patients receiving Ozurdex had a significant IOP rise or progression of cataract [8].

In University College Hospital Galway (UCGH), Ozurdex is used in the management of patients with refractory macular oedema secondary to diabetes or retinal vein occlusions. Prior research has indicated that Ozurdex may improve Central Subfield Thickness (CST) but leads to limited visual acuity gain [9, 10]. The purpose of this study is to assess the effectiveness and risk profile of intravitreal Ozurdex implant for the treatment of macular oedema secondary to retinal vein occlusions and diabetic eye disease in Ireland.

2. MATERIALS AND METHODS

2.1. Study Design

This was a retrospective observational study of adult patients in Galway University Hospital who received intravitreal Ozurdex implant for the treatment of refractory cystoid macular oedema secondary to diabetic eye disease and retinal vein occlusions between August 2019 and January 2020 (6 months).

2.2. Participants

The criteria for study eligibility were as follows:

(i) Adult patients (>18 years) with type 1 or type 2 diabetes mellitus, clinically significant macular oedema (CSMO), defined by the Early Treatment Diabetic Retinopathy Study (ETDRS 1985) [11] and BCVA ≤6/9 at baseline,

OR

(i) Adult patients (>18 years) with foveal involving macular oedema secondary to retinal vein occlusions (mean central subfield thickness ≥250um on optical coherence tomography) and BCVA ≤6/9 at baseline;

(ii) Refractory macular oedema defined as Snellen equivalent BCVA ≤6/9 with a <5 letter gain in BCVA or <50um decrease in central subfield thickness after receiving either intravitreal anti-VEGF agents or focal laser treatment in the past;

(iii) Follow up for at least 3 months after receiving intravitreal Ozurdex implant

(iv) And without any of the following exclusion criteria: history of glaucoma, optic nerve head appearance or visual field defects consistent with glaucoma and ocular hypertension (IOP ≥24mmHg without antiglaucoma mediation).

2.3. Visit Schedules

In line with local care pathways, patients were reviewed in the outpatient clinic 2-3 weeks after Ozurdex implant, then at 3-month intervals thereafter to assess response to treatment as well as adverse events.

2.4. Outcome Measures

The main outcome measure was the mean change in visual acuity 3-6 months after receiving intravitreal Ozurdex implant. Secondary outcome measures include the proportion of patients with <5, 5-10 and >10 letter gains in BCVA and mean change in CST from baseline.

2.5. Data Collection and Analysis

Baseline demographic and clinical information was recorded after a review of clinical notes. In the Eye Department at Galway University Hospital, Best-Corrected Visual Acuity (BCVA) using ETDRS methods is measured by staff nurses at every clinic visit. OCT characteristics are assessed by an experienced technician using spectral-domain (SD) OCT (Heidelberg). For the recording of adverse events, glaucoma was defined as an increase in IOP ≥24mmHg requiring topical or surgical treatment. Patients subsequently listed for cataract surgery were used as a proxy measure for significant cataract progression. Patients with missing data for some of the outcome measures were excluded from the relevant analyses.

Statistical analysis was conducted using SPSS. Results are presented in Tables **1-4**, and linear regression analyses were conducted in order to assess potential predictors of visual acuity outcome. All variables significant with $P<0.05$ in simple regression analyses were included in a multiple regression model to identify potential predictors of VA improvement.

Table 1. Baseline demographic and clinical characteristics of eligible patients.

Characteristic	Overall (n=36)	RVO (n=8)	DED (n=28)
Mean age (SD)	68.0 (10.8)	71.6 (13.2)	67.6 (10.2)
Male, n (%)	25 (69)	6 (75)	19 (68)
Mean ETDRS score at baseline (SD)	57.25 (14.4)	61.5 (12.7)	55.8 (14.9)

(Table 1) contd.....

