Effectiveness of the Dexamethasone Intravitreal Implant for Treatment of Patients with Diabetic Macular Oedema

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Abstract

Diabetic macular oedema (DMO) is a leading cause of vision loss in the working-age population worldwide. Corticosteroid drugs have been demonstrated to inhibit the expression of both the vascular endothelial growth factor (VEGF) gene and other anti-inflammatory mediators, such as prostaglandins. Triamcinolone, fluocinolone and dexamethasone are the main steroids that have been studied for the treatment of macular oedema. Over the last few years, several studies have suggested an important role for dexamethasone in the management of DMO. The dexamethasone intravitreal implant (DEX implant) (Ozurdex®; Allergan, Inc., Irvine, CA) is a novel approach approved by the US Food and Drug Administration (FDA) and by the EU for the intravitreal treatment of macular oedema after branch or central retinal vein occlusion, and for the treatment of non-infectious uveitis affecting the posterior segment of the eye. We reviewed manuscripts that had investigated the pharmacokinetics, efficacy and safety of the DEX implant regarding DMO treatment.

Keywords

Refractory diabetic macular oedema, pathogenesis, inflammatory mediators, corticosteroids, dexamethasone intravitreal implant, implantable drug delivery system.

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Diabetic retinopathy (DR) is the leading cause of blindness among working-aged adults around the world.[1] Despite the significance of this problem, and the rising prevalence of diabetes, notably in emerging Asian countries, such as India and China,[2,3] there are few precise contemporary estimates of the worldwide prevalence of DR, particularly severe vision-threatening stages of the disease, including proliferative DR (PDR) and diabetic macular oedema (DMO).

Yau et al. provided a global estimate of the prevalence of DR and the severe stages of DR (PDR, DMO) using individual-level data from population-based studies worldwide.[4] On the basis of the data from all 35 studies on more than 20,000 participants with diabetes, they estimated that among individuals with diabetes, the overall prevalence of any DR was 34.6 %, PDR was 7.0 %, DMO was 6.8 % and VTDR was 10.2 %.

DR is a highly specific vascular complication of both type 1 and 2 diabetes, with prevalence strongly related to the duration of diabetes.[5] In addition to the duration of diabetes, factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycaemia,[6] nephropathy[7] and hypertension.[8] Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomised studies to prevent and/or delay the onset and progression of DR.[9–11] Lowering blood pressure has been shown to decrease the progression of retinopathy.[12]

DMO is a frequent complication of DR and the most common cause of vision loss in patients with diabetes. Left untreated, up to 33 % of patients with DMO will experience moderate vision loss.[13] Laser photocoagulation has been considered, for a long time, as the main treatment option for DMO, based on the results of the Early Treatment Diabetic Retinopathy Study (ETDRS) clinical trial.[14] Focal laser treatment reduced the risk of moderate visual loss in patients with DMO by 50 %.[15]

In more recent studies that involved only patients with DMO-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.[16–17]

In DMO, 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 DMO.[18–20] The pathological processes leading to MO involve numerous inflammatory cells, cytokines, growth factors and intercellular adhesion molecules, which are associated with increased vascular permeability, breakdown of the blood–retinal barrier, remodelling of the extracellular matrix and upregulation of proangiogenic factors.[19–22]

Actually, studies suggest that the expression of vascular endothelial growth factor (VEGF) is elevated in DMO.[22–24] This has recently been confirmed by randomised clinical trials, which led to considering intravitreal anti-VEGF as a valuable treatment option for DMO.[25,26]

Nevertheless, some patients can be refractory to both macular laser photocoagulation and intravitreal anti-VEGF treatment. Indeed, MO refractory to laser photocoagulation remains the most prevalent cause of untreatable vision loss in diabetes.[27–28] The lack of an effective therapeutic solution accounts for the range of interventions proposed, prior to the appearance of the dexamethasone intravitreal implant (DEX implant). These included intraocular delivery of corticosteroids and anti-VEGF antibodies, as well as the surgical alternative of vitrectomy with or without removal of the internal limiting membrane (ILM).[29–33]

Dexamethasone is a potent corticosteroid and suppresses inflammation by inhibiting oedema, fibrin deposits, capillary leakage and phagocytic migration.[34] Glucocorticoids such as dexamethasone exert their anti-inflammatory effects by influencing multiple signal transduction pathways, including VEGF.[34–37] By binding to cytoplasmic glucocorticoid receptors, corticosteroids in high doses increase the activation of anti-inflammatory genes, whereas at low concentrations, they have a role in the suppression of activated inflammatory genes.[35–38] Therefore, a drug-release profile that consists of an initial phase of high concentration of dexamethasone, followed by a second phase of lower concentration, may continue to contribute to the anti-inflammatory action of dexamethasone for the duration of the implant.

