INTRAVITREAL DEXAMETHASONE IMPLANT FOR REFRACTORY MACULAR EDEMA SECONDARY TO VITRECTOMY FOR MACULAR PUCKER

CLAUDIO FURINO, MD, PHD, FRANCESCO BOSCIA, MD, NICOLA RECCHIMURZO, MD, CARLO SBORGIA, MD, GIOVANNI ALESSIO, MD

Purpose: To study the efficacy of a single 0.7 mg dexamethasone intravitreal implant in vitrectomized eyes with refractory macular edema secondary to combined cataract extraction and macular pucker removal.

Methods: In 8 eyes of 8 consecutive patients with refractory macular edema secondary to combined cataract extraction and 25-gauge vitrectomy with internal limiting membrane peeling for macular pucker removal, the injection of the 0.7 mg dexamethasone implant was performed. Best-corrected visual acuity, central retinal thickness measured by spectral domain optical coherence tomography, and intraocular pressure were evaluated at baseline, 1 month, and 6 months.

Results: After a mean follow-up of 6.75 ± 0.71 months, best-corrected visual acuity was significantly increased ($P < 0.0001$) from 20/50 to 20/23 ($P < 0.0001$), mean central retinal thickness decreased significantly from 439 ± 45 μm to 296 ± 49 μm ($P < 0.0001$), and intraocular pressure changed significantly (P = 0.02) from 14.63 ± 1.19 to 16 ± 0.93. In no case postoperative hypotony or other complication was observed.

Conclusion: A single injection of the 0.7 mg dexamethasone intravitreal implant resulted effective in the treatment of refractory macular edema secondary to combined cataract extraction and vitrectomy for macular pucker removal allowing a stable visual acuity recovery.

RETINA 0:1–5, 2014

Macular edema (ME) is due to abnormal retinal capillary permeability, which leads to extravascular swelling in the macula. It is associated with a variety of underlying disease and is a source of visual loss in postvitrectomy eyes and those that have undergone cataract extraction. Although widely recognized, little information exists in the current literature regarding the incidence of postvitrectomy ME.

In pre-optical coherence tomography (OCT) era, Staudt et al[1] and McDonald et al[2] observed ME on fluorescein angiography in 80% of macular hole surgeries and 70% of epiretinal membrane surgeries. Recently, in OCT era, Kim et al[3] reported that 47% of eyes undergoing vitrectomy for epiretinal membrane, macular hole, or vitreous hemorrhage had evidence of ME on OCT. Combined vitrectomy and phacoemulsification has shown postoperative visual acuity improvement in many series, without rise in frequency of complication.[4,5] Still remains the risk of postoperative ME after combined vitrectomy and phacoemulsification. Whether or not inner limiting membrane (ILM) peeling may influence the genesis of ME in vitrectomized eyes still remains an unsolved question.

In 8 cases of ME after cataract surgery, 700 mg dexamethasone intravitreous drug delivery system showed statistically significant improvements in visual acuity and fluorescein leakage.[6]

This retrospective consecutive case series presents the results of 0.7 mg dexamethasone intravitreous drug delivery system injection (Ozurdex; Allergan, Irvine, CA) for the treatment of persistent refractory ME secondary to combined cataract extraction and

From the Department of Ophthalmology, University of Bari, Bari, Italy.

None of the authors have any financial/conflicting interests to disclose.

Reprint requests: Claudio Furino, MD, PhD, Department of Ophthalmology, University of Bari, Piazza Giulio Cesare, 11, Bari 70124, Italy; e-mail: claudiofurino@gmail.com

25-gauge pars plana vitrectomy with ILM peeling for idiopathic epiretinal membrane removal.

Methods

This study is a retrospective non-randomized study and includes consecutive patients with persistent postoperative ME secondary to 25-gauge transconjunctival sutureless vitrectomy with ILM peeling combined with uncomplicated phacoemulsification and in bag intraocular lens implant for idiopathic epiretinal membrane removal, who underwent the 0.7 mg dexamethasone intravitreous drug delivery system injection. All patients gave written consent to the intravitreal injection procedure. All eyes underwent at least a 6-month follow-up after the injection of the implant. No patients showed the presence of any other retinal pathology, ME, history of ocular hypertension, glaucoma, uveitis or were a known steroid responder or diabetic at the time of the intravitreal injection.

