

Safety and efficacy of dexamethasone intravitreal implant injection for macular edema associated with retinal vein occlusion

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Abstract

Purpose: To evaluate the safety and efficacy of dexamethasone intravitreal implant injection for retinal vein occlusion.

Methods: Twenty-two patients with central or branch retinal vein occlusion who were treated with dexamethasone intravitreal implant (Ozurdex) injection for macular edema at the Hong Kong Eye Hospital between December 2011 and December 2013 were retrospectively reviewed. Best-corrected visual acuity, proportion of patients with 3-line gain in visual acuity, central macular thickness and intraocular pressure before and after implant were recorded, as were any complications.

Results: Of the 22 patients, 11 each had central or branch retinal vein occlusion. The mean duration of follow-up was 9.6 months. The mean overall logMAR visual acuity improved from 1 to 0.67 ($p < 0.0001$) at 3 months and to 0.88 ($p = 0.048$) at final follow-up. The mean gain in visual acuity was 3.6 lines at 3 months, and 1.5 lines at final follow-up; 63.6% and 45.5% of patients at the respective follow-ups had gained ≥ 3 lines of vision. Nonetheless, 2 eyes lost ≥ 3 lines of vision at final follow-up. The mean central retinal thickness

decreased from 589 μm to 327 μm at 3 months ($p < 0.0001$), and to 409 μm at final follow-up ($p = 0.0001$). Fifteen eyes had recurrence of macular edema after a mean of 4.5 months; recurrence was earlier in central than branch retinal vein occlusion by 1.1 months ($p = 0.031$). Three eyes had intraocular pressure > 21 mm Hg. Five eyes out of 8 phakic patients developed cataract progression, of whom 2 subsequently underwent cataract extraction. Two eyes developed ischemic central retinal vein occlusion and had lost vision at final follow-up. There were no retinal tear, retinal detachment or endophthalmitis.

Conclusion: Ozurdex is efficacious in treating macular edema associated with retinal vein occlusion in terms of the gain in visual acuity and reduction in central retinal thickness, even for patients with a long duration of macular edema and poor baseline visual acuity. It has a good safety profile. The main complications are cataract progression and increased intraocular pressure (IOP). The duration of effect may be shorter than 6 months, especially in patients with central retinal vein occlusion. Earlier retreatment may be considered in order to maximize visual benefits.

Key words: Dexamethasone; Macular edema; Retinal vein occlusion; Treatment outcome; Visual acuity

Introduction

Retinal vein occlusion (RVO) is a common retinal vascular disorder, with an age and sex standardized prevalence of 5.2 per 1000.¹ It is the second most common cause of vision loss amongst retinal vascular diseases in developed countries, second only to diabetic retinopathy. The main cause of vision loss in RVO is macular edema (ME),^{2,3} secondary to non-perfusion and leakage of the retinal capillaries. Current treatment for ME in RVO includes the use of anti-vascular endothelial growth factor (VEGF) agents such as ranibizumab^{4,5} and aflibercept,⁶ intravitreal injection of steroids such as triamcinolone⁷ and dexamethasone,^{8,9} and focal laser for ME secondary to branch retinal vein occlusion (BRVO).¹⁰

Ozurdex (Allergan, Irvine, CA, USA) is a sustained-release dexamethasone implant that was approved in June 2009 by the US Food and Drug Administration for the treatment of ME secondary to RVO. Its efficacy and safety have been demonstrated in a large randomized controlled trial with over a thousand patients followed up over 1 year (the GENEVA study).^{8,9} It has a longer duration of effect (3–6 months), compared with monthly ranibizumab (Lucentis; Genentech, South San Francisco, CA, USA).^{8,9,11} Its main complications are cataract progression and IOP rise.^{8,9}

Ozurdex has been shown to have similar safety and efficacy to intravitreal triamcinolone in the treatment of ME in RVO in terms of visual acuity gain and decrease in central macular thickness (CMT). Nonetheless, dexamethasone has a longer duration of effect than triamcinolone and therefore requires fewer re-injections.¹²

In this study we report the efficacy and safety of Ozurdex implants in patients with ME associated with BRVO and central retinal vein occlusion (CRVO) at the Hong Kong Eye Hospital.