The dexamethasone implant (Ozurdex®; Allergan, Inc., Irvine, CA) is a novel approach approved by the US Food and Drug Administration (FDA) and by the EU for the intravitreal treatment of MO after branch or central retinal vein occlusion, and for the treatment of non-infectious uveitis affecting the posterior segment of the eye.[39] However, there is evidence for efficacy in multiple clinical situations, including DMO MO associated with uveitis or Irvine-Gass syndrome, DMO in vitrectomised eyes, persistent MO and non-infectious vitritis.[23–30,39–46] Compared with published data addressing other routes of administration of dexamethasone analogues, several results demonstrate a few advantages of this implant (see *Table 1*).

Implantable Drug-delivery Systems

Therapeutic levels, minimum inhibitory concentrations, pharmacokinetics, the blood–brain barrier and patient adherence are just some of the obstacles associated with the traditional topical and systemic administrations of medicine.[47] Even intravitreal injections, long favoured for posterior segment disease, fall short. In fact, molecules injected into the vitreous have a brief intraocular half-life.[48]

Recently, intravitreal sustained delivery-drug devices were introduced to allow corticosteroids to be delivered in a slow, sustained manner to optimise the efficacy and safety of treatment and reduce the number of intravitreal injections a patient may require. [49–51]

In accordance, implants have already proved themselves in inflammatory diseases.[50] Actually, a wide array of chronic illnesses stand to gain from implant delivery, which is advantageous, given the ageing population of most societies.[51,52]

Reservoir Implants

Although reservoir implants require surgical placement or replacement, simplicity, longevity and steady-state pharmacokinetics are their benefits.

Vitrasert. Approved in early 1996 for the treatment of AIDS-related cytomegalovirus retinitis, this implantable was a form of ganciclovir.[53] There were limited ocular complications and the efficacy far exceeded the standard of care, which was the same drug, ganciclovir, administered intravenously. Surgically implanted through a 5.5 mm pars plana incision, Vitrasert lasts 5 to 8 months. With the advent of more potent combination therapies for HIV infection, however, opportunistic infections were more easily controlled or prevented, and so the need for Vitrasert waned.[54,55]

Retisert. The next generation of implant, Retisert, achieved even better targeted delivery and duration.[56,57] Sutured to the sclera after surgical implantation through a 3.5 mm pars plana incision, Retisert releases fluocinolone acetonide and lasts about 30 months.[58] However, that duration comes with the downside of ocular side effects. Although FDA-approved in 2005 for non-infectious uveitis after achieving dramatically reduced recurrence of uveitis, the toxicities were considered too much for patients with DMO. Studies emphasised that the risk of cataract was upward of 90 % with Retisert.[58,59] On the other hand, the risk of glaucoma is about 50 % with a Retisert implant, and about a third of those patients end up needing surgery because the glaucoma cannot be controlled with medication alone.

Iluvien. This is an injectable, non-degradable intravitreal implant for the treatment of DMO.[60,61] Iluvien is designed to release the drug fluocinolone acetonide for up to 3 years.[61,63] The device is small enough to be injected into the back of the eye with a 25-gauge needle, creating a self-sealing hole. Due its non-biodegradability, it is necessary to surgically remove the implant 3 years later. Recently, Iluvien was approved for DMO in several European countries, receiving marketing authorisation in the UK, Austria, France, Germany, Portugal and Spain. These marketing authorisations followed a positive outcome of the European Decentralised Procedure.

Biodegradable Implants

Although biodegradable implants are newer, they offer the prospect of certain benefits over reservoir systems, such as the lack of need for removal and a reduced potential for ocular toxicity. Biodegradable implants are more easily tailored by modifying polymer chemistry to change release rates and accommodate different drugs.

