

Review of the Drug-infused Eye Implant—Ozurdex® (Dexamethasone Intravitreal Implant)

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Abstract

Ozurdex® (dexamethasone intravitreal implant, Allergan, Inc., Irvine, CA) is an intravitreal implant designed to provide sustained, controlled release of dexamethasone to treat inflammatory conditions in the posterior segment of the eye. Ozurdex is approved by the US Food and Drug Administration for the treatment of macular edema (ME) following branch and central retinal vein occlusion (RVO) and for the treatment of non-infectious uveitis that involves the posterior segment. A single intravitreal injection of Ozurdex has been shown to improve visual acuity and reduce central retinal thickness in eyes with these conditions for up to six months. Increases in intraocular pressure are typically transient and controlled with topical medication. Repeated treatment with Ozurdex at a six-month interval has been shown to be safe and effective in patients with ME related to RVO. Although cataract progression has been noted upon repeated injection, cataract extraction has remained rare in clinical studies of up to one year in duration. Ozurdex has demonstrated efficacy in the treatment of diabetic ME (DME) and may be particularly valuable for treatment of ME in difficult-to-treat vitrectomized eyes. Ozurdex is currently under investigation in Phase III trials for the treatment of DME.

Keywords

Biodegradable implant, dexamethasone, drug-delivery system, macular edema, uveitis

Disclosure: Careen Y Lowder, MD, PhD, is on the Advisory Board of Allergan, Inc. David A Hollander, MD, MBA, is an employee of Allergan, Inc.

Acknowledgment: A freelance medical writer, Kate Ivins, PhD, funded by Allergan, Inc., assisted in the development of the manuscript.

Received: August 22, 2011 **Accepted:** September 9, 2011 **Citation:** *US Ophthalmic Review*, 2011;4(2):107–12 DOI: 10.17925/USOR.2011.04.02.107

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Intraocular inflammation and related complications are important causes of vision loss in posterior segment disease. Inflammatory processes contribute to blood–retinal barrier breakdown, vascular leakage, and the development of vision-threatening macular edema (ME) in retinal vein occlusion (RVO), uveitis, diabetic retinopathy, and Irvine–Gass syndrome.¹ Inflammation also has a key role in the development of neovascularization that threatens vision in posterior segment disease. Inflammatory cell activation and the expression of growth and angiogenic factors stimulate choroidal neovascularization, a major cause of vision loss, in exudative age-related macular degeneration² as well as the growth of new, abnormal retinal vessels in proliferative diabetic retinopathy.

Local delivery of anti-inflammatory medication to the posterior segment by intravitreal injection reduces the patient’s overall drug exposure and improves the systemic safety of treatment. Intravitreal injections of corticosteroids have been used for many years to treat ME of various etiologies and uveitis.³ Recently, intravitreal sustained-delivery drug devices were introduced to allow corticosteroids to be delivered in a slow, sustained manner to optimize the efficacy and safety of treatment and reduce the number of intravitreal injections a patient may require.

