

Intraocular Pressure Changes Following the Administration of Intravitreal Dexamethasone Implant: A Mini -Review

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ABSTRACT

Intravitreal Dexamethasone Implant (IDI) (Ozurdex®, Allergan, Inc. Irvine, CA) is the sustained-release corticosteroid device approved by the US Food and Drug Administration for the treatment of macular edema resulted from diabetes mellitus, non-infectious uveitis and retinal vein occlusion. Along with its anti-inflammatory effects, the most common side effects associated are cataract formation and intraocular pressure (IOP) elevation. Although the exact pathophysiological mechanism remains unclear, increased aqueous outflow resistance resulted from the biochemical and structural changes in the trabecular meshwork is deemed responsible for the well-known IOP elevation. This mini-review investigated major clinical trials evaluating the IOP changes after 0.7 mg IDI

administration and summarized their results on IOP changes and its management.

Key words: Intraocular pressure; Intravitreal dexamethasone implant; Glaucoma; Macular edema; Steroids; Trabecular meshwork.

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INTRODUCTION

Intravitreal Dexamethasone Implant (IDI) (Ozurdex®, Allergan, Inc. Irvine, CA) is approved by the US Food and Drug Administration (FDA) for the treatment of macular edema (ME) secondary to diabetes mellitus (DM), non-infectious uveitis (NIU), and branch or central retinal vein occlusion (RVO)^[1]. Although off-label, clinical efficacy of the implant in various other disease entities characterized with ME such as post-surgical ME including Irvine-Gass syndrome, Coats disease and retinitis pigmentosa has also been shown by many researchers^[2-6].

STRUCTURAL AND PHARMACOKINETIC PROPERTIES OF IDI

IDI is a sustained-release device composed of biodegradable glycolic-lactic acid copolymer containing 700 µg of dexamethasone^[7,8]. The implant is inserted into the vitreous cavity through the pars plana with a 22 gauge injector^[9]. While the implant is metabolized into water and carbon dioxide, the drug is gradually released into the vitreous cavity. The clinical effectiveness of the drug is determined by its pharmacokinetic properties. There are two phases of the drug release occurring during after each injection: first phase displaying higher drug concentrations beginning just after the injection and peaking at two month, followed by a second phase exhibiting a lower drug concentration sustaining up to 6 months^[10]. Pharmacokinetic

properties of the implant have been found similar in both vitrectomized and non-vitrectomized eyes^[7]. The biological effects of dexamethasone are mediated through the cytoplasmic glucocorticoid receptors.

STERIOD RESPONDERS AND STEROID-INDUCED IOP ELEVATION

Although IDI is a potent and effective modality for the intraocular inflammation control, it may lead to some undesirable sight-threatening adverse events during the follow-up. Along with the cataract formation, steroid-induced ocular hypertension (OHT) or glaucoma is the most common side-effect associated with the implant^[11]. OHT is identified as an increase of > 10 mmHg compared with baseline IOP or IOP > 25 mmHg. Steroid-induced glaucoma is one of the causes of secondary glaucoma and its clinical and pathophysiological features are similar to primary open-angle glaucoma (POAG). IOP elevation occurs in approximately 40% of general human population who receive long-term steroids. The individuals who develop steroid-induced IOP elevation are identified as steroid responders, while those who do not develop IOP elevation are identified as non-responders. Clinical trials have shown that more than 90% of POAG patients are steroid responders. It has been suggested that steroid responders are at greater risk for development of POAG^[12-15].

POSSIBLE MECHANISMS OF STEROID-INDUCED IOP ELEVATION

Although the exact mechanism remains unclear, it is considered that increased aqueous outflow resistance resulted from biochemical and structural changes in the trabecular meshwork (TM) is responsible for steroid-induced IOP elevation or glaucoma. As a result of histologic studies on human TM specimens obtained from the eyes with steroid-induced glaucoma, several mechanisms have been proposed for steroid-induced IOP elevation including increased accumulation of extracellular matrix materials (fibronectin, glycosaminoglycan, laminin and elastin), decreased phagocytotic capacity, decreased activity of protease and stromelysin, increased DNA content and nuclear size, reorganization of the TM cytoskeleton, formation of intercellular junctions and rearrangement of specific protein synthesis^[16-19]. Experimental studies have reported that steroids significantly increases expression of MYOC gene at locus GLCA1 (myocilin) which is closely linked to POAG in cultured TM cells^[17]. Alpha1-antichymotrypsin, pigment epithelium-derived factor, decorin, ferritin light chain, fibulin-1C, insulin-like growth factor binding protein 2, growth arrest specific 1, cornea-derived transcript 6, prostaglandin D₂ synthase are other genes to be considered to play a role in steroid responsiveness^[18-22].