Surodex. The first sustained-release biodegradable steroid implant, this device was placed behind the iris for postoperative inflammation after cataract surgeries.[64] A market did not materialise, however, because Medicare would not reimburse for its placement during cataract surgery.

Ozurdex. Inserted surgically in the operating room or with a special injector, this device secured FDA approval for Allergan in June of 2009 for MO caused by vein occlusion.[39] Called Posurdex during testing, the FDA required a name change for the version distributed in the US. Now called Ozurdex, this implant is a biodegradable copolymer in pellet form that hydrolyses to lactic and glycolic acids, releasing 700 µg over 6 months. Because it is a more water-soluble steroid than triamcinolone or fluocinolone acetonide, Ozurdex may be able to control several retinal diseases without causing as many ocular complications.[39–52]

Dexamethasone Intravitreal Implant

Dexamethasone has the highest relative strength of any corticosteroid used in ophthalmic practice, with an anti-inflammatory activity that is sixfold greater than that of triamcinolone and 30-fold greater than

Table 1: Clinical Studies Published Up to Now, Regarding Dexamethasone Intravitreal Implant in Diabetic Macular Oedema

Author, Year (Reference)	Purpose	Study Design	Outcomes Measures	Type of DMO	Duration	Number of Study	Results of Eyes
Dutra Medeiros 2014[83]	DEX implant for DMO	Retrospective interventional case series	FT BCVA	Refractory	6 months	58	Both FT and BCVA improved from baseline by 1 month. The improvement remained statistically significant throughout the 6-month study. The peak effectiveness was seen at 3 months, when FT had decreased by 37 %, and BCVA improved to 0.44±0.27 logMAR
Pacella 2013[82]	DEX implant for DMO	Prospective interventional case series	FT BCVA Retinal structure	Refractory	6 months	20	Substantial improvement in BCVA and FT from day 3. The peak efficacy of the implant appears to be reached at month 1 through to month 3. It then slowly decreases from month 4 to 6
Callanan PLACID Study Group 2013[79]	DEX implant with laser photocoagulation compared with laser alone for DMO	Randomised, controlled, multicentre, double-masked	BCVA Fluorescein leakage	Diffuse DMO	12 months	253	No significant between-group difference at month 12. Significantly greater improvement in BCVA up to 9 months occurred in patients with diffuse DMO treated with DEX implant plus laser, than in patients treated with laser alone
Rishi 2012[81]	DEX implant for DMO	Retrospective interventional case series	FT BCVA	Refractory	5 months	18	The maximum reduction in FT was seen at month 1 followed by reappearance of DMO at month 4. The peak effect of the drug was between 1 and 4 months
Zucchiatthi 2012[80]	DEX implant for DMO	Retrospective interventional case series	FT BCVA	Refractory	6 months	9	Improvement in BCVA and FT as soon as the first days after the injection. Such improvement maintained until month 4
Boyer CHAMPLAIN Study Group 2011[41]	DEX implant for DMO	Randomised, controlled, multicentre, double-masked	FT BCVA	DMO in vitrectomised eyes	26 weeks	315	Both FT and BCVA improved from baseline by 1 week after treatment with a DEX implant. Improvement remained statistically significant throughout the 26-week study. The peak effectiveness of DEX implants was seen at week 8 to week 13
Haller 2010[40]	DEX implant (700 µg or 350 µg) for DMO		BCVA FT Fluorescein leakage	Persistent MO ≥90 days despite treatment)	6 months	171	DEX implant of 700 µg produced significant improvement in BCVA, FT and fluorescein leakage compared with observation (statistically significant at day 90)
Kuppermann 2007[46]	DEX implant (700 µg or 350 µg) for patients with DMO, vein occlusion, uveitis or Irvine-Gass syndrome MO		BCVA FT Fluorescein leakage	Persistent MO (≥90 days despite treatment)	6 months	315	At day 90 (primary end point), an improvement in BCVA of 10 letters or more was achieved by a greater proportion of patients treated with DEX implant, 700 µg (35%) or 350 µg (24 %). An improvement in BCVA of 15 letters or more was achieved in 18 % of patients treated with DEX implant, 700 µg, versus 6 % of observed patients

BCVA = best corrected visual acuity; DEX = dexamethasone intravitreal; DMO = diabetic macular oedema; FT= foveal thickness. Refractory MO = refractory DMO was defined as persistent MO with FT more than 250 µm by spectral-domain optical coherence tomography (OCT), lasting for at least 90 days after laser or intravitreal anti-vascular endothelial growth (VEGF)/steroid treatment.