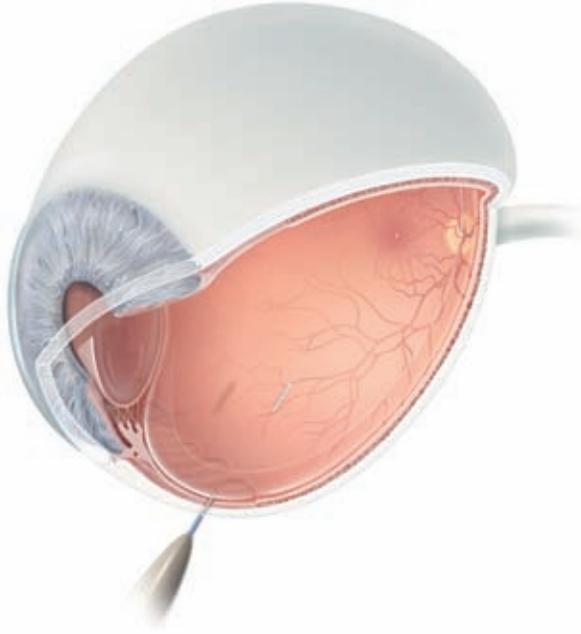
Ozurdex®

Ozurdex® (dexamethasone intravitreal implant, Allergan, Inc., Irvine, CA) is an intravitreal drug-delivery system that contains 0.7 mg of micronized dexamethasone (DEX) in a biodegradable copolymer of polylactic-co-glycolic acid (see *Figure 1*). A single-use, specially designed applicator with a 22-gauge needle is used to place the sustained-release DEX implant in the vitreous in a sutureless office procedure.⁴ DEX is released slowly from the implant over several months, as the copolymer matrix degrades to lactic acid and glycolic acid, which are metabolized to water and carbon dioxide. Ozurdex (DEX implant) was approved by the US Food and Drug Administration for the treatment of ME following branch RVO (BRVO) or central RVO (CRVO) in 2009 and for the treatment of non-infectious uveitis affecting the posterior segment of the eye in 2010. It is currently under investigation in phase III trials for the treatment of diabetic ME (DME).

Differences among Corticosteroids

Corticosteroids have multiple anti-inflammatory effects that are beneficial in the treatment of ME, including stabilization of endothelial tight junctions, reduction of vascular permeability, and inhibition of the expression of vascular endothelial growth factor (VEGF), prostaglandins, and other cytokines. The current most commonly used corticosteroids

Figure 1: Schematic Showing the Placement of Ozurdex® in the Vitreous—A Single-use Applicator is Used for the Pars Plana Injection



in intraocular therapy are DEX, triamcinolone acetonide (TA), and fluocinolone acetonide (FA). These corticosteroids differ in aqueous and lipid solubility, delivery system requirements, and pharmacologic activity.^{5,6} TA is administered by frequent intravitreal injections of a drug suspension of insoluble TA crystals, which gradually release TA.⁷ Preserved TA (Kenalog®, Bristol-Myers Squibb, Princeton, NJ) contains benzyl alcohol as an excipient; it was not designed for, and has not been approved for, ophthalmic use. Preserved TA has been associated with sterile endophthalmitis,⁸ possibly related to the excipient. Preservative-free TA (Triesence®, Alcon Laboratories, Fort Worth, TX) has been approved for ophthalmic use. TA preparations may differ in duration of action because of differences in the size of the crystalline aggregates and their dispersion in the vitreous,⁹ or differences in rates of clearance from the vitreous. DEX and FA have greater water solubility than TA and are administered by intravitreal injection of sustained-delivery implants.^{4,10,11} DEX, TA, and FA have been shown to activate transcription of unique sets of genes, as well as common sets of genes, in trabecular meshwork cell lines,¹² which could potentially lead to differences in the safety profiles of these corticosteroids.⁵

Advantages of a Sustained-delivery Implant

An intravitreal implant that provides controlled, prolonged release of a drug may reduce the need for systemic drug administration or reduce the frequency of required ocular injections. Though DEX is a potent corticosteroid,⁶ it is cleared rapidly from the vitreous (half-life of two to three hours) following a single intravitreal injection of drug solution.⁵ A continuous-release implant is necessary to provide sustained levels of DEX and optimal efficacy.

Pharmacokinetics of Ozurdex®

A study in monkeys demonstrated that DEX is present at measurable levels in the vitreous and retina up to six months after intravitreal

DEX implant injection.¹³ The pharmacokinetic profile of DEX implant was characterized by two distinct phases. In the first phase, the concentration of DEX in both tissues was high from seven days to two months after placement of the implant, with the peak concentration of DEX achieved in the retina at two months.¹³ In the second phase, the concentration of DEX in both tissues was lower and slowly declined from three to six months after placement of the implant.¹³ This biphasic pharmacokinetic profile resembles that obtained with the systemic pulse administration of corticosteroids¹³ and is consistent with the sustained duration of action of DEX implant seen in clinical studies.

Diffusion of substances in the vitreous is increased in eyes that have undergone vitrectomy.¹⁴ This may have beneficial effects in facilitating the removal of inflammatory mediators from the retina,¹⁴ but it also leads to more rapid clearance of some drugs, including TA,¹⁵ from the vitreous, and may limit the effectiveness of these drugs in vitrectomized eyes. In a preclinical study in rabbits, the pharmacokinetics of DEX implant were similar in vitrectomized and non-vitrectomized eyes.¹⁶

