Dexamethasone: a therapeutic perspective in diabetic macular edema during and beyond the COVID-19 pandemic

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Abstract: Intravitreal injections are useful in the management of diabetic macular edema (DME), but during the coronavirus disease 2019 (COVID-19) pandemic, it has become difficult because of low patient adherence. Dexamethasone (DEX) demonstrated good results when switched from Aflibercept, showing good effectiveness in the treatment of edema. Compliance was greater and depended on fewer injections with optimal anatomical and clinical results. This drug presented an important spectrum of action, because it can be used not only for the management of diabetes but also in other different situations such as: non-infectious posterior segment uveitis, central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) and after cataract surgery. Anti-vascular endothelial growth factor (anti-VEGF) is the first line of treatment, but Ozurdex could be considered a valid alternative for naïve patients or for patients who are refractive to treatment. Optical coherence tomography (OCT) and OCT angiography (OCTA) biomarkers represent a good system to follow the response and adhesion therapy. Biomarkers were used to evaluate the improvements in patients who were treated with DEX implant and who did not complete the anti-VEGF treatment, however during the COVID-19 pandemic the number of ophthalmic procedures decreased reserving treatment only for urgent and emergency cases. Anti-VEGF agents and corticosteroids are very effective in treating DME; however, there is still a proportion of patients with a sub-optimal response to medical treatment, so new therapeutic targets and new molecules will be necessary to grant a larger number of therapeutic alternatives.

Keywords: Corticosteroids; diabetic retinopathy; dexamethasone implant (DEX implant); switch during intravitreal injections; coronavirus disease 2019 (COVID-19)

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Introduction

Intravitreal injection is an important medication delivery system which acts on the retina and choroid (1). Dexamethasone (DEX; Ozurdex®, Allergan Pharmaceuticals, Irvine, CA, USA) is a long delivery system that has a 3–6 months action, the drug is released into the vitreous chamber after the implantation of a biodegradable capsule, but due to its limited duration of action, multiple injections are necessary to maintain the therapeutic effect (2,3). Ozurdex such as other corticosteroids has an anti-

inflammatory action that depends on its action against cytokines associated with a reduction of edema, fibrin deposition, inhibition of capillary leakage, and migration of inflammatory cells (4). This action is achieved by modulating the integrity of the tight junction and inhibiting different molecules that are involved in controlling inflammation and vascular permeability, related to stroma-derived factor 1 and vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), and intracellular adhesion molecule-1 (ICAM-1). DEX also acts on prostaglandins and leukotrienes blocking phospholipase A2, permeability of Muller cells and downregulating aquaporin 4. A reduction of vasoactive proteins (hepatocyte growth factor, pentraxin 3, persephin, endocrine gland-VEGF, and insulin-like growth factor binding proteins) was reported after DEX implant (5,6). It is used for the treatment of macular edema associated with different pathologies such as: diabetic retinopathy, non-infectious posterior uveitis, and central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) (4).