Methods

The study was approved by the Research Ethics Committee (Kowloon Central/ Kowloon East) of the Hong Kong Hospital Authority (rec no: KC/KE-13-0218/ER-3).

Twenty-two eyes in 15 women and 7 men aged ≥ 18 years with ME secondary to BRVO or CRVO who were treated with Ozurdex implant injection and followed up for > 3 months at the Hong Kong Eye Hospital between December 2011 and December 2013 were retrospectively reviewed.

Clinical data collected included pre-existing eye diseases, prior treatment for ME, best-corrected visual acuity (BCVA), pre- and post-injection central subfield thickness measured by spectral domain optical coherence tomography (OCT), slit lamp and indirect ophthalmoscopy findings, IOP and any associated complications. Fundus fluorescein angiography (FFA), if performed, was also noted.

The efficacy outcome measures were BCVA, OCT central subfield retinal thickness and proportion of patients with gain/loss in BCVA at 3 months post injection and at final follow-up. The safety outcome measures were the rates of cataract progression and IOP increase, and any serious complications such as endophthalmitis, retinal detachment, suprachoroidal hemorrhage.

Statistical analysis

All statistical analysis was performed using SPSS 17.0 statistics software. Qualitative variables were described using percentages, and quantitative variables were described using mean and standard error. For univariate analyses, Student's *t* test was used for independent data, and paired *t*-test was used for paired observations. Statistical significance was defined as $p < 0.05$.

Results

Demographics and clinical characteristics

The patient demographics and clinical characteristics are shown in **Table 1**. The mean patient age was 73 years (standard deviation [SD], 11; range, 51 to 97). The mean duration of follow-up was 9.6 months (SD, 4.9; range, 4 to 23). Of the 22 eyes, 11 each had CRVO or BRVO for a mean of 9.7 months (SD, 13.7; range, 0.5 to 54). Five eyes had pre-existing ocular disease. Five patients with CRVO and 1 patient with BRVO underwent concomitant phacoemulsification and intraocular lens insertion. Eight eyes were pseudophakic and 8 eyes were phakic.

Mean change in visual acuity

The mean visual acuity changes are shown in **Figure 1**. The mean $\pm$ SD logMAR score improved from 1.03 ± 0.07 to 0.67 ± 0.06 at 3 months, with a gain of 0.36 ± 0.06 ($p < 0.0001$), to 0.88 ± 0.08 at final follow-up, with a gain of 0.15 ± 0.07 ($p = 0.048$).

In the BRVO group, the mean $\pm$ SD logMAR score improved from 1.03 ± 0.11 to 0.74 ± 0.1 at 3 months, with a gain of 0.29 ± 0.07 ($p = 0.002$), to 0.91 ± 0.14 at final follow-up, with a gain that was not significant ($p = 0.29$). In the CRVO group, the mean $\pm$ SD logMAR score improved from 1.03 ± 0.1 to 0.6 ± 0.08 at 3 months, with a gain of 0.12 ± 0.11 ($p = 0.002$), to 0.85 ± 0.1 at final follow-up, with a gain that was also not significant ($p = 0.1$).

Proportion of patients with visual acuity changes at 3 months and final follow-up (Figure 2)

At 3 months, 63.6% of patients had a visual gain of ≥ 3 lines, 13.6% had a gain of 2 lines, 4.5% had a gain of 1 line and none lost vision. At final follow-up, 45.5% of patients had a visual gain of ≥ 3 lines, 4.5% had a gain of 2 lines, 4.5% had a gain of 1 line, 36% had no change and 9% (2 patients) had a vision loss of ≥ 3 lines owing to progression to ischemic disease, with neovascularization of pre-retinal hemorrhage and vitreous hemorrhage. The 2 patients presented initially with blurring of vision for months with a VA of 6/60 and 6/30 and were diagnosed with non-ischemic CRVO;

Table 1. Demographics and clinical characteristics of patients.