cortisol.[65] A single dose of 0.18 mg/ml dexamethasone is equivalent to 1 mg/ml triamcinolone in terms of corticosteroid efficacy and is short-acting, with faster clearance from the vitreous.[66] As stated above, 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. In the DEX implant, the active drug is dispersed through a biodegradable copolymer of lactic acid and glycolic acid (PLGA), forming a matrix structure (Novadur®, Allergan Inc).[67] These polymers have been used in a number of products, including absorbable sutures.[68,69] For several years, PLGA has been used to prepare nanoparticles and microparticles for intraocular drug delivery. These drug delivery systems have been tested in animal models and humans.[70–73]

Experience has shown that PLGA is biocompatible and, inside the eye, is metabolised into carbon dioxide and water. Thus, sequential implants can be placed in an office setting without the need for surgical removal.[74]

A study in monkeys demonstrated that DEX is present at measurable levels in the vitreous and retina up to 6 months after intravitreal DEX implant injection.[42] The implant is made of a solid biodegradable polymer that enables dual-phase pharmacokinetics. Ozurdex allows sustained delivery of dexamethasone to the vitreous cavity, initially releasing a burst of dexamethasone to rapidly achieve a therapeutic concentration followed by a lower sustained release. In the first phase, the concentration of DEX in both tissues was high from 7 days to 2 months after placement of the implant, with the peak concentration of DEX achieved in the retina at two months. 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.[42] This biphasic pharmacokinetic profile resembles that obtained with the systemic pulse administration of corticosteroids 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.[41] This may have beneficial effects in facilitating the removal of inflammatory mediators from the retina, but it also leads to more rapid clearance of some drugs, including triamcinolone acetonide (TA), from the vitreous, and may limit the effectiveness of these drugs in vitrectomised eyes.

In the early clinical studies, the DEX implant was surgically implanted into the vitreous cavity via a pars plana incision.[40,46] Subsequently, a single-use, sutureless dexamethasone posterior-segment drug-delivery system (DDS) applicator was developed, allowing injection of the DEX implant in the office, rather than in a surgical setting.[64]

Clinical Studies

Comparison Between Two Doses of Dexamethasone Intravitreal Implant

Kuppermann et al. evaluated the efficacy and safety of two doses of DEX implant in the treatment of persistent ME of various aetiologies, in a 6-month, multicentre, randomised clinical phase II study.[46] The 315 patients in the trial had persistent MO due to either DR (n=172), RVO (n=102), Irvine-Gass syndrome (n=27), or uveitis (n=14). In each patient, one eye was randomised to treatment with 350 µg versus 700 µg versus observation.

Implantation resulted in a statistically significant increase in patients gaining two and three lines or more of visual acuity in a dose-dependent fashion at 90 and 180 days compared with observation ($p<0.025$). The percentages of patients who gained two or more lines of visual acuity 180 days after implantation were 32.4 % in the 700 µg group, 24.3 % in the 350 µg group and 21 % in the observation group ($p=0.06$). The percentages of patients who gained three or more lines of visual acuity 180 days after implantation were 18.1 % in the 700 µg group, 14.6 % in the 350 µg group and 7.6 % in the observation group ($p=0.02$). The visual acuity improvements achieved with the 700 µg implant were consistent across all subgroups at day 90.

In this sample, the DEX implant was well tolerated and had a favourable safety profile. The incidence of a ≥10 mmHg increase in intraocular pressure (IOP) from baseline was 3 % in the observation group, 12 % in the 0.35 mg dexamethasone implant group and 17 % in the 0.7 mg dexamethasone implant group. No significant between-group differences were found in the number of reports of cataract. However, treatment-related cataract formation may take longer than 180 days to become apparent.