Retinal Vein Occlusion

RVO is a common retinal vascular disease associated with occlusion of the central retinal vein or one of the smaller branch retinal veins. The sequelae of the occlusion include ME, a frequent cause of vision loss in both CRVO and BRVO.¹⁷ Increased vascular pressure behind the occlusion leads to vascular leakage and the development of ME.¹⁷ In addition, vascular endothelial damage in the affected vein results in chronic inflammation and the production of inflammatory mediators, including prostaglandins, tumor necrosis factor- α (TNF- α), and VEGF, which exacerbate and perpetuate the ME.¹⁷

Laser photocoagulation, traditionally considered the standard of care in the treatment of ME secondary to BRVO, improves vision in many, but not all, patients.¹⁸ Laser therapy is not recommended for ME associated with CRVO, though it reduces the edema, because it fails to improve vision.¹⁹ Other treatment options for RVO-associated ME include intravitreal injections of corticosteroids and anti-VEGF agents. In a randomized, controlled, Phase II study in patients with RVO, diabetic retinopathy, uveitis, or Irvine-Gass syndrome who had persistent ME after laser or medical therapy, those patients who received a surgically implanted DEX implant 0.7 or 0.35 mg had reduced vascular leakage demonstrated by fluorescein angiography, reduced central retinal thickness by optical coherence tomography (OCT), and improved vision compared with untreated, observed patients.²⁰ An increase in best-corrected visual acuity (BCVA) of at least 10 letters from baseline to day 90 was seen in 35 % of patients treated with DEX implant 0.7 mg and 13 % of observed patients ($p < 0.001$); an increase in BCVA of at least 15 letters from baseline to day 90 was seen in 18 % of patients treated with DEX implant 0.7 mg and 6 % of observed patients ($p = 0.006$).²⁰

Two randomized, sham-controlled, phase III studies evaluated the efficacy and safety of DEX implant 0.7 and 0.35 mg placed with an applicator compared with sham treatment in 1,267 patients with vision loss caused by ME associated with BRVO or CRVO.²¹ Approximately 66 % (830/1,267) of the patients had BRVO and 34 % (437/1,267) of the patients had CRVO. The duration of ME was 90 days or longer in the majority (83 %) of patients. After an initial six-month, double-masked period of treatment

with DEX implant or sham, the studies were extended in an open-label manner for an additional six months. DEX implant 0.7 mg (Ozurdex) treatment was given as needed at month six to all patients, regardless of their initial treatment assignment, to assess the long-term safety of single and repeated DEX implant treatments.²²

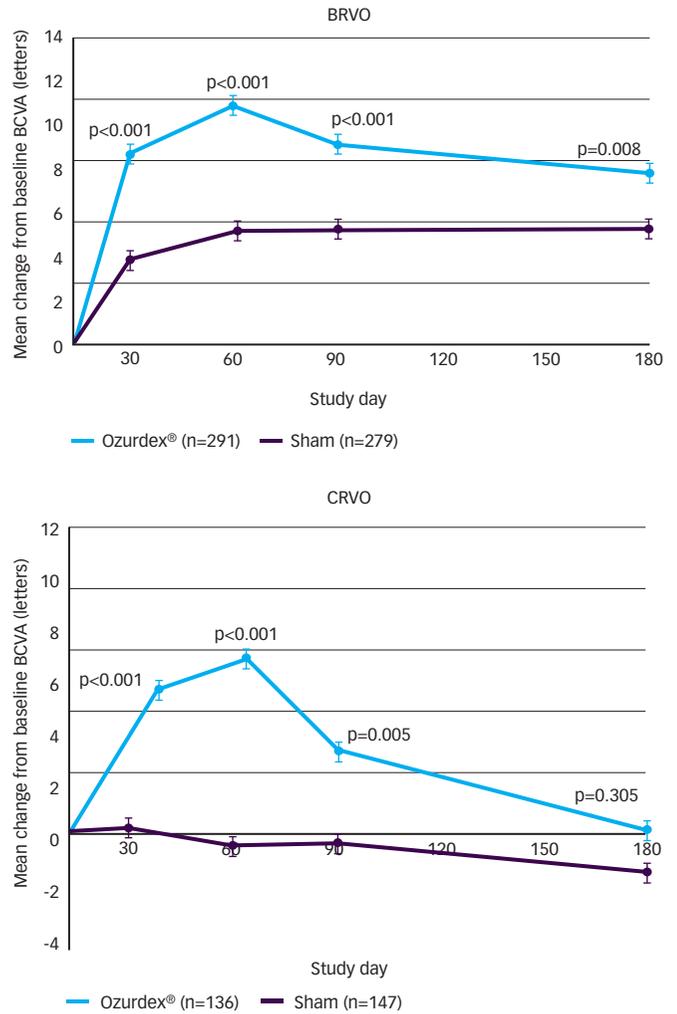
In the initial masked phase of the study,²¹ the time to achieve at least a 15-letter improvement in BCVA was shorter in the DEX implant groups than in the sham group ($p < 0.001$, primary endpoint of the pooled data analysis) and the mean improvement in BCVA was greater in the DEX implant groups than in the sham group at all follow-up visits ($p \leq 0.006$). At two months (peak response), the mean improvement in BCVA was approximately 10 letters in the DEX implant 0.7 mg group and three letters in the sham group. The percentage of patients who had gained at least 15 letters was significantly higher in the DEX implant groups than in the sham group at months one, two, and three, but not at month six. At two months, 29 % of patients in the DEX implant groups and 11 % in the sham group had gained at least 15 letters in BCVA ($p < 0.001$). Decreases in BCVA of 15 letters or more were less common in the DEX implant 0.7 mg group than in the sham group at all follow-up visits through six months ($p \leq 0.036$). At day 180, 6 % of patients in the DEX implant 0.7 mg group and 11 % in the sham group had lost at least 15 letters in BCVA. Subgroup analysis showed that the effects of treatment on vision were qualitatively similar in patients with BRVO and patients with CRVO (see Figure 2). Together these results indicate that DEX implant treatment both increased the likelihood of visual improvement and reduced the risk of further vision loss in patients with ME secondary to BRVO or CRVO.