Characteristic	Data
No. of patients	22
No. of eyes	22
Age (years)	73 ± 11
Gender	
Male	7 (32%)
Female	15 (68%)
Pre-existing eye disease (n = 5)	
Dry age-related macular degeneration	2 (9%)
Diabetic retinopathy (non-proliferative)	1 (4.5%)
Narrow angle with peripheral iridotomy	1 (4.5%)
Retinal arteriole macroaneurysm	1 (4.5%)
Type of retinal vein occlusion	
BRVO	11 (50%)
CRVO	11 (50%)
Prior treatment for ME secondary to retinal vein occlusion (n = 6)	
Anti-VEGF	3 (13.6%)
Anti-VEGF plus focal/grid laser	3 (13.6%)
Concomitant cataract extraction (n = 6)	
BRVO	5 (45%)
CRVO	1 (9%)
Lens status	
Pseudophakic	8 (36.4%)
Phakic	14 (63.6%)
Mean duration of ME prior to Ozurdex injection	9.7 ± 13.7 (0.5-54)
BRVO	9.6 ± 11.9 (1-44)
CRVO	9.8 ± 15.9 (0.5-54)
Mean follow-up duration	9.6 ± 4.9 (4-23)

Abbreviations: BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; ME = macula oedema; VEGF = vascular endothelial growth factor.

* Data are shown as No., No. (%), or mean ± standard deviation (range).

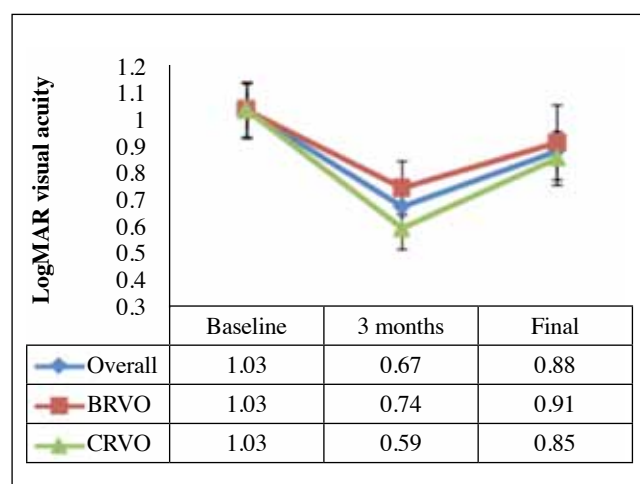


Figure 1. Change in mean visual acuity (LogMAR) after Ozurdex injection at baseline, 3 months and final follow-up.

baseline FFA was not performed. Their clinical findings included no relative afferent pupillary defect, diffuse retinal hemorrhage without cotton wool spots, tortuous retinal vessels, hard exudates and macula edema without signs of retinal neovascularization. FFA was subsequently performed in 1 patient and revealed capillary drop-out of >10 DD confirming ischemia.

Mean central subfield thickness

The change in mean ± SD CST is shown in **Figure 3**. The decrease in mean ± SD CST from baseline to 3 months was 265 ± 44 µm ($p < 0.0001$) overall, 256 ± 80 µm ($p = 0.01$) in BRVO patients and 273 ± 50 µm ($p < 0.0001$) in CRVO patients. At final follow-up, the decrease in CST in the overall and CRVO subgroups remained significant by 175 ± 67 µm ($p = 0.02$) and 247 ± 108 µm ($p = 0.046$), respectively, whereas the decrease in CST in the BRVO subgroup was not significant.