The use of Ozurdex during the coronavirus disease 2019 (COVID-19) pandemic

In 2019, Italy was one of the countries involved in decision-making related to coronavirus disease. In March, the Italian government established a quarantine to contain the spread of the infection. The measures were very restrictive limiting the possibility of going out to public places, visiting non-essential activities, and restricting access pharmacies and food markets. The hurdles presented by the COVID-19 pandemic, have heightened the likelihood of non-adherence to intravitreal therapy. Across the globe, several studies indicated a substantial decrease in adherence rates to intravitreal injection during the COVID-19 pandemic (7,8). An Italian study noted improved adherence rates among younger patients, those with poorer vision in the fellow eye, and during periods without lockdown restrictions (7). Carnevali *et al*. reported that during the widespread outbreak of COVID-19, hospitals reorganized their services, limiting assistance to urgent patients, while there was a suspension of non-urgent and surgical activities. This decision also affected the administration of anti-VEGF treatments because many patients refused to continue their treatment due to the fear of contracting COVID-19. Anti-VEGF often required multiple injections in a month, making Ozurdex, with its longer duration of action, a good alternative to maintain compliance. However, guidelines for this situation were lacking, so it was necessary to divide patients considering the gravity of their conditions, giving priority to more severe diseases (9). Timing played a crucial role in achieving positive outcomes in edema management. Therefore, even a slight delay in intravitreal injections, even in the short term, could result in a deterioration of optical coherence tomography (OCT) features and a decline in visual acuity. The creation of extended-release injections could alleviate the treatment burden and reduce the necessity for frequent visits linked to current anti-VEGF therapy (10). A study directed by Scorcia *et al*. evaluated patients who were treated with anti-VEGF and Ozurdex during the COVID-19 pandemic (11). This study resulted that was very difficult to treat patients with anti-VEGF, cause of minor compliance, but it was possible with Ozurdex, even if an evidence-based clinical practice guideline is not available (9,11). Since there is no clear line between elective and emergency surgery, different societies and experts share their recommendations for identifying "emergent and urgent" ophthalmologic procedures (9). The global COVID-19 pandemic has in fact resulted in many countries using very strict measures that limited the ability of patients to be treated with anti-VEGF and this difficult condition was published on Euretina by the Working Group on Medical Retina of the Netherlands Ophthalmological Society (9). The studies of Carnevali *et al*. and Brar *et al*., illustrate the importance of not delaying or reducing patient injections, as this may be associated with an increased risk of vision loss (9,10). While COVID-19-related morbidity and mortality led to a decline in ambulatory and surgical procedures, most hospitals reserved necessary treatments for emergency cases. In such circumstances, DEX could be a valid alternative for eyes treated previously with anti-VEGF as well as for eyes not previously treated (9,12-14). Many patients were selected for intravitreal injection through telephone consultations, evaluating their symptoms such as: fever and upper respiratory tract infection. Additionally, during any contact with infected persons, it was obligatory to evaluate temperature measurement and to perform a nasopharyngeal swab. Suspected or contagious cases were postponed until the swab results were negative, and an interval of 30 minutes was maintained between injections to prevent overcrowding (9). Long-term therapy became crucial for a better management of chronic patients, so switching from an anti-VEGF implant to a DEX implant yielded good results for patients who were unable to

Table 1 Priority level, disease, and procedure delay according to recommendations during COVID-19 outbreak

Priority level	Disease	Procedure delay	Treatment
High	Monocular patients	3–7 days max	Anti-VEGF or DEX
Moderate	nAMD, other MNVs	10–15 days max	Anti-VEGF
Low	DME, RVO	30–40 days max	Preferred DEX
	CSC with MNV	30–40 days max	PDT

Reproduced from Carnevali *et al.* (9). COVID-19, coronavirus disease 2019; VEGF, vascular endothelial growth factor; DEX, dexamethasone; nAMD, neovascular age-related macular degeneration; MNV, macular neovascularization; DME, diabetic macular edema; RVO, retinal vein occlusion; CSC, central serous chorioretinopathy; PDT, photodynamic therapy.

complete treatment with anti-VEGF (11,15). Scorcia *et al.* investigated the effect of the switch, evaluating functional and anatomic outcomes in patients with diabetic macular edema (DME). Patients who were switched to DEX after an incomplete treatment with aflibercept showed a significant improvement in anatomical outcomes (11). Carnevali *et al.* reported their experience during a COVID-19 outbreak for intravitreal injections in patients with maculopathy. They proposed a treatment plan based on priority levels: high, moderate, and low (*Table 1*) (9,14).