In the combined surgery procedure, phacoemulsification and in-bag intraocular lens implantation was completely carried out before 25 G vitrectomy. In all patients, ILM peeling was performed by the aid of indocyanine-green 0.05% solution staining. Surgery was performed always by the same surgeon. In all eyes, ME was detected by spectral domain OCT in consideration of the absence of postoperative visual acuity improvement and of the presence of a subjective visual discomfort, than treated with topic anti-inflammatory therapy for at least 2 months without any resolution or tomographic decreasing of ME. Topical therapy included betamethasone and diclofenac sodium drops four times a day.

The intravitreal implant injection was carried out by a single surgeon following a biplanar intrascleral path to reduce the risk of scleral leakage, and at the end of the injection a cauterization of the scleral wound was performed to obtain a watertight sclerotomy to avoid ocular hypotony as previously described.[7] In all cases, the 0.7 mg dexamethasone implant did not require any scleral suture.

At baseline and at each follow-up visit, the ophthalmic examination included evaluation of best-corrected visual acuity (BCVA) using Snellen charts, intraocular pressure (IOP) using Goldmann applanation tonometer, slit-lamp biomicroscopy, fundus examination with dilated pupils, and the central macular thickness using spectral domain OCT (Cirrus; Carl Zeiss Meditec, Inc, Dublin, CA or Spectralis Heidelberg Retinal Angiograph; Heidelberg Engineering, Heidelberg, Germany). For each patient, the same OCT machine was used for all follow-up visit. Follow-up visit were obtained at 1 day, 1, 2, 4, and 6 months.

The BCVA was converted to logarithm of the minimum angle of resolution (logMAR) value for statistical analysis. The main outcome parameters were changes in BCVA, central macular thickness, and IOP between baseline and follow-up examination at 1 day, 1 month, and 6 months. All data were statistically analyzed using the two-tailed *t*-test. A *P* value of 0.05 was considered to be statistically significant.

Results

The clinical characteristics and results of enrolled patients are summarized in Table 1. In this consecutive series of patients (mean age, 74 ± 3 years; range, 69–79 years), the mean interval from combined cataract extraction with vitreoretinal surgery and ME diagnosis was 35.6 ± 6 days (range, 29–45 days), whereas the interval from ME diagnosis and intravitreal Ozurdex injection was 2.3 ± 0.4 months. This interval corresponded to the duration of cystoid ME refractory to

Table 1. Population Characteristics and Results

	BCVA		Spectral Domain OCT, μm		IOP, mmHg		
Patient	Pre	Post	Pre	Post	Pre	Post	Follow-up, months
1	20/50	20/28	405	280	15	16	7
2	20/50	20/22	416	291	13	15	6
3	20/40	20/22	397	298	14	16	7
4	20/50	20/25	401	288	16	16	7
5	20/40	20/22	446	256	15	16	6
6	20/63	20/25	448	244	15	18	8
7	20/63	20/22	531	406	16	16	7
8	20/50	20/22	467	308	13	15	6
Mean	20/50	20/23	438.88	296.38	14.63	16.00	6.75
SD			45.15	49.13	1.19	0.93	0.71
P	0.000005		0.000014		0.02		

SD, standard deviation.

topical therapy before the decision to inject Ozurdex was made.

After a mean follow-up of 6.75 ± 0.71 months (range, 6–8 months) from the time of the implant, mean BCVA significantly improved from 20/50 to 20/23 ($P < 0.0001$); in the same trend, mean central retinal thickness decreased significantly from 438 ± 45 μm to 296 ± 49 μm ($P < 0.0001$). At the end of follow-up, IOP changed significantly ($P = 0.011$) and in no cases it was higher than 18 mmHg.