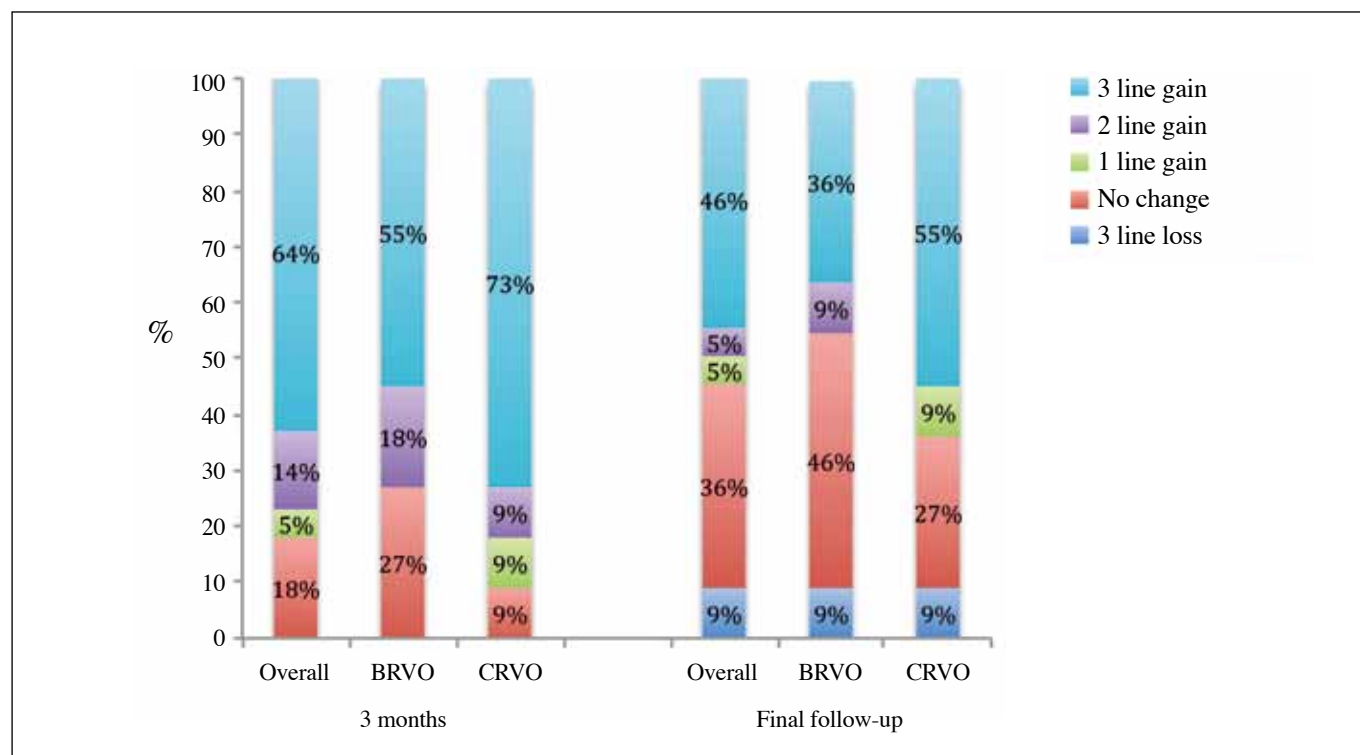


Figure 2. Proportion of patients with different changes in visual acuity (LogMAR) compared with baseline after Ozurdex injection at 3 months and at final follow-up.

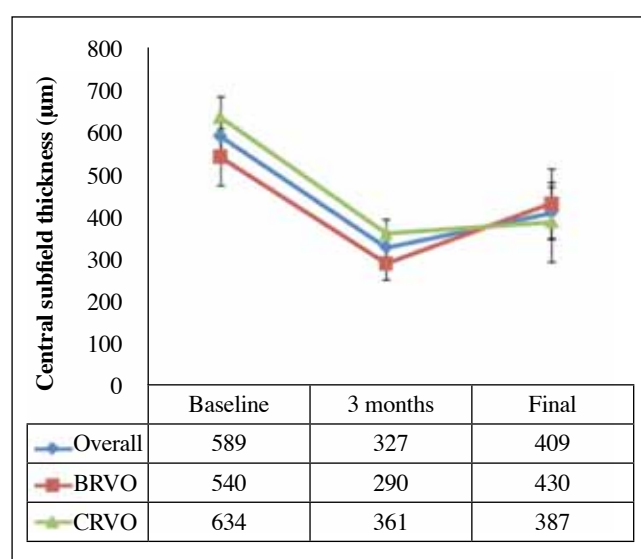


Figure 3. Change in mean central subfield thickness after Ozurdex injection at baseline, 3 months and final follow-up.