Subgroup analysis of results in the patients with DMO showed that best corrected visual acuity (BCVA) improved more in patients treated with DEX implant than in untreated patients. Haller et al.[40] demonstrated that, in eyes with DMO treated with dexamethasone intravitreal drug delivery 0.7 mg, BCVA and foveal thickness (FT) significantly improved at 3 months compared with the observation group. Interestingly, they found that BCVA improvement was no longer significant at 6 months. Unfortunately, this randomised trial did not investigate the corresponding change in FT at the same time-point. Interestingly, in the subset of patients with DMO, an improvement in BCVA of ≥10 letters at day 90 was observed in 33.3 % of patients treated with the 0.7 mg DEX implant compared with 12.3 % of patients in the observation group. Among patients with diabetes, this significant difference was maintained when patients were stratified according to their pattern of DMO, i.e. focal, diffuse, cystoid and both cystoid and diffuse.[75] Overall, the pattern of adverse events seen in these subpopulations was similar to that seen in the overall population of patients included in the phase II study.

Phase III randomised, multicentre, 3-year clinical studies to evaluate the long-term efficacy and safety of DEX implant in the treatment of DMO are ongoing.[76]

Comparison Between Vitrectomised versus Non-vitrectomised Patients

Pars plana vitrectomy (PPV) has been shown to be useful in the treatment of DMO in some patients.[41–44] The mechanism for the effect of vitrectomy on DMO may involve both the release of vitreomacular traction and increased diffusion of advanced glycation end products, VEGF and other cytokines away from the retina.[41,44] These findings suggest that sustained drug delivery with an implant could be particularly useful in vitrectomised eyes, thus enhancing and boosting the primary effect of vitrectomy.

PPV has also been shown to affect the intraocular concentration of TA after intravitreal injection in human eyes.[77,78] In a vitrectomised eye, the vitreous would be removed, and less-viscous liquid would fill the space, increasing intravitreal circulation. This pathophysiological process leads to a much faster corticosteroid absorption in the vitrectomised eye than in the normal eye. An implant that provides sustained drug release and is both safe and effective may be the best option for therapy.

Moreover, Chang-Lin et al. performed an earlier preclinical study examining the release of DEX from the DEX implant in a more-recent study was similar between non-vitrectomised and vitrectomised eyes in rabbit eyes.[44] These results suggest that DEX implants may be particularly useful in the treatment of inflammation and MO in vitrectomised eyes.

Boyer et al. undertook a prospective open-label study that assessed the efficacy and safety of the DEX implant in the treatment of chronic DMO in 56 patients with a history of PPV. In most cases, previous treatment had been attempted and had failed to resolve the DMO.[41] This trial in postvitrectomised eyes with persistent DMO (the CHAMPLAIN trial) was a 26-week open-label single Ozurdex injection trial. The study showed that 30 % of eyes had experienced a two-line improvement in BCVA by 13 weeks, although this effect diminished by the study endpoint of 26 weeks.

The peak effectiveness of the DEX implant was seen between 8 and 13 weeks after the injection. In this study, the efficacy of the DEX implant in reducing retinal thickness and improving BCVA in vitrectomised patients with DMO was similar to that seen in the subgroup of patients with DMO in the phase II study.[40] Actually, the DEX implant may be especially beneficial in the treatment of inflammation and ME in difficult-to-treat vitrectomised eyes.

Dexamethasone Intravitreal Implant as a Combination Therapy with Laser Photocoagulation

The DEX implant was also investigated as a combination therapy with laser photocoagulation in DMO patients in the PLACID trial.[79] The goal of the study was to evaluate the DEX implant 0.7 mg, combined with laser photocoagulation compared with laser alone for treatment of diffuse DMO. For this trial, 253 patients with retinal thickening and impaired vision resulting from diffuse DMO in at least one eye (the study eye) were enrolled.

Patients were randomised to treatment in the study eye with DEX implant at baseline, plus laser, at month 1 (combination treatment; n=26) or sham implant at baseline and laser at month 1 (laser alone; n=127). They could also receive up to three additional laser treatments and one additional DEX implant or sham treatment as needed.

The percentage of patients who gained 10 letters or more in BCVA at month 12 did not differ between treatment groups, but the percentage of patients was significantly greater in the combination group at month 1 ($p<0.001$) and month 9 ($p=0.007$). Increased IOP was more common with combination treatment. No surgeries for elevated IOP were required.

There was no significant between-group difference at month 12. However, significantly greater improvement in BCVA, as demonstrated by changes from baseline at various time-points up to 9 months, and across time based on the area under the curve analysis, occurred in patients with diffuse DMO treated with DEX implant, plus laser, than in patients treated with laser alone.