On the base of this classification was proposed that: high level included monocular patients whose treatment couldn't be delayed and should be performed within 3 to 7 days from the expected date; moderate was for patients with active neovascularization whose procedure should be performed within 10 to 15 days; and low in patients with DME or retinal vein occlusion (RVO) where treatment was expected to occur within 30–40 days. This patient management target was very interesting as during the lockdown and the percentage of DEX implants for DME and RVO treatment increased from the same period in 2019 (9). The intraocular pressure (IOP) was checked between 6 and 8 weeks and this was very useful to evaluate efficacy and safety of the treatment. This evaluation showed that was possible to have an increasing of the IOP after the injection of Ozurdex (9). On the other hand, Borrelli *et al.* have demonstrated that in Italy there has been a drastic reduction in the intravitreal injections of approximately 53.6% compared with 2019 (16).

Anti-VEGF such as aflibercept or ranibizumab represent the first line of treatment of macular edema, instead the second line is represented by steroids such as DEX or fluocinolone acetonide (17-21). Despite the anti-VEGF represents the first line of treatment for various retinal disorders, DEX is a good alternative for refractory patients and naïve treatment because for anti-VEGF is needed to carry out periodic injections, especially during the loading phase (12,14,17).

Ozurdex in the treatment of DME and OCT biomarkers

Diabetes mellitus is a significant and widespread issue worldwide. According to the World Health Organization, the number of people with diabetes increased from 108 million to 422 million between 1980 and 2014, with a higher prevalence in low- and middle-income countries. In 2019, WHO reported approximately 2,000 deaths caused by kidney disease due to diabetes (22). This is a severe issue due to high medical costs, visual disability, and blindness caused by DME. Additionally, managing patients for an extended period can be challenging (23). Improvements in diagnostic imaging and therapeutics have changed the strategies for diagnosing and treating this pathology, allowing for earlier detection of diabetes. In the past, laser treatment was the primary approach for DME, but now intravitreal injections have emerged as significant competitors. Laser photocoagulation is no longer recommended for DME, and anti-VEGF and steroids have become the first-line therapies (19). DME is the result of a chronic process where inflammation plays an important role and includes leukostasis, characterized by the accumulation of leukocytes on retinal capillaries which appears to be a pathological mechanism causing retinal barrier dysfunction (24). Leukostasis leads to upregulation of ICAM, which is responsible of retinal leukostasis and vascular permeability leading to a breakdown of the blood-retinal barrier (BRB) (25). Following attachment to the vascular endothelium, leukocytes produce reactive oxygen species and inflammatory cytokines, resulting in increased vascular permeability (26). Experiments in animals have shown that elevated blood serum glucose levels may cause

the expression of IL-6, tumor necrosis factor, lymphotoxin, and cyclooxygenase-2 (27).