Characteristic	Overall (n=36)	RVO (n=8)	DED (n=28)
ETDRS letter score at baseline, n (%) o ≥70 o 35-70 o ≤35	10 (27.8) 19 (52.8) 7 (19.4)	3 (37.5) 4 (50) 1 (12.5)	7 (25) 15 (53.6) 6 (21.4)
Mean CST at baseline, um (SD)	444.2 (139.3)	451.5 (77.4)	442.1 (153.5)
Previously treated for CMO, n (%) o Focal/grid laser o Anti-VEGF	11 (30.6) 32 (88.9)	1 (12.5) 1 (12.5)	10 (35.7) 3 (10.7)
Mean number of anti-VEGF injections in last 12 months, n (SD)	4.6 (2.55)	6.67 (2.34)	4.79 (2.59)
Lens status, n (%) o Phakic o Pseudophakic	28 (77.8) 8 (22.2)	8 (100) 0 (0)	20 (71.4) 8 (28.6)

Table 2. Effectiveness of Ozurdex for visual Acuity and CST.

	Overall (n=32)*	RVO (n=8)	DED (n=24)
Mean change in VA, ETDRS letters (SD)*	1.66 (11.8)	3.5 (6.2)	1.04 (6.0)
Proportion of patients (%) o <5 letter gain o 5-10 letter gain o >10 letter gain	23 (71.9) 4 (12.5) 5 (15.6)	5 (62.5) 2 (25) 1 (12.5)	18 (75) 2 (8.3) 4 (16.7)
Mean reduction in CST, um (SD)	110.6 (255.7)	129.3 (239.3)	105.2 (139.3)

Note *Missing data for 4 patients

Table 3. Analysis of the effect of potential predictors on mean VA change.

Parameter	Simple Regression	
	β (90% CI)	P-value
Lens status o Phakic o Pseudophakic	Reference -1.571 (-6.561 to 3.418)	0.597
Age (yrs)	-0.023 (-0.219 to 0.161)	0.797
Gender o Female o Male	Reference 1.827 (-2.608 to 6.262)	0.490
Condition o RVO o DED	Reference -2.458 (-7.183 to 2.267)	0.384
ETDRS letter score at baseline	0.062 (-0.083 to 0.207)	0.474
Previous focal laser o No o Yes	Reference -3.583 (-8.471 to 1.306)	0.223
Anti-VEGF injections in the previous 12 months o <5 o ≥5	Reference 0.913 (-3.255 to 5.081)	0.713

Table 4. Adverse events.

	Overall (n=36)	RVO (n=8)	DED (n=28)
Significant cataract progression, n (%)*	4 (14.3)	0 (0)	4 (20)
Significant IOP rise, n (%)**	7 (20.6)	2 (25)	5 (19.2)

Note *Missing data for 8 patients.
**Missing data for 2 patients

3. RESULTS

Overall, 36 patients met the eligibility criteria of the study (mean age 68.0 years, 69% male). Of these patients, 77.8% had clinically significant CMO secondary to DED and 22.2% had

CMO secondary to RVO. Mean ETDRS letter score at baseline was 57.25 (SD 14.4) and mean CST at baseline was 444.2 (SD 139.3). The mean follow-up duration was 5.6 months. Prior to intravitreal Ozurdex implant, 30.6% and 88.9% of patients had received focal laser treatment and intravitreal anti-VEGF injections, respectively, in the previous 12 months. None of the included patients had previously undergone a vitrectomy. The mean number of intravitreal injections was 4.6 (SD 2.55), and at baseline, 80% of patients were phakic. Four patients did not have final visual acuity recorded due to non-attendance at the clinic and were not included in the analysis of the primary outcome.

In all included patients, there was a 1.66 mean letter gain (SD 11.8) with 3.5 letter (SD 6.2) and 1.04 letter (SD 6.0) gains in the RVO and DED groups, respectively. The proportion of patients who gained >10 letters was 15.6% overall, 12.5% in the RVO group and 16.7% in the DED group. Overall mean reduction in CST was 110.6um (SD 255.7), 129.3um (SD 239.3) in the RVO group, and 105.2um (SD 139.3) in the DED group. In the linear regression analyses, no variables were found to be significantly associated with a change in visual acuity.

In terms of adverse events, 14.3% of patients had significant cataract progression and 20.6% of patients had a significant rise in IOP following intravitreal Ozurdex implant, which required treatment. No cases of endophthalmitis were observed, nor were there any instances of significant post-operative pain or vitreous bleeding reported during the follow-up period.