The rates of IOP elevation caused by intravitreal steroids are different. IDI leads to less frequent and less severe IOP elevation than triamcinolone acetonide (TA) and fluocinolone acetonide (FA), which are other intravitreal steroids. This difference may be explained by its pharmacokinetic and pharmacological properties. Because of more lipophilic properties, TA and FA result in a greater accumulation in TM than the dexamethasone. Also different steroids activate different gene expressions in human TM^[22-24]. In a meta-analysis study conducted by Kiddee *et al.*^[22], the percentages of OHT following the steroid administration were found 32% (28.2-36.3%) in 4 mg TA injected eyes, 79% (72.2-84.5%) and 66% (50.2-78.8%) in high and low-dose (2.1 mg vs. 0.59 mg) FA implant inserted eyes and 15% (9.2-

24.3%) and 11% (6.4-17.9%) in high and low-dose IDI (0.70 mg vs. 0.35 mg) inserted eyes. Retisert® (Bausch & Lomb, Inc., Rochester, NY, USA) and Iluvien® (Alimera Sciences Limited, Aldershot, UK) are two commercial forms of steroid devices containing FA on the market. While the Retisert® consists of 0.59 mg FA approved by US FDA for the treatment of posterior NIU in 2005, Iluvien® contains 0.19 mg FA approved by US FDA for the treatment of chronic DME in 2014^[25]. The percentages of IOP elevation in Retisert®^[26] and Iluvien®^[27] inserted eyes were found 59% and 37-45% (low (0.2 µg/d)-high dose (0.5 µg/d)), respectively.

MAJOR CLINICAL TRIALS EVALUATING IOP CHANGES AFTER 0.7 MG IDI ADMINISTRATION

IOP elevation is considered a common adverse event that may occur after the administration. IOP outcomes in clinical trials of IDI are summarized in Table 1^[28-42]. Different studies have reported the rates of IOP of > 25 mmHg in patients who developed IOP elevation following IDI administration are ranged from 7.1% to 58.7%. In addition, percentage of patients who required IOP-lowering medication following the injection has been reported between 10.9% and 54%. IOP elevation is usually well-controlled with IOP-lowering medication in most of studies and the rate of patients who underwent glaucoma surgery is not reported more than 2% in any study^[28-42].

In a very recent study conducted by Ventura *et al.*^[28], the authors evaluated the long-term (24 months) cumulative probability of IOP elevation associated with the IDI that was administered in various indications (DME, RVO, NIU). They suggested that IOP elevation was common, generally mild and well-tolerated. Moreover, the cumulative probability of having an IOP > 35 mmHg, > 25 mmHg and > 21 mmHg were found 7%, 30% and 60% at 24 months, respectively. The authors reported that probability of initiating IOP-lowering medication was 54% at 24 months and glaucoma surgery was required in 0.9% (4 eyes) of the eyes. They demonstrated that cumulative effect of repeated injections of IDI did not appear to increase the risk of IOP elevation.

Malclès *et al.*^[31] (SAFODEX study) investigated the safety of the IDI used in different indications (DME, RVO, NIU, and post-surgical ME), and reported the incidence and risk factors of OHT. The authors reported that the percentage of patients who developed OHT during the study was 28.5%. The percentages of patients with IOP of > 35 mmHg and > 25 mmHg and were 6% and 20%, respectively. The authors reported that the increase in IOP was most common at two month within a range of day eight to month three after the injection. Also, authors searched whether the IOP elevation was different or not in various disease entities and the patients who developed OHT was significantly more in the NIU (38%) and RVO (36%) groups than in the DME group (17%). In this trial, male gender, younger age, high myopia (> 25 mm), preexisting glaucoma treated with multiple IOP-lowering medications, and diagnosis of RVO, NIU and type 1 DM were found as significant risk factors for developing OHT following the IDI administration, but vitreous (vitrectomized or not) or lens (phakic/pseudophakic) status were not associated with an increased risk of IOP elevation. Interestingly, the authors suggested that type 2 DM might have a protective effect with less IOP elevation.

MEAD study group^[33] investigated the IOP changes after IDI in the DME patients. They revealed that a significant IOP elevation was revealed in approximately one-third of the patients during the follow-up of three years and IOP elevation occurred between 1.5 and 3 months after the injection and returned to its baseline at 6 months

Table 1 Summary of Intraocular Pressure Changes Reported after the Intravitreal Administration of 0.7 mg Dexamethasone Implant in Several Clinical Trials.