In the open-label study extension, improvements in BCVA after a second DEX implant treatment were similar to those seen after the initial treatment.²² In patients who received DEX implant 0.7 mg at both baseline and month six, at least a 15-letter improvement in BCVA was achieved, at two months after injection of the first and second implants, by 30 and 32 % of patients, respectively. Reduction in central retinal thickness by OCT was also similar after the first and second treatments.²²

Non-infectious Intermediate and Posterior Uveitis

Approximately 10–15 % of cases of blindness in the developed world result from uveitis, a group of intraocular inflammatory diseases that involve the uveal tract or adjacent ocular structures.²³ Most cases of severe uveitis-related vision loss are associated with intermediate or posterior uveitis, in which inflammation is present in the vitreous and retina.²⁴ Corticosteroids remain the mainstay in the treatment of uveitis.²⁵ Topical are typically effective only in the treatment of anterior uveitis. Traditionally, the treatment of intermediate or posterior uveitis required systemic corticosteroids or other immunosuppressive treatments. However, systemic corticosteroid treatment is not effective in all patients and frequently is associated with a variety of potentially severe side effects, including hypertension, hyperglycemia, osteoporosis, peptic ulcers, and serious infections.²⁶ The use of intravitreal injections has allowed for the delivery of corticosteroids to the posterior segment, though intravitreal treatment with TA, for example, may require repeat injections every two to three months and has been associated with

Figure 2: Mean Changes in Best-corrected Visual Acuity in Patients with Macular Edema Associated with Branch or Central Retinal Vein Occlusion who Received Ozurdex® or a Sham Procedure at Baseline in a Six-month Study



Error bars are standard error of the mean. *p*-values are for between-group comparisons. BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion. Reprinted from 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(6):1134–46. © 2011, with permission from the American Academy of Ophthalmology.²¹

cataract and intraocular pressure (IOP) elevations that often require glaucoma surgery.^{3,27} An intravitreal implant that provides targeted, sustained delivery of corticosteroid to the posterior segment potentially may reduce the frequency of injections required and improve the efficacy and safety of treatment.