IL-6 and pigment epithelium-derived factor expression were found to be enhanced in the vitreous of diabetic eyes (28). The synthesis of inflammatory mediators and a reduction of the anti-VEGF synthesis were observed after the use of corticosteroids (29). This appears to be related to the anti-inflammatory action, significantly affecting the inflammatory and improving the BRB function through inhibition of ICAM-1 expression in rat retinas (30). The changes in aqueous levels of inflammatory [IL-6, IL-8, interferon-induced protein-10, monocyte-chemoattractant protein-1, platelet-derived growth factor (PDGF)-AA] and angiogenic (VEGF) cytokines after intravitreal injection of corticosteroid triamcinolone in comparison to the anti-VEGF agent bevacizumab in patients with DME, were investigated by Sohn *et al.* and Scott *et al.* which found that IL-6, inducible-protein 10, monocyte-chemoattractant protein-1, PDGF-AA, and VEGF were significantly decreased in eyes treated with triamcinolone, because it has an important inflammatory action about passages of the inflammatory cascade. On the other hand, VEGF levels were reduced in the bevacizumab group, because it has a direct action against this molecular target showing a more circumscribed action (31,32). New diagnostic parameters from OCT have been used to stage the disease, leading to improved therapeutic management. Macular edema is characterized by the accumulation of intraretinal fluid, caused by an alteration of the BRB, resulting in capillary leakage and edema formation. DME can be associated with or without other signs of diabetes, so it may be considered a separate entity. However, it is often associated with hard exudates, which are localized in the deep choriocapillary plexus and in combination with edema cause a significant reduction of the visual acuity (19). OCT is an important diagnostic tool enabling early identification of edema at the foveal level and faciliting the development of an appropriate therapeutic strategy. OCT biomarkers such as: submacular fluid, intraretinal cystoid fluid, retinal layers disruptions or thickness changes, disorganization of the retinal inner layers (DRIL), absence of hyperreflective intraretinal foci, the integrity of ellipsoid zone and the status of the vitreomacular interface, represent an important system of biomarkers to manage patients treated with DEX. This system of biomarkers permits to select patients who benefit from a single DEX intravitreal injection instead of being treated with anti-VEGF and this could reduce the burden on patients and the health care system to provide care (33). Chronic pathologies like diabetes require long-term treatment, and Ozurdex proves to be an optimal alternative in such cases (6,16). The effectiveness of Ozurdex lasts for about 3–6 months demonstrating good efficacy and safety, which has been tested and verified in clinical trials. However, its effectiveness declines after this period (12,34). OCT angiography (OCTA) is another essential examination that allows the visualization of vascularization, enabling the evaluation of microvascular modifications such as: microaneurysms, vascular loops, neovascularization, modification of the foveal avascular zone (FAZ), venous beading, or capillary modification and distinguishing perfusion and non-perfusion areas in the macula. An effective response to Ozurdex can be assessed by studying the superficial capillary plexus, deep capillary plexus, and choriocapillary. A reperfusion of these areas associated with the preservation of the FAZ area can be considered an important marker of a proper therapeutic response. OCTA may lead to new hypotheses on imaging biomarkers, and individualized retreatment criteria using OCT and OCTA biomarkers could be very useful in the future (35). An important study, that evaluated the effects of DEX in the DME was the PLACID assay. In this study 253 patients with DME were enrolled, meeting criteria such as best corrected visual acuity (BCVA) score of 34–70 letters and a central retinal thickness (CRT) ≥275 μm. All patients were randomized to a sham implant injection with laser monotherapy and to 0.7 mg Ozurdex implant and laser therapy at month 1. At the 1-year mark, there was no difference between the groups, but afterwards, the group treated with laser and Ozurdex, showed a more substantial improvement in visual acuity compared to the laser monotherapy group. Regarding the IOP there was an increase in pressure values in the group that was treated with Ozurdex rather than the group that was treated only with laser, necessitating IOP-reducing therapy, but no eye required a surgery treatment. Additionally, the risk of cataract development was found to be higher in the phakic group treated with DEX implant plus laser compared to the laser monotherapy group (36). The MEAD study was the largest trial about Ozurdex and DME. This study enrolled 1,048 patients, additionally, the risk of cataract development was found to be higher in the phakic group treated with DEX implant plus laser compared to the laser monotherapy group of 20/50 to 20/200, central DME and CRT of ≥300 μm. All patients were randomized to Ozurdex treatment with different dosages or a sham procedure with