Interventional Case Series Studies

Most recently, four interventional case series studies evaluated the efficacy of a dexamethasone intravitreous drug-delivery system in persistent ME secondary to diabetes.[80-85]

In the first study, Zucchiatti et al.[80] showed that a single intravitreal injection of Ozurdex produced improvement in BCVA and FT in eyes with persistent DMO. Such improvement was evident from the third day to the first month after injection, peaked at the third month and was no more significant 6 months after the injection.

Analogously, Rishi et al.[81] undertook another retrospective study, enrolling 18 patients with refractory DMO. All patients experienced a significant reduction in FT compared with baseline levels at month 1. The maximum reduction in FT was seen at month 1, followed by reappearance of clinically significant MO at month 4. The peak effect of the drug was between 1 and 4 months.

In 2013, Pacella et al. performed a prospective interventional case series to assess the efficacy of DEX implant in patients with persistent DMO over a 6-month follow-up period.[82] Seventeen patients (20 eyes) affected by DMO were selected. Thirteen patients had also previously been treated with anti-VEGF medication. Ozurdex produced substantial improvement in BCVA and significant reduction of FT from day 3. The peak efficacy of the implant appears to be reached at month 1 through to month 3, then slowly decreases from month 4 to 6.

Similarly, we performed a retrospective interventional case series study to evaluate the effectiveness of a single intravitreal injection of Ozurdex, over 6 months in 58 patients with diabetes with persistent DMO.[83] The patient population included severe cases that had not responded to multiple previous therapies. Both mean FT and mean BCVA had improved from baseline by 1 month after treatment with a DEX implant, and the improvement remained statistically significant throughout the 6-month study. The peak effectiveness of DEX implants was seen at 3 months after injection when mean FT had decreased by 37 %. The mean BCVA improved to 0.44±0.27 logMAR from baseline. Our data were consistent with those results named previously.

Twenty-four patients had undergone PPV before entering in our sample. The improvement in FT and BCVA seen in this sample was similar to the improvement seen in the remaining non-vitrectomised patients with persistent MO. Our data were consistent with those from a recent analysis of the earlier publications addressing this matter.[41]

To our knowledge, there have been no differences on the relative effectiveness of dexamethasone implants in pseudophakic versus phakic eyes. Further studies will be needed to determine whether the effects of dexamethasone implants are affected by lens status.

The target population addressed in our trial was difficult to treat because it included severe cases of long-standing DMO that had failed to respond to therapy with PPV, focal laser and/or pharmacotherapy, (most commonly intravitreal injection of the corticosteroid TA or the anti-VEGF therapy). In fact, one-third of the patients had previously undergone triple therapy. In these cases, the potential for improvement in vision was likely limited by secondary functional and structural changes related to chronic oedema.

Conclusion

The treatment of DMO has evolved to encompass a combination of multi-target therapeutic approaches. In recent decades, corticosteroids have raised interest in the treatment of DMO due to their anti-

inflammatory effects and because they inhibit the synthesis of VEGF and reduce vascular permeability. However, due to safety concerns (i.e. IOP elevation and cataract progression), in the last few years the use of corticosteroids has been drastically reduced in most developed countries. Recently, the safety profile of Ozurdex, which is currently an approved treatment for retinal vein occlusion, has been reported in the GENEVA study.[39] In the series previously described, no major side effects were registered.[86] All these case studies cited above have several limitations, in that they were short-term, open-label, uncontrolled, retrospective or evaluate a small study population. These limitations preclude any estimation of the long-term efficacy or safety of intravitreal Ozurdex.

So far, a literature review indicates that the single-injection of the implant is well tolerated and produces meaningful improvements in MO and visual acuity that persist through 6 months. The available 6-month data also indicate that this implant confers much less of a risk of ocular hypertension than do other forms of intraocular steroid therapy. However, future longer-term trials are needed to evaluate the efficacy and safety data in patients who receive multiple injections.

All published studies provide evidence supporting the use of the DEX implant, Ozurdex, for treatment of either naïve or persistent DMO in the short and long term, given its efficacy, safety and ease of use in the outpatient setting. ■

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Erratum

The authors would like to make the following adjustment to the above mentioned article.

On page 68 and in the section titled "Iluvien" the sentence "Due its non-biodegradability, it is necessary to surgically remove the implant 3 years later" should be amended to "The implant does not need to be surgically removed once implanted."