The efficacy and safety of DEX implant in the treatment of non-infectious uveitis that involves the posterior segment was evaluated in a six-month, randomized, double-masked, sham-controlled clinical study.²⁴ A total of 229 adult patients diagnosed with non-infectious intermediate or posterior uveitis who had BCVAs from 10 to 75 letters (20/640 to 20/32 Snellen) and a vitreous haze score of at least +1.5 were enrolled in the study. Patients were randomized to treatment at baseline with a single injection of DEX implant 0.7 or 0.35 mg or to a sham procedure that used a needleless applicator. The randomization was stratified

by the baseline vitreous haze score, and the mean vitreous haze score at baseline was approximately +2 in each treatment group. During follow-up, patients treated with DEX implant 0.7 mg were significantly more likely than sham-treated patients to have resolution of vitreous inflammation (a vitreous haze score of 0) at each follow-up visit from week six through month six ($p \leq 0.014$, see *Figure 3*). At week eight, the percentage of patients with a vitreous haze score of 0 was 47 % in the DEX implant 0.7 mg group and 12 % in the sham group ($p < 0.001$, primary endpoint). Substantial decreases (at least two units) in the vitreous haze score were more common in patients treated with DEX implant 0.7 mg than in sham-treated patients throughout six months of follow-up ($p \leq 0.023$).

DEX implant also demonstrated superiority to the sham procedure in secondary outcome measures of visual acuity, retinal thickness, and use of rescue medications. Improvements in BCVA from baseline were significantly larger in the DEX implant 0.7 mg group than in the sham group throughout the study ($p \leq 0.002$). Patients treated with DEX implant 0.7 mg were 2–6 times more likely than sham-treated patients to achieve at least a 15-letter improvement in BCVA at each follow-up visit through month six. At week eight, 43 % of patients treated with DEX implant 0.7 mg compared with 7 % of sham-treated patients had gained at least 15 letters in BCVA. Mean central macular thickness by OCT was decreased significantly from baseline in the DEX implant groups ($p \leq 0.004$), but not the sham group, at both week eight and month six. Patients treated with DEX implant 0.7 mg were less likely than patients in the sham group to require rescue medication to treat their uveitis. The cumulative percentage of patients who needed rescue medication was lower in the DEX implant 0.7 mg group than in the sham group throughout follow-up ($p \leq 0.030$). By month six, 22 % of patients treated with DEX implant 0.7 mg compared with 38 % of sham-treated patients had needed rescue medication ($p = 0.030$).

Diabetic Macular Edema

DME is a frequent complication of diabetic retinopathy and the most common cause of vision loss in patients with diabetes. In DME, vascular leakage from dilated hyperpermeable capillaries and microaneurysms leads to accumulation of extracellular fluid in the macula. Inflammation has a key role in the pathogenesis and maintenance of DME. Leukocyte recruitment and adhesion to the retinal vasculature endothelium (leukostasis) precipitates the breakdown of the blood–retinal barrier.²⁸ Inflammatory factors, such as intercellular adhesion molecule-1, VEGF, TNF- α , and interleukin-6, are also involved.^{29,30} Standard care for DME includes medical control of diabetes and laser therapy—focal laser photocoagulation to treat leaking microaneurysms and grid laser photocoagulation to treat areas of diffuse capillary leakage.³¹ In the Early treatment of diabetic retinopathy study, laser therapy was demonstrated to reduce the risk of vision loss caused by clinically significant DME by 50 %, but did not generally result in improved vision.³² In more recent studies that involved only patients with DME-associated vision loss, repeated applications of focal/grid laser photocoagulation treatment resulted in at least a 10-letter improvement in visual acuity in 28–32 % of patients, but 13–19 % of patients lost at least 10 letters in visual acuity.^{33,34}

In the Phase II study of the efficacy and safety of DEX implant in the treatment of persistent ME of various etiologies,²⁰ 171 patients were

diagnosed with DME. Subgroup analysis of results in the patients with DME showed that BCVA improved more in patients treated with DEX implant than in untreated patients.³⁵ At month three, 33.3 % of patients in the DEX implant 0.7 mg group compared with 12.3 % in the observation group had gained at least 10 letters in BCVA ($p = 0.007$). Decreases in central retinal thickness by OCT and decreases in vascular leakage by fluorescein angiography were also greater in the DEX implant 0.7 mg group than in the observation group at month three ($p < 0.001$).³⁵ Phase III randomized, multicenter, three-year clinical studies to evaluate the long-term efficacy and safety of DEX implant in the treatment of DME are ongoing.³⁶

Altered pharmacokinetics in vitrectomized eyes may affect the efficacy of intravitreal treatments. In a retrospective case series, repeated intravitreal injections of an anti-VEGF agent (bevacizumab) were ineffective in reducing foveal thickness or improving visual acuity in vitrectomized eyes with DME, likely because of increased clearance of drug from the vitreous.^{15,37} Though TA is cleared from the vitreous more rapidly in vitrectomized eyes,³⁸ the pharmacodynamics of DEX implant appear to be unaffected by vitrectomy. The pharmacokinetics of DEX implant have been shown to be similar in vitrectomized and non-vitrectomized rabbit eyes.¹⁶