In no case, postoperative hypotony was observed. During follow-up visits, when observable, the implant was always evident in the inferior remaining pre-equatorial vitreous. No complication as retinal tears, retinal detachments, dislocated IOL, or retinal hemorrhages were seen in any of these cases follow-up.

Discussion

Macular edema is a source of visual limitation in vitrectomized eyes and those that have undergone cataract extraction.[1,3,8] In a recent prospective cohort study with the objective to evaluate the incidence of postvitrectomy (41% for epiretinal membrane removal with or without ILM peeling) ME using OCT on 109 eyes undergoing nonemergent vitrectomy surgery with a follow-up of 1 day and 1 month, the authors concluded that postvitrectomy ME is common with an incidence of 47%, delays visual recovery, and underlined that eyes with greater reduction in central retinal thickness from baseline after 1-month follow-up experienced more rapid visual recovery.[3] In ME after combined vitrectomy and cataract extraction, the risk remains uncertain if the edema is secondary to phacoemulsification or vitrectomy or both.

Despite treatment options for Irvine–Gass syndrome, which include nonsteroidal anti-inflammatory drugs, corticosteroids, acetazolamide, and anti-vascular endothelial growth factor, resistant cases of ME are common.[9,10]

Corticosteroids are potent anti-inflammatory agents that can counteract many of the pathological processes thought to play role in the development of ME by several ways: they prevent leukocyte migration, reduce fibrin deposition, stabilize endothelial cell tight junctions, and inhibit synthesis of vascular endothelial growth factor, prostaglandins, and proinflammatory cytokynes.[11] However, the route of corticosteroid administration dramatically affects the risk to benefit ratio of corticosteroid therapy. Oral corticosteroids are complicated with many adverse events such as osteoporosis, adrenal suppression, a Cushingoid state, and exacerbation of diabetes.[12–16] Topical and local administrations deliver suboptimal vitreous drug level with a very short half-life and may be associated with relatively high systemic concentrations.[17–19] Direct intravitreal corticosteroid injection bypasses the blood–retinal barrier, leading to high local drug concentrations with no or little systemic adverse event but has potential ophthalmic adverse event as cataract formation and transient elevation of IOP.[20]