Study design, Number of patients Follow-up period	Treatment indications	IOP rise	Management of IOP
Zarranz-Ventura et al^[28] 2019			
*Retrospective study *403 patients (429 eyes) *24 months	DME (47%), NIU (13%), RVO (29%), and others (11%)	IOP > 35 mmHg→7% (at 26 week); IOP > 25 mmHg→30% (at 26 week).	IOP-lowering medication→ 54% Glaucoma surgery→0.9%
Singer et al^[29] REINFORCE Study 2018			
*Prospective study *177 patients (180 eyes) *12 months	DME	IOP > 35 mmHg →2.8% (5 eyes); IOP > 25 mmHg →12.2% (22 eyes); > 10 mmHg increase from the baseline→12.8% (23 eyes).	IOP-lowering medication→22.8% (41 eyes); Glaucoma surgery→ 0%
Choi et al^[30] 2018			
*Retrospective study *503 patients (540 eyes) *12 months	RVO (54.6%), DME (30.6%), NIU (8.5%), and others (6.3%)	IOP > 35 mmHg→1.7% (9 eyes); IOP > 25 mmHg→10.6% (57 eyes); > 10 mmHg increase from the baseline→11.3% (61 eyes).	IOP-lowering medication→10.9% (59 eyes); Glaucoma surgery→ 0.2% (1 eye)
Malclès et al^[31] SAFODEX Study 2017			
*Retrospective study *361 patients (421 eyes) *16 months	RVO (34%), DME (30%), postsurgical ME (17%), NIU (14%), and others (5%)	IOP > 35 mmHg→6% (24 eyes); IOP > 25 mmHg→20% (85 eyes); > 10 mmHg increase from the baseline →28.5% (120 eyes).	IOP-lowering medication→ 31% (129 eyes); Glaucoma surgery→0.7% (3 eyes)
Eter et al^[32] German Ozurdex in RVO Real World Study Group 2017			
*Prospective study *573 patients *6 months	RVO	IOP > 25 mmHg→58.7% (at week 6), 38.7% (at week 12), and 17.3% (at week 24)	IOP-lowering medication→ 7.3% (at baseline), 16.6% (during study); Glaucoma surgery→ 0%
Maturi et al^[33] Ozurdex MEAD Study Group 2016			
*Randomized-controlled *347 patients *3 years	DME	IOP > 35 mmHg→6.6%; IOP > 25 mmHg→32%; > 10 mmHg increase from the baseline→27.7%.	IOP-lowering medication→41.5%; Glaucoma surgery→0.9%; *Trabeculectomy→0.6% (2 eyes); *Iridectomy→0.3% (1 eyes)
Lam et al^[34] Ozurdex CHROME Study Group 2015			
Retrospective study *101 patients (120 eyes) *6 months	DME (<i>n</i> = 34), RVO (<i>n</i> = 30), NIU (<i>n</i> = 23), others (<i>n</i> = 14)	IOP > 35 mmHg→2.9% in DME, 4.3% in NIU, and 6.7% in RVO; IOP > 25 mmHg→26.5% in DME, 17.4% in NIU, and 26.7% in RVO	IOP-lowering medication→29.4% in DME, 8.7% in NIU, and 16.7% in RVO; Glaucoma surgery→1.7% (2 eyes)
Mazzarella et al^[35] 2015			
*Retrospective study *85 patients (92 eyes) group 1 (<i>n</i> = 65) no history of glaucoma); group 2 (<i>n</i> = 27) previously diagnosed with glaucoma or ocular hypertension) *6 months	DME (<i>n</i> = 34 eyes), RVO (<i>n</i> = 31 eyes), others (<i>n</i> = 27 eyes)	IOP > 21 mmHg→32.6% (30 eyes); group 1→21.5% (14 eyes); group 2→59.3% (16 eyes).	IOP-lowering medication→32.6%; group 1→12.3% (8 eyes); group 2→100.0% (27 eyes); Glaucoma surgery: group 1→ 0%; group 2→ 3.3% (1 eye)
Capone et al^[36] Ozurdex SHASTA Study 2014			
*Retrospective study *289 patients (289 eyes) *6 months	RVO	IOP > 35 mmHg→ 9.4% (27 eyes); IOP > 25 mmHg→ 33.7% (97 eyes); > 10 mmHg increase from the baseline→ 32.6% (91 eyes).	IOP-lowering medication→ 29.1% (84 eyes); Glaucoma surgery→1.7% (5 eyes)
Guigou et al^[37] MOZART Study 2014			
*Retrospective study *74 patients *6 months	DME	IOP > 25 mmHg →13.4%	Glaucoma surgery→ 0%
Gillies et al^[38] the BEVORDEX Study Group 2014			
*Prospective study *46 eyes *12 months	DME	> 10 mmHg increase from the baseline→19.6% (9 eyes); IOP > 25 mmHg →26% (12 eyes) (during the follow-up)	IOP-lowering medication→ 26% (12 eyes); Glaucoma surgery→ 0%
Callanan^[39] Ozurdex PLACID Study Group 2013			
*Randomized-controlled *126 patients *12 months	DME	IOP > 35 mmHg→4% (5 eyes); IOP > 25 mmHg→16.8% (21 eyes); Increase of > 10 mmHg from the baseline→15.2% (19 eyes).	IOP-lowering medication→15.9% (20 eyes); Glaucoma surgery→ 0%
Boyer et al^[40] Ozurdex CHAMPLAIN Study Group 2011			
*Prospective study *55 patients *6 months	DME (vitrectomized eyes)	IOP increase→ 16% (9 patients); IOP > 35 mmHg → 2% (1 patient) (at week 8); IOP > 25 mmHg → 9% (5 patients) (at week 8).	IOP-lowering medication→ 17% (8 patients); Glaucoma surgery→ 0%
Lowder et al^[41] Ozurdex HURON Study Group 2011			
*Randomized-controlled *77 patients *6 months	NIU	IOP > 35 mmHg → < 5% IOP > 25 mmHg→ 7.1%	IOP-lowering medication→ < 23%; Glaucoma surgery→ 0%