A prospective open-label study evaluated the efficacy and safety of DEX implant in the treatment of DME in eyes with a history of pars plana vitrectomy.³⁹ The 56 patients enrolled in the study had a mean duration of DME of 43 months and a mean BCVA of 55 letters (approximately 20/100 Snellen). In most cases, previous treatment had been attempted and had failed to resolve the DME. Previous treatment included anti-VEGF therapy (up to 20 intravitreal injections) in 48 % of patients, intravitreal or subtenon TA (up to 20 injections) in 55 % of patients, and laser therapy (up to five treatments) in 66 % of patients. Both central retinal thickness by OCT and BCVA improved by one week after injection of the DEX implant and remained improved throughout six months of follow-up ($p \leq 0.046$).³⁹ The peak effectiveness of DEX implant was seen between eight and 13 weeks after the injection. At week 13, 30.4 % of patients had gained at least 10 letters in BCVA, 10.7 % of patients had gained at least 15 letters in BCVA, and no patients had lost 10 or more letters of BCVA.³⁹ At month six, 21.4 % of patients had gained at least 10 letters in BCVA, 21.4 % of patients had gained at least 15 letters in BCVA, and 10.7 % of patients had lost 10 or more letters in BCVA.³⁹ The efficacy of DEX implant in reducing retinal thickness and improving BCVA in vitrectomized patients with DME in this study was similar to that seen in the subgroup of patients with DME in the Phase II study,³⁵ which suggests that DEX implant may be especially beneficial in the treatment of inflammation and ME in difficult-to-treat vitrectomized eyes.

Safety Profile

DEX implant 0.7 mg was well tolerated in each of the reported clinical trials. The safety profile of DEX implant is acceptable and similar across disease states. The most common adverse events associated with DEX implant treatment are conjunctival hemorrhage and increased IOP. Conjunctival hemorrhage, eye pain, and conjunctival hyperemia have been associated with the DEX implant injection, but typically these effects are transient and resolve without sequelae. The overall incidence of these adverse events in the DEX implant/sham treatment groups

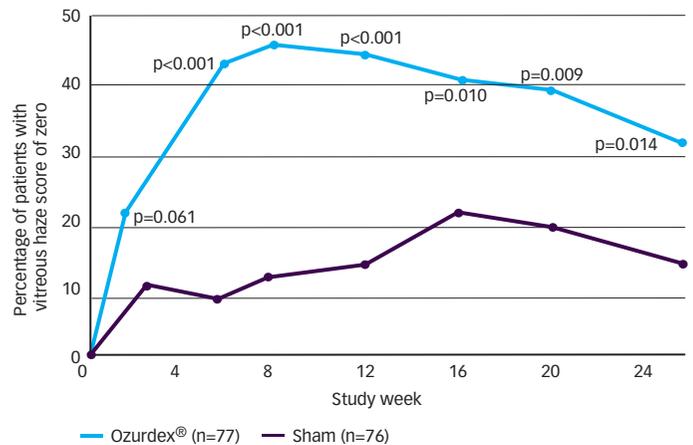
in the six-month studies in patients with posterior segment uveitis and RVO-related ME were conjunctival hemorrhage (22/16 %), eye pain (8/5 %), and conjunctival hyperemia (7/5 %).⁴⁰

The clinically important adverse effects typically associated with any ophthalmic corticosteroid are increases in IOP and cataract. The increases in IOP associated with DEX implant are usually transient and typically are controlled with topical IOP-lowering medications or observation alone. In the six-month study of a single DEX implant treatment in patients with posterior segment uveitis, at each follow-up visit fewer than 8 % of patients in the DEX implant 0.7 mg group had an IOP of 25 mmHg or higher, and no more than 23 % of the patients were using IOP-lowering medication.²⁴ No patients required a laser or surgical procedure to lower IOP, and at six months the IOP in all patients was less than 25 mmHg. In the 12-month study of single and repeated DEX implant treatment in patients with RVO-associated ME, among patients who received two DEX implant injections at six-month intervals, the incidence of elevated IOP peaked at 60 days after each treatment and was similar after the first and second injection (see *Table 1*).²² An IOP rise that necessitated the initiation of topical IOP-lowering medication occurred in 25.5 % of patients after the first implant and in an additional 10.3 % of patients after the second implant. Most cases of elevated IOP were managed successfully with topical IOP-lowering medication or observation. Laser or surgical procedures for elevated IOP were performed in 1.2 % of treated eyes during the one-year study. Elevations in IOP had resolved by 180 days after each DEX implant treatment (see *Table 1*).