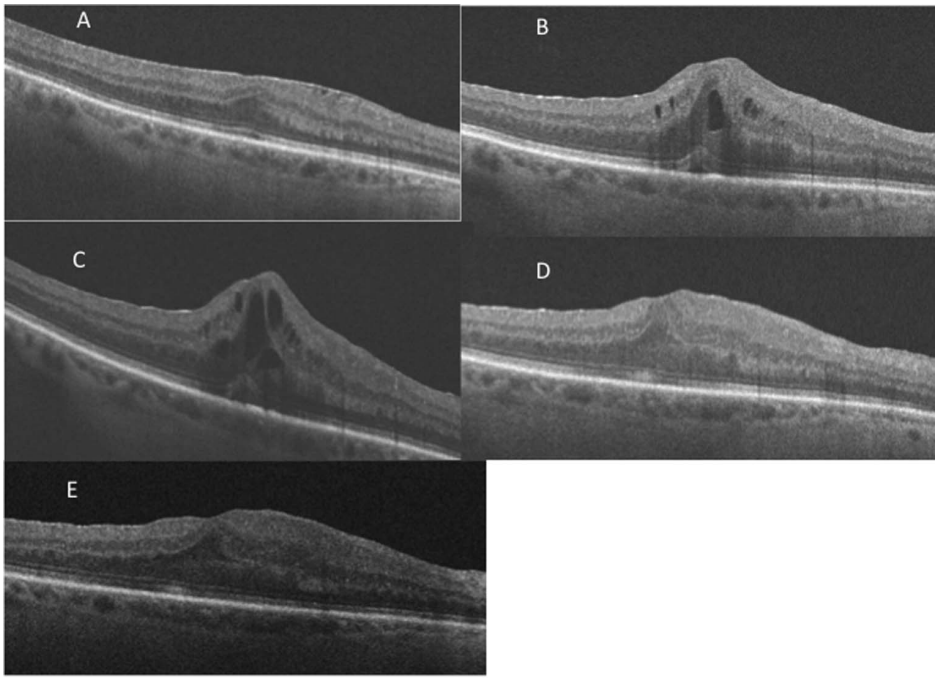

Fig. 1. Patient 7 before surgery (**A**). The patient with 20/28 and macular pucker with central metamorphopsia underwent 25 G vitrectomy and cataract extraction; after 14 days (**B**), referred central scotoma with a decreased visual acuity and at SD-OCT a ME was present (**B**). After 2 months (**C**), visual acuity was decreased to 20/63, and central macular thickness was 531 μm even if topical and systemic anti-inflammatory therapy was used. Dexamethasone intravitreal implant was injected. After 15 days (**D**), BCVA improved to 20/22 and macular thickness decreased to 406 μm: At OCT, intraretinal pseudocysts were absorbed and photoreceptors-external limiting membrane layers complex was restored. Functional and tomographic condition remained stable after 7 months (**E**).

Among the corticosteroids, dexamethasone is one of the most potent with an anti-inflammatory activity 6-fold greater than triamcinolone and 30-fold greater than cortisol.[21] In recent years, given the short half-life of dexamethasone in vitreous cavity, the development of a sustained-release intravitreal dexamethasone implant (Ozurdex) enabled more controlled delivery of the drug, with a potentially lower rate of adverse events. Preclinical studies show that after implantation, vitreous and retina dexamethasone concentrations in vitrectomized eyes are similar to those in nonvitrectomized eyes.[22]

It has been already implanted with good results in vitrectomized eyes for the treatment of diabetic and uveitic ME.[23,24]

A Phase II trial evaluated the safety and efficacy of 300 μg or 700 μg dexamethasone implant in patients with persistent macular resulting from uveitis or postcataract Irvine–Gass syndrome.[25] In this trial, vitrectomized eyes were excluded, and OCT was not performed in any eye. The group of patients with Irvine–Gass syndrome who underwent 700 μg intravitreal dexamethasone implant was composed of 8 eyes, but the analysis of this group was not isolated from that of the whole population of the study.

In our study, a single intravitreal injection of Ozurdex seemed to achieve a complete and stable resolution of ME and increase of BCVA in all vitrectomized patients without any retinal complication (Figure 1); IOP did not change significantly. Even if IOP changed significantly, in no cases it reached a value higher than 18 mmHg. In not any cases, a recurrence of ME was observed. Even if Ozurdex injector was a 22-gauge diameter, no leaking wound was observed because of a complete wound cauterization.

Limitations of this study are its retrospective nature, the few number of patients, the lack of a control group, and the relatively short follow-up.

The findings of this study suggest that a single 0.7 mg dexamethsone intravitreal implant may be an effective new treatment for patients with persistent and refractory ME secondary to combined cataract extraction and vitrectomy with ILM peeling for macular pucker removal.

Key words: dexamethasone implant, intravitreal injection, macular edema, Ozurdex.