Non-responder and recurrence

Two eyes (9%) showed a poor response to Ozurdex, as evidenced by no decrease in OCT or an increase in CRT after injection. Fifteen eyes (75%) had recurrence of ME after a mean of 4.5 ± 1.1 months; 8 of them (80%) opted for repeat Ozurdex injections, with a mean of 1.1 ± 0.8 extra injections. Of the 15 eyes, 7 (46.6%) had BRVO and 8 (53.3%) had CRVO. Recurrence of ME was earlier in eyes with CRVO (4 ± 0.8 [range, 3 to 5] months) than BRVO (5 ± 1.1 [range, 3 to 6] months) by a mean of 1.1 months ($p = 0.031$).

Complications

Complications are shown in **Table 2**. Five eyes (63%) in 8 phakic patients developed cataract progression; 2 of them (40%) subsequently underwent cataract extraction. The rise in IOP was mild and none required surgical intervention. Two eyes (9%) had ischemic conversion and ultimately vision loss despite panretinal photocoagulation. There were no cases of retinal tear, retinal detachment or endophthalmitis.

Table 2. Complications after Ozurdex injection.		
Complication (n = 22)	No. of eyes (%)	Treatment
Raised IOP (mm Hg)	3 (13.6%)	
>21	2 (9.1%)	Topical IOP lowering medication
>25	1 (4.5%)	Topical IOP lowering medication
Cataract (posterior subcapsular cataract) progression (n = 8)	5 (63%)	Two (40%) eyes underwent cataract operation

Abbreviations: IOP = intraocular pressure.

Discussion

In our study, Ozurdex injection was effective in the treatment of ME associated with RVO in terms of VA improvement and CST. Although these findings echo those of the GENEVA study,⁹ there are some important differences. First, our study included patients with very poor baseline VA (worse than 6/60) compared with the GENEVA trial that included only patients with VA between 6/60 and 20/50. The mean baseline VA was also worse in our patients. We had a greater proportion of eyes with CRVO (50%) compared with 38% in the GENEVA study that may partially explain the poorer baseline VA. The duration of ME prior to Ozurdex injection was also longer in our patients, with a mean of 9.7 months compared with 5.2 months in the GENEVA study. The mean baseline CST was slightly higher (589 μ m vs 562 μ m) in our study. Overall, our patients had a longer duration of ME with poorer VA and thicker macula at baseline. Despite this, we had a greater proportion of patients with 15-letter gain at 3 months overall (63.6% vs 22%) and in BRVO (54.5% vs 24%) and CRVO (72.7% vs 18%) subgroups. There was also a greater mean change in VA from baseline (overall gain of 3.6 lines vs 1.4 lines) at 3 months. This contrasts with the post hoc analysis of pooled data from the GENEVA trial at 12 months that revealed longer duration of ME was associated with a lower likelihood of achieving a gain of ≥ 15 letters in BCVA.¹³ One reason for the difference may be that our sample was confounded by concomitant cataract extraction performed in 6 patients (5 in the CRVO group and 1 in the BRVO group). The improvement in vision was 2.9 lines, which was comparable to the 3-line improvement in the Geneva study. Our findings suggest that Ozurdex is effective even in patients with a longer duration of ME and poorer baseline VA, especially in those with BRVO.

The duration of effect of Ozurdex has been reported to be 3

to 6 months, peaking at month 2.8.¹⁴ In our study, the mean duration of effect overall was 4.5 months. ME recurred in eyes with CRVO significantly earlier than eyes with BRVO after a mean of 4 and 5 months, respectively. Similar results were reported in the SOLO study where early reinjection at 16 weeks was required for 50% and 41% of eyes with CRVO and BRVO respectively.¹⁴ Mathew et al. using monthly OCT monitoring to evaluate retreatment strategy also reported 4 months to be an optimal time for re-treatment.¹⁵ Similarly, our study found that early re-treatment (4 months for CRVO and 5 months for BRVO) is useful in maximizing visual benefits in these eyes.