4. DISCUSSION

In patients receiving intravitreal Ozurdex for the treatment of refractory cystoid macular oedema, the mean visual acuity gain was 1.66 letters (SD 11.8) and the mean reduction in central subfield thickness was 110.6um (SD 255.7), as measured with SD optical coherence tomography. These findings are consistent with previous studies showing improvements in anatomical outcomes seemingly uncorrelated to visual acuity or visual function [9, 10]. In terms of adverse effects, our findings were consistent with previous studies indicating that 20-27% of patients receiving Ozurdex experience a significant IOP rise [8, 12 - 14]. In previous studies, reduction of IOP to baseline levels with topical treatment was the most common outcome and <1% of patients required trabeculectomy or tube shunt surgery [5, 15].

This study is limited by its short follow-up period, which may have underestimated the rate of adverse events, such as cataract development. In a large multicentre randomised controlled trial, 67.9% of patients developed cataracts within 3 years compared to 20.4% in the sham injection group, and other studies with longer follow-up durations have estimated this rate to be between 30 to 60% [16, 17]. Furthermore, our relatively small sample size limited our assessment of possible predictors of visual acuity, particularly with pseudophakic lens status, which was previously shown to be independently associated with visual acuity gain [5]. None of the patients in our study reported significant post-operative pain, and no cases of vitreous haemorrhage were recorded. Again, this may be a reflection of our small sample size, but additionally, our study used the newer iteration of the Ozurdex drug delivery system, which has a reduced penetration force compared to the original version [18]. The fact that none of the patients in our study had previously undergone a vitrectomy may also have contributed to this finding due to the greater drag force in the vitreous body [19].

CONCLUSION

Overall, the safety profile and effectiveness of Ozurdex were within expectations, supporting it as a safe drug to use in patients with macular oedema secondary to diabetic eye disease and retinal vein occlusion. As some patients had better visual improvements, further studies with larger patient samples should be carried out to evaluate the possible predictors of visual acuity outcome.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by Bobby Tang and Casserene E Shen Yeow. The first draft of the manuscript was written by Bobby Tang, and all authors read and approved the final manuscript.

LIST OF ABBREVIATIONS

DMO	=	Diabetic Macular Oedema
NICE	=	National Institute for Health and Care Excellence
RVO	=	Retinal Vein Occlusions
UCGH	=	University College Hospital Galway
CST	=	Central Subfield Thickness
ETDRS	=	Early Treatment Diabetic Retinopathy Study
BCVA	=	Best-Corrected Visual Acuity
SD	=	Spectral Domain

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Galway University Hospital Healthcare Audit & Patient Safety Committee on September 21st, 2020. Project approval number: 161.

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. All the human procedures used were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Informed consent was obtained from all study participants.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIAL

The data that support the findings of this study are available from the corresponding author, [BT], on special request.

FUNDING

None.

CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to declare.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Adamis AP, Berman AJ. Immunological mechanisms in the pathogenesis of diabetic retinopathy. Semin Immunopathol 2008; 30(2): 65-84. [http://dx.doi.org/10.1007/s00281-008-0111-x] [PMID: 18340447]

[2] Funatsu H, Noma H, Mimura T, Eguchi S, Hori S. Association of vitreous inflammatory factors with diabetic macular edema. Ophthalmology 2009; 116(1): 73-9. [http://dx.doi.org/10.1016/j.ophtha.2008.09.037] [PMID: 19118698]

[3] Noma H, Mimura T, Eguchi S. Association of inflammatory factors with macular edema in branch retinal vein occlusion. JAMA Ophthalmol 2013; 131(2): 160-5. [http://dx.doi.org/10.1001/2013.jamaophthalmol.228] [PMID: 23411880]

[4] European Medicines Agency. Ozurdex (dexamethasone). 2019. Available from: https://www.Ema.europa.eu/en/documents/overview/ozurdex-eparmedicineoverview_en.pdf

[5] Boyer DS, Yoon YH, Belfort R Jr, *et al.* Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology 2014; 121(10): 1904-14. [http://dx.doi.org/10.1016/j.ophtha.2014.04.024] [PMID: 24907062]

[6] Callanan DG, Loewenstein A, Patel SS, *et al.* A multicenter, 12-month randomized study comparing dexamethasone intravitreal implant with ranibizumab in patients with diabetic macular edema. Graefes Arch Clin Exp Ophthalmol 2017; 255(3): 463-73. [http://dx.doi.org/10.1007/s00417-016-3472-1] [PMID: 27632215]