References

1. Staudt S, Miller DW, Unnebrick K, et al. Incidence and extent of postoperative macular edema following vitreoretinal surgery with and without cataract operation [in German]. Ophthalmologe 2003;100:702–707.
2. McDonald HR, Johnson RN, Schatz H. Surgical results in the vitreomacular traction syndrome. Ophthalmology 1994;101: 1397–1402.
3. Kim SJ, Martin DF, Hubbard GB, et al. Incidence of postvitrectomy macular edema using optical coherence tomography. Ophthalmology 2009;116:1531–1537.
4. Jun Z, Pavlovic S, Jacobi KW. Results of combined vitreoretinal surgery and phacoemulsification with intraocular lens implantation. Clin Experiment Ophthalmol 2001;29:307–311.
5. Chaudry NA, Cohen KA, Flynnn HW Jr, Murray TG. Combined pars plana vitrectomy and lens management in complex vitreoretinal disease. Semin Ophthalmol 2003;18:132–141.
6. Williams GA, Haller JA, Kuppermann BD, et al. Dexamethasone DDS Phase II study group: dexamethasone posterior segment drug delivery system in the treatment of macular edema resulting from uveitis or Irvine-Gass syndrome. Am J Opthalmol 2009;147:1048–1054.
7. Boscia F, Besozzi G, Recchimurzo N, et al. Cauterization for the prevention of leaking sclerotomies after 23-gauge transconjunctival pars plana vitrectomy: an easy way to obtain sclerotomy closure. Retina 2011;31:988–990.
8. Sheidow TG, Gonder JR. Cystoid macular edema following combined phacoemulsification and vitrectomy for macular hole. Retina 1998;18:510–514.
9. Shelsta HN, Jampol LM. Pharmacologic therapy of pseudophakic cystoid macular edema: 2010 update. Retina 2011;31: 4–12.
10. Sivaprasad S, Bunce C, Wormald R. Non-steroidal anti-inflammatory agents for cystoid macular edema following cataract surgery: a systematic review. Br J Ophthalmol 2005;89: 1420–1422.
11. Leopold IH. Nonsteroidal and steroidal anti-inflammatory agents. In: Sears ML, Tarkkanen A, eds. Surgical Pharmacology of the Eye. New York, NY: Raven press; 1985, 83–133.
12. Pagano G, Bruno A, Cavallo-Perin P, et al. Glucose intolerance after short-term administration of corticosteroids in healthy subjects. Prednisone, deflazacort and betamethasone. Arch Intern Med 1989;149:1098–1101.
13. Robinson BH, Mattingly D, Cope CL. Adrenal function after prolonged corticosteroid therapy. Br Med J 1962;1:1579–1584.
14. Saag KG. Glucocorticoid-induced osteoporosis. Endocrinol Metab Clin North Am 2003;32:135–157.
15. Stanbury RM, Graham EM. Systemic corticosteroid therapy-side effects and their management. Br J Ophthalmol 1998;82: 704–708.
16. Weijtens O, Schoemaker RC, Cohen AF, et al. Dexamethasone concentration in vitreous and serum after oral administration. Am J Ophthalmol 1998;125:673–679.
17. Weijtens O, van der Sluijs, Schoemaker RC, et al. Peribulbar corticosteroid injection: vitreal and serum concentration after dexamethasone disodium phosphate injection. Am J Ophthalmol 1997;123:358–363.
18. Weijtens O, Feron EJ, Schoemaker RC. High concentration of dexamethasone in aqueous and vitreous after subconjunctival injection. Am J Ophthalmol 1999;128:192–197.
19. Weijtens O, Schoemaker RC, Romijn FP, et al. Intraocular penetration and systemic absorption after topical application of dexamethasone disodium phosphate. Ophthalmology 2002;109:1887–1891.
20. Haller JA, Bandello F, Belfort R, et al; Ozurdex GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology 2010;117:1134–1146.
21. Goldfien A. Adrenocorticosteroids and adrenocortical antagonists. In: Katzung BG, ed. Basic and Clinical Pharmacology. 6th ed. London, United Kingdom: Prentice Hall International; 1995:592–607.

22. Chang-Lin JE, Burke JA, Peng Q, et al. Pharmacokinetic of a sustained-release dexamethasone intravitreal implant in vitrectomized and nonvitrectomized eyes. Invest Ophthalmol Vis Sci 2011;52:4605–4609.
23. Boyer DS, Faber D, Gupta S, et al; Ozurdex CHAMPLAIN Study Group. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. Retina 2011;31:915–923.
24. Adan A, Pelegrin L, Rey A, et al. Dexamethasone intravitreal implant for treatment of uveitic persistent cystoid macular edema in vitrectomized patients. Retina 2013. In press.
25. Williams GA, Haller JA, Kuppermann BD, et al. Dexamethasone posterior-segment drug delivery system in the treatment of macular edema resulting from uveitis or Irvine Gass syndrome. Am J Ophthalmol 2009;147:1048–1054.