The large clinical trials of DEX implant excluded patients with glaucoma or a history of steroid-induced IOP elevations.^{22,24} In a recent case report, a patient with chronic posterior uveitis, glaucoma (on two IOP-lowering medications), and prior steroid-induced IOP elevations developed elevated IOP following treatment with Ozurdex. The IOP remained elevated for several months despite four IOP-lowering medications.⁴¹ Patients with a known steroid-related IOP response who are already being treated with IOP-lowering medications for glaucoma should be monitored carefully when treated with DEX implant.⁴²

The development and progression of cataracts is a well-described adverse effect of corticosteroid treatment. In the six-month study to evaluate DEX implant for treatment of intermediate and posterior uveitis, cataract was reported as an adverse event in 15 % (9/62) of phakic eyes in the DEX implant group and 7 % (4/55) of phakic eyes in the sham group.²⁴ One patient in the DEX implant group and two in the sham group underwent cataract surgery during the study. In the 12-month study of single and repeated DEX implant treatment in patients with RVO-associated ME, cataract adverse events were reported in 29.8 % (90/302) of phakic study eyes in patients who received two DEX implant 0.7 mg injections at six-month intervals, 7.6 % (5/66) of phakic study eyes in patients who received one DEX implant 0.7 mg injection at baseline, 10.5 % (31/296) of phakic study eyes in patients who received one DEX implant 0.7 mg injection at month six (delayed treatment), and 5.7 % (5/88) of phakic study eyes in patients in the untreated group (treated with the sham procedure only).²² These results suggest that the likelihood of cataract progression is increased with repeated treatment. Despite cataract progression, cataract extractions were performed in only four study eyes (1.3 % of phakic eyes) in the

Figure 3: Resolution of Vitreous Haze in Patients with Non-infectious Intermediate or Posterior Uveitis who Received Ozurdex® or a Sham Procedure at Baseline in a Six-month Study



p-values are for between-group comparisons. Adapted with permission. Archives of Ophthalmology, 129(5):545–53.²⁴ © 2011. American Medical Association. All rights reserved.

Table 1: Occurrence of Elevated Intraocular Pressure in Patients With Retinal Vein Occlusion-associated Macular Edema Who Received Two Treatments with Ozurdex® in a 12-month Study (n=341)²²

Study Day	Percentage of Patients with IOP≥25 mmHg
0-first DEX implant	0.0
1	0.6
7	3.2
30	9.0
60	13.6
90	5.0
180-second DEX implant	0.9
181	1.2
187	2.7
210	13.8
240	15.7
270	8.3
360	0.9

DEX = dexamethasone intravitreal; IOP = intraocular pressure.

re-treated DEX implant 0.7 mg/0.7 mg group and one study eye (1.1 % of phakic eyes) in the untreated group during the study. There were no cataract extractions in eyes that had received a single DEX implant 0.7 mg injection at baseline or month six.

Endophthalmitis, retinal tears, and retinal detachments have been rare and reported with similar frequency in the DEX implant and sham treatment groups in clinical trials.^{22,24}

Conclusions

Ozurdex effectively treats both ME associated with RVO and non-infectious uveitis that involves the posterior segment. Phase III evaluation of Ozurdex in the treatment of DME is underway. The implant is well tolerated. Those IOP elevations that do occur are typically transient and managed with topical medication or observation alone. IOP generally returns to

baseline levels by six months. Cataract progression has been seen in patients treated with repeated injections of Ozurdex, but has rarely led to cataract surgery in studies of up to one year in duration. Studies over longer periods are needed to evaluate further the long-term efficacy

and safety of treatment and to determine optimal dosing algorithms for Ozurdex, both alone and in conjunction with other treatment modalities, in the treatment of inflammation and inflammatory complications in posterior segment disease. ■

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