Haller et al ^[42] GENEVA Study Group 2011			
*Randomized-controlled *421 patients *12 months	RVO	Patients who received two IDI ($n = 341$); > 10 mmHg increase from the baseline→32.8% (during the study); *After the first injection > 10 mmHg increase from the baseline→12.6% (at 60 days); *After the second injection → > 10 mmHg increase from the baseline→15.4% (at 60days)	IOP-lowering medication→25.9%; Glaucoma surgery→1.4%;

IOP: intraocular pressure; IDI: intravitreal dexamethasone implant; DME: diabetic macular edema; RVO: retinal vein occlusion; NIU: non-infectious uveitis.

after the implantation. They stated that increased IOP was mostly controlled by the topical IOP-lowering medication and surgical treatment was required in only four patients. Similar to SAFODEX study^[31], the authors also stated that the patient's lens status (pseudophakic or phakic eyes) had no effect on IOP.

In the CHAMPLAIN study^[40] in which the effect of the IDI was evaluated in vitrectomized eyes, the authors reported an IOP elevation in 16% of the eyes and the rate of patients who had an IOP elevation (> 25 mmHg) peaked at week eight (9%), but decreased to 0% at week 26 following the injection. In addition, they stated that the increase in IOP could be controlled by IOP-lowering medications and no patients required surgical intervention. This study shows that peak time of IOP elevation in vitrectomized eyes is similar to non-vitrectomized eyes after the injection.

Mazzarella *et al*^[35] examined the effect of IDI on IOP in ME patients. The patients were divided into two groups; group 1 (no history of OHT or glaucoma) and group 2 (preexisting glaucoma or OHT). Before the injection, all patients in group 2 were under IOP-lowering medication and had a controlled IOP. The authors reported that the percentages of patients who had an IOP higher than 21 mmHg were 21.5% in group 1 and 59.3% in group 2. The authors reported that the risk of IOP elevation was higher in patients who had a history of glaucoma or OHT. They suggested that the IOP elevation was temporary and only one patient with neovascular glaucoma required glaucoma surgery. As in the SAFODEX study^[31], CHAMPLAIN study^[40], and GENEVA study^[42], Mazzarella *et al*^[35] also reported an IOP peak of two months after the IDI administration. Although the IOP elevation response to topical steroid treatments is more frequent in children than adults^[43], the percentages of the patients with childhood uveitis who developed IOP elevation, requiring IOP-lowering medication and surgical intervention are similar to adult uveitis patients. In an adult study, Lowder *et al.* (HURON study)^[41] reported that less than 10% of patients had a moderate (> 25 mmHg) IOP elevation and less than 23% of patients required IOP-lowering medication during the study period. In a pediatric study conducted by Sella *et al*^[44], the authors investigated safety and effectiveness of IDI in pediatric uveitis, they reported a transient IOP elevation in two eyes (2/14, 14%) at week 4 following the injection and they stated that both patients were treated with IOP-lowering medications and IOP was normalized within 6 months. In another pediatric study on uveitis conducted by Tomkins-Netzer *et al*^[45], four eyes (4/22) had IOP of > 25 mmHg. Of these, three patients were treated successfully with IOP-lowering medication. One case with previous glaucoma surgery required a surgical revision.

CONCLUSIONS

As clinical evidence is growing with each passing day, dexamethasone implant related IOP elevation is considered as usually transitory and also manageable with temporarily prescribed anti-glaucomatous medications. Glaucoma surgery is advised only in a very small number of patients. However, the risk of IOP elevation is higher in patients who had preexisting glaucoma or OHT. Patients

having risk factors for IOP elevation should be closely monitored to detect possible IOP rise.

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