Local Safety Concerns of Repited Dexamethasone Intravitreal Implant (Ozurdex®) For Macular Diseases

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Abstract: *Introduction*: The objective of the present study was to analyze the expanding indications for the dexamethasone intravitreal implant (Ozurdex®) in macular edema of varied diseases, and determine its safety concerns.

Materials and Methods: We retrospectively reviewed the ophthalmic charts of patients treated with at least one intravitreal injection of Ozurdex® since April 2010 to October 2011. Data regarding complications of the procedure as well as the need for cataract surgery were collected. No patient with the diagnosis of glaucoma was included in the present study. Early recurrences where treated with laser photocoagulation or intravitreal ranibizumab at the discretion of the physician; late recurrences where treated with a new Ozurdex® injection.

Results: The causative diseases of ME in the 214 eyes of our sample were: diabetic macular edema (101 eyes of 84 patients); branch retinal vein occlusion (27 eyes of 27 patients with superior temporal branch occlusion; 6 eyes of 6 patients with inferior temporal branch occlusion); central retinal vein occlusion (23 eyes of 23 patients); uveitic macular edema (13 eyes of 11 patients). Patients with other indications such as exudative age-related macular degeneration (27 eyes of 27 patients), and pseudophakic cystoid macular edema (7 eyes of 7 patients). Regarding complications, we found a rate of posterior cataract progression in 69.6% of phakic eyes after receiving a second intravitreal Ozurdex® for the treatment of ME. A significant IOP increase was evidenced in 21.18% of cases following the first Ozurdex® implant. Patients with uveitic macular edema (UME) showed the greatest rate of IOP increase (53.86%) following Ozurdex® implant. In addition, anterior chamber migration of the Ozurdex® implant was seen in 2 cases with lens posterior capsule rupture.

Discussion: This is a descriptive study of 214 eyes of 189 patients treated with intravitreal Ozurdex® in real-life conditions, which adds an important value for the retinal physicians. Further long-term studies are warranted in order to establish a more accurate safety profile of Ozurdex® for retinal diseases.

Keywords: Cataract, Dexamethasone Intravitreal Implant, Macular Diseases, Macular Edema, Ocular Hypertension, Ozurdex®, Safety.

INTRODUCTION

Macular edema (ME) is believed to be due to abnormal retinal capillary permeability, manifesting by retinal swelling in and around the macula. The common pathological processes leading to extravascular swelling of the macula involve several inflammatory cytokines, growth factors, intercellular adhesion molecules and other anatomical considerations. All these contribute to an increase in the vascular permeability, breakdown in the blood-retinal barrier, remodelling of the extracellular matrix, and upregulation of proangiogenic factors [1-5].

Macular edema can occur in association with a variety of underlying retinal disorders like diabetes [6], vein occlusion [7], uveitis [8], pseudophakic cystoid macular edema [9], and other less prevalent entities. In all these diseases, macular edema is a leading cause of vision loss.

The main current medical therapeutic approaches for ME are laser photocoagulation, periocular or intravitreal triamcinolone, and intravitreal antiangiogenic agents such as ranibizumab, pegaptanib or the off-label drug bevacizumab. Recently, a new intravitreal sustained-release dexamethasone implant has become available (Ozurdex®, Allergan, Inc, Irvine, CA); the implant is composed of a biodegradable copolymer of lactic acid and glycolic acid containing micronized

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dexamethasone. This drug-copolymer gradually releases the total dose of 0.7 mg of dexamethasone after insertion into the vitreous using a customized applicator system with a 22 gauge injector [10].

The objective of our study was to analyze the expanding indications for the dexamethasone intravitreal implant (Ozurdex®) in macular diseases, and determine its safety concerns.

MATERIALS AND METHODS

We retrospectively reviewed the ophthalmic charts of patients treated with at least one intravitreal injection of Ozurdex® since April 2010 to October 2012 in the Department of Ophthalmology of the University and Polytechnic Hospital La Fe of Valencia (Spain). Data regarding complications of the procedure as well as the need for cataract surgery were collected. No patient with the diagnosis of glaucoma was included in the present study.