The safety profile was similar to that reported in other studies,^{5,8} with a mean follow-up of 10 months. The most common complications were cataract progression and increased IOP. The long-term safety profile of Ozurdex has been shown to be good.¹⁶⁻¹⁸ Despite this, physicians should keep in mind the potential for steroid-related complications when using Ozurdex, especially in patients who receive repeated injections.

This current study was limited by its small sample size, recruitment of patients from a single center and the lack of a control arm. Concomitant cataract surgery in a number of patients, especially in eyes with CRVO, acted as a confounding factor for the gain in VA.

Conclusion

Ozurdex is effective and safe in the treatment of ME associated with RVO, with significant gain in VA and reduction in macular thickness, even in patients with poor baseline VA and a long duration of ME. Its effect may be shorter than previously reported, especially in CRVO patients. Earlier follow-up with repeat injections of Ozurdex may maximize visual benefits.

References

1. Rogers S, McIntosh RL, Cheung N, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmology*. 2010;117:313-9.
2. McIntosh RL, Rogers SL, Lim L, et al. Natural history of central retinal vein occlusion: an evidence-based systematic review. *Ophthalmology*. 2010;117:1113-23.
3. Rogers SL, McIntosh RL, Lim L, et al. Natural history of branch retinal vein occlusion: an evidence-based systematic review. *Ophthalmology*. 2010;117:1094-101.
4. Brown DM, Campochiaro PA, Bhisitkul RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. *Ophthalmology*. 2011;118:1594-602.
5. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. *Ophthalmology*. 2011;118:2041-9.
6. Brown DM, Heier JS, Clark WL, et al. Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPENICUS study. *Am J Ophthalmol*. 2013;155:429-37.
7. Scott IU, Ip MS, VanVeldhuisen PC, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6. *Arch Ophthalmol*. 2009;127:1115-28.
8. Haller JA, Bandello F, Belfort R Jr, et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology*. 2010;117:1134-46.
9. 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;118:2453-60.
10. Argon laser photocoagulation for macular edema in branch vein occlusion. The Branch Vein Occlusion Study Group. *Am*

- J Ophthalmol* 1984;98:271-82.
11. Mayer WJ, Wolf A, Kernt M, et al. Twelve-month experience with Ozurdex for the treatment of macular edema associated with retinal vein occlusion. *Eye (Lond)*. 2013;27:816-22.
 12. Ozkok A, Saleh OA, Sigford DK, Heroman JW, Schaal S. The OMAR Study: Comparison of Ozurdex and Triamcinolone Acetonide for refractory cystoid macular edema in retinal vein occlusion. *Retina*. 2015;35:1393-400.
 13. Yeh WS, Haller JA, Lanzetta P, et al. Effect of the duration of macular edema on clinical outcomes in retinal vein occlusion treated with dexamethasone intravitreal implant. *Ophthalmology*. 2012;119:1190-8.
 14. Bezatis A, Spital G, Hohn F, et al. Functional and anatomical results after a single intravitreal Ozurdex injection in retinal vein occlusion: a 6-month follow-up -- the SOLO study. *Acta Ophthalmol* 2013;91:e340-7.
 15. Mathew R, Pearce E, Muniraju R, Abdel-Hay A, Sivaprasad S. Monthly OCT monitoring of Ozurdex for macular oedema related to retinal vascular diseases: re-treatment strategy (OCTOME Report 1). *Eye (Lond)*. 2014;28:318-26.
 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 (Lond)*. 2013;27:65-71.
 17. Querques L, Querques G, Lattanzio R, et al. Repeated intravitreal dexamethasone implant (Ozurdex®) for retinal vein occlusion. *Ophthalmologica*. 2013;229:21-5.
 18. Coscas G, Augustin A, Bandello F, et al. Retreatment with Ozurdex for macular edema secondary to retinal vein occlusion. *Eur J Ophthalmol*. 2014;24:1-9.