[7] National Institute for Health and Care Excellence. Dexamethasone intravitreal implant for treating diabetic macular oedema. Available from: https://www.nice.org.uk/guidance /ta349/chapter/1-Guidance

[8] Garweg JG, Zandi S. Retinal vein occlusion and the use of a dexamethasone intravitreal implant (Ozurdex®) in its treatment. Graefes Arch Clin Exp Ophthalmol 2016; 254(7): 1257-65. [http://dx.doi.org/10.1007/s00417-016-3350-x] [PMID: 27178087]

[9] Maturi RK, Glassman AR, Liu D, *et al.* Effect of adding dexamethasone to continued ranibizumab treatment in patients with persistent diabetic macular edema. JAMA Ophthalmol 2018; 136(1): 29-38. [http://dx.doi.org/10.1001/jamaophthalmol.2017.4914] [PMID: 29127949]

[10] Teja S, Sawatzky L, Wiens T, Maberley D, Ma P. Ozurdex for refractory macular edema secondary to diabetes, vein occlusion, uveitis and pseudophakia. Can J Ophthalmol 2019; 54(5): 540-7. [http://dx.doi.org/10.1016/j.jcjo.2018.12.005] [PMID: 31564342]

[11] Photocoagulation for diabetic macular edema. Early treatment diabetic retinopathy study report number 1. Early treatment diabetic retinopathy study research group. Arch Ophthalmol 1985; 103(12): 1796-806. [http://dx.doi.org/10.1001/archopht.1985.01050120030015] [PMID: 2866759]

[12] Tservakis I, Koutsandrea C, Papaconstantinou D, Paraskevopoulos T, Georgalas I. Safety and efficacy of dexamethasone intravitreal implant (Ozurdex) for the treatment of persistent macular edema secondary to retinal vein occlusion in eyes previously treated with anti-vascular endothelial growth factors. Curr Drug Saf 2015; 10(2): 145-51. [http://dx.doi.org/10.2174/1574886309666140805142245] [PMID: 25092480]

[13] Schmitz K, Maier M, Clemens CR, *et al.* Reliability and safety of intravitreal ozurdex injections. Ophthalmologe 2014; 111(1): 44-52. [http://dx.doi.org/10.1007/s00347-012-2737-2] [PMID: 23559321]

[14] Chin EK, Almeida DRP, Velez G, *et al.* Ocular hypertension after intravitreal dexamethasone (ozurdex) sustained-release implant. Retina 2017; 37(7): 1345-51. [http://dx.doi.org/10.1097/IAE.0000000000001364] [PMID: 27806001]

[15] Mishra SK, Gupta A, Patyal S, *et al.* Intravitreal dexamethasone implant *versus* triamcinolone acetonide for macular oedema of central retinal vein occlusion: Quantifying efficacy and safety. Int J Retina Vitreous 2018; 4(1): 13. [http://dx.doi.org/10.1186/s40942-018-0114-2] [PMID: 29632703]

[16] Moisseiev E, Goldstein M, Waisbourd M, Barak A, Loewenstein A. Long-term evaluation of patients treated with dexamethasone intravitreal implant for macular edema due to retinal vein occlusion. Eye 2013; 27(1): 65-71. [http://dx.doi.org/10.1038/eye.2012.226] [PMID: 23154502]

[17] Haller JA, Bandello F, Belfort R Jr, *et al.* Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. Ophthalmology 2011; 118(12): 2453-60. [http://dx.doi.org/10.1016/j.ophtha.2011.05.014] [PMID: 21764136]

[18] Meyer CH, Liu Z, Brinkmann CK, Rodrigues EB, Bertelmann T. Penetration force, geometry, and cutting profile of the novel and old ozurdex needle: The mono study. J Ocul Pharmacol Ther 2014; 30(5): 387-91. [http://dx.doi.org/10.1089/jop.2013.0231] [PMID: 24801111]

[19] Meyer CH, Klein A, Alten F, *et al.* Release and velocity of micronized dexamethasone implants with an intravitreal drug delivery system: Kinematic analysis with a high-speed camera. Retina 2012; 32(10): 2133-40. [http://dx.doi.org/10.1097/IAE.0b013e31825699e5] [PMID: 23060033]