Prior to each treatment, the eye was anesthesized with 0.4 cc of a peribulbar injection of bupivacaine 0.25% and mepivacaine 2%. The Ozurdex® implant was inserted in accordance with the manufacturer's instructions using the 22 gauge applicator system (http://www.allergan.com/assets/pdf/ozurdex_pi.pdf), with a personal modification consisting of pressuring firmly down the sclera with a cotton swab, which makes easier the penetration of the needle and may make suitable a beveled "self-sealing" sclerotomy. Therafter a new application of povidone iodine and gentamicin ointment were administered.

Through the follow-up, recurrence of ME was considered as macular thickness increase with BCVA decrease compared to the prior visit. We divided theses recurrences in early –before 6 months after Ozurdex® injection-, and late –after 6 months after Ozurdex® injection-. Early recurrences where treated with laser photocoagulation or intravitreal ranibizumab at the discretion of the physician; late recurrences where treated with a new Ozurdex® injection.

RESULTS

The causative diseases of ME in the 214 eyes of our sample were: diabetic macular edema (101 eyes of 84 patients); branch retinal vein occlusion (27 eyes of 27 patients with superior temporal branch occlusion; 6 eyes of 6 patients with inferior temporal branch occlusion); central retinal vein occlusion (23 eyes of 23 patients); uveitic macular edema (13 eyes of 11 patients). Patients with other indications such as exudative age-related macular degeneration (27 eyes of 27 patients), pseudophakic cystoid macular edema (7 eyes of 7 patients), and other uncommon diagnosis were excluded from this safety assessment study.

Diabetic Macular Edema (DME)

The mean age of the patients with DME included in the study was 65.4 (standard deviation: 10.4), with 54.9% males, and 63.9% pseudoaphakic. All eyes had previously received macular laser photocoagulation –at least one session-; intravitreal injections of ranibizumab (72.3% of eyes; median number: 2; range: 1-9), 4mg triamcinolone acetonide (14.85% of eyes; median number: 1; range: 1-3), or 0.4mg dexamethaseone phosphate (28.71% of eyes; median number: 1; range: 1-4). No vitrectomized patient was identified within the study sample of cases with DME.

We evidenced an ocular hypertensive response in 13.86% of eyes, with a range of intraocular pressure (IOP) of 29-42 mmHg. The peak of IOP was registered between weeks 11 and 18 after the Ozurdex® implant. In all these cases topical medications was enough to control de IOP.

Fifteen eyes received a second Ozurdex® intravitreal implant. Within this sample, 57.14% of the phakic cases (4 of 7 eyes) showed a marked progression of posterior capsular lens opacities conditioning the visual improvement, and all of them were scheduled for cataract surgery. Patients with ocular hypertensive response after the first implant received prophylactic topical hypotensive medications to avoid a new IOP peak. No case without this response after the first implant showed significant IOP increases after the second implant.

No systemic adverse event was recorded following any of the Ozurdex® intravitreal implant. However, we registered two cases of severe intraocular sterile inflammation which on one of the eyes induced tractional retinal detachment resulting in amaurosis; and we also registered one case of anterior chamber migration in patient with angle-support anterior chamber intraocular lens, resulting in bullous keratopathy secondary to the endothelial trauma despite the explant of the Ozurdex® device.

Branch Retinal Vein Occlusion (BRVO)

The mean age of the patients with BRVO included in the study was 72.4 (standard deviation: 8.4), with

53.9% males, and 61.5% pseudoaphakic. The following therapies had been previously administered in these cases: 44.6% had previously received macular photocoagulation; 100% had previously received intravitreal injections of ranibizumab (median number: 4.5; range: 2-7), and 38.4% of 0.4mg dexamethasone phosphate (median number: 1.5; range: 1-3). No vitrectomized patient was identified within the study sample of cases with DME.

We evidenced an ocular hypertensive response in 24.24% of eyes, with a range of intraocular pressure (IOP) of 27-39 mmHg. The peak of IOP was registered between 4 and 15 weeks after the Ozurdex® implant. In all these cases topical medications was enough to control de IOP.

Five eyes received a second Ozurdex® intravitreal implant. Within this sample, 75.0% of the phakic cases (4 of 5 eyes) showed a marked progression of posterior capsular lens opacities conditioning the visual improvement, and all of them were scheduled for cataract surgery.

No systemic adverse event was recorded following any of the Ozurdex® intravitreal implant. We registered one case of anterior chamber migration in a patient with iris-claw anterior chamber intraocular lens, resulting in a bullous keratopathy which made necessary a keratoplasty.

Central Retinal Vein Occlusion (CRVO)

The mean age of the patients with CRVO included in the study was 68.3 (standard deviation: 14.9), with 47.8% males, and 65.2% pseudophakic. The following therapies had been previously administered in these cases: 100% had previously received intravitreal injections of ranibizumab (median number: 4; range: 1-10), 17.4% 4mg triamcinolone acetonide, and 40.7% of 0.4mg dexamethasone phosphate.

We evidenced an ocular hypertensive response in 21.21% of eyes, with a range of intraocular pressure (IOP) of 29-46 mmHg. The peak of IOP was registered between weeks 3 and 19 after the Ozurdex® implant. In all these cases topical medications was enough to control de IOP.

Nine eyes received a second Ozurdex® intravitreal implant. Within this sample, 66.7% of the phakic cases (4 of 6 eyes) showed a marked progression of posterior capsular lens opacities conditioning the visual improvement, and all of them were scheduled for cataract surgery.

No systemic adverse event was recorded following any of the Ozurdex® intravitreal implant in patients with CRVO.

Uveitic Macular Edema (UME)

The mean age of the patients with UME included in the study was 62.8 (standard deviation: 10.6), with 36.4% males, and 18.2% pseudophakic. No intravitreal therapy had been administered in any case prior to the Ozurdex® implant. All cases were under immunosuppressive therapy to control intraocular inflammation and macular edema (adalimumab, cyclosporine, methotrexate).

We evidenced an ocular hypertensive response in 53.86% of eyes, with a range of intraocular pressure (IOP) of 31-58 mmHg. The peak of IOP was registered between weeks 7 and 15 after the Ozurdex® implant. In all these cases topical medications was enough to control de IOP.

Six eyes received a second Ozurdex® intravitreal implant. Within this sample, 80.0% of the phakic cases (4 of 5 eyes) showed a marked progression of posterior capsular lens opacities conditioning the visual improvement, and all of them were scheduled for cataract surgery.

No systemic adverse event was recorded following any of the Ozurdex® intravitreal implant in patients with UME.

DISCUSSION

Macular edema is the leading cause of visual impairment in the main retinal diseases. Although intravitreal antiangiogenic agents, mainly ranibizumab, have been proven clearly superior to laser photocoagulation and intravitreal triamcinolone, one of the limiting factors related to their use is the short lifetime and therefore their transient effect on ME, and the need of numerous retreatments through the follow-up. This is the reason why new therapies may look for a new therapeutic target or for increase length of their activity.

Dexamethasone is a synthetic glucocorticoid with physiological effects 25 to 30 times greater than hydrocortisone [11-12]. In previous reports, the main limiting factor for its use was the short life-time [13-14]. Actually, the sustained-release system provided by Ozurdex® may extend the period of efficacy of dexamethasone inside the vitreous cavity. The questions is: could repeated injections of Ozurdex® be

associated with more local adverse reactions? According to our data the answer is definitely “yes”.

Overall, we found a rate of posterior cataract progression in 69.6% of phakic eyes after receiving a second intravitreal Ozurdex® for the treatment of ME. Previous short-term studies did not report this complication as far as only one injection was performed [15-16].

On the other hand, it is of particular interest to underline the anterior chamber migration of the Ozurdex® implant in 2 cases with lens posterior capsule violation, confirming the previous reports regarding the danger of injecting Ozurdex® in eyes with lack of posterior lens capsule integrity [17-18]. We believe that in these cases the indication of Ozurdex® should be completely avoided.

A significant IOP increase was evidenced in 21.18% of cases following the first Ozurdex® implant. Such cases may benefit of prohyplactic IOP-lowering medications in cases with need for further retreatments. We did not need to perform surgery in any of these cases given the excellent response to IOP-lowering topical drops. Patients with UME showed the greatest rate of IOP increase (53.86%) following Ozurdex® implant, so these cases may be closely monitored in order to early detect these IOP peaks.

Limitations of the present study include its retrospective uncontrolled non-comparative nature, the wide spectrum of previous treatments for ME in some of the patients included, and the lack of a determined endpoint with a large variety in the follow-up periods.

In summary, this is a descriptive study of 214 eyes of 189 patients treated with intravitreal Ozurdex® in real-life conditions, which adds an important value for the retinal physicians. Further long-term studies are warranted in order to establish a more accurate safety profile of Ozurdex® for retinal diseases.

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