a follow-up of 3 years. Dosages of Ozurdex were 0.35 and 0.7 mg, and retreatment was performed no more frequently than every 6 months. At the end of 3 years, there was a significant improvement of the BCVA of about 15 or more letters in the group that was treated with Ozurdex (0.7/0.35 mg) compared to the control group. Evaluating the IOP was found an increase in pressure in the Ozurdex group (0.7/0.35 mg) versus the control group, necessitating management therapy for the first group, but only one patient in each Ozurdex treatment group needed surgical therapy to manage glaucoma. At the same time, cataract occurrence was more frequent in the group treated with the DEX implant compared to the control group (13). The CHAMPLAIN study involved 55 patients with a history of Pars plana vitrectomy and treatment-refractory DME, who were treated with a single injection of Ozurdex at a dosage of 0.7 mg. The study provided a 26-week evaluation period and found an average BCVA gain of 6 letters from baseline at 8 weeks and a gain of 3 letters at 26 weeks. No patient required surgery to control IOP, and an increase in the IOP was reported only in a few patients. Lastly, only one patient underwent cataract surgery (37). The use of Ozurdex was approved by the Food and Drug Administration (FDA) for the treatment of DME only in September 2014, while approval by the European Medicines Agency (EMA) for pseudophakic patients or those with an insufficient response to non-corticosteroid therapy, arrived only in July 2014. Chang-Lin *et al.* reported that the period of action of the drug into the vitreous was ≤6 months (38). The CHROME study reported after a retrospective investigation that the average time of re-injection was between 2.3 and 4.9 months in case of pathologies such as: RVO, uveitis, or DME. However, the official label of the product recommends re-treatment after about 6 months, even if a re-injection before 6 months was supported by recent evidence, avoiding at the same time a simultaneous subministration to both eyes (39). Swelling may occur at any stage of diabetes, but it often occurs in mild to moderate retinopathy. The significance of Ozurdex in patients with diabetes was discussed in the Diabetes Retinopathy Clinical Research Network (DRCR.net) Protocol, evaluating intravitreal triamcinolone acetonide (TA) or ranibizumab in combination with laser treatment. This study demonstrated similar efficacy of both drugs in pseudophakic eyes, but DEX demonstrated a higher anti-inflammatory effect than TA and fewer side effects (13,40). Morphologic and functional changes were assessed in a 12-month follow-up by Mastropasqua *et al.* and showed an improvement just 1 month after the DEX implant and a persistence of its action up to 5 months after the injection (41). Lo Giudice *et al.* evaluated the rapidity of the effect of Ozurdex and it shows on OCT in some patients a maximal reduction of the CRT only after 3 h by the injection and in others within 3 days, while the BCVA improvement was significant 7 days after treatment (42). In the BEVORDEX study, anti-VEGF and Ozurdex were compared. Patients who received the DEX implant showed better anatomic results with fewer injections, but both drugs induced an important resolution of hard exudates (43). Callanan *et al.* compared DEX with ranibizumab and it shows similar changes in visual acuity, CRT, and leakage reduction on fluorangiography (44). Cytokine expression in the aqueous humor was considered in a small study that compares the concentration after the use of DEX implant and anti-VEGF, the conclusion is that ranibizumab appears to have a protracted impact on VEGF and placental growth factor rather than Ozurdex which shows rapid action on inflammatory mediators (45). Even if there are some side effects related to the use of Ozurdex such as cataract and rising of IOP, they can be easily treated and Ozurdex may be used in various situations (37).

The effect of DEX implant on the DME and cataract surgery

DEX is commonly used during cataract surgery to prevent swelling from forming 1 month after surgery (46). Irvine-Gass syndrome is a post-cataract pathological condition that shares with Diabetes the formation of intraretinal cysts as a result of an inflammatory process. The inflammation alters vascular permeability resulting in edema and the risk is higher in patients with diabetes rather than non-diabetics (47-51). This condition is caused by the pro-inflammatory condition triggered by the surgery with the release of pro-angiogenic and pro-inflammatory cytokines which damage the BRB causing an increment of vascular permeability and determining loss of endothelial cells and pericytes (49-51). Several studies, including the Reldex study, have evaluated the effect of DEX on the DME 1 month before cataract, showing interesting and encouraging functional and anatomical results (52). The use of DEX implant 1 month before the cataract surgery seems to improve the DME after the procedure, but this effect diminishes after 3 months, possibly due to the loss of DEX implant's action (53). Intraretinal cysts can occur even after 1 month, in fact in pseudophakic is possible to have this condition between 4 and 12 weeks after surgery peaking at 4–6 weeks (54).

Another approach involved injecting DEX simultaneously with cataract surgery, resulting in better edema management, possibly due to different action durations, with a decline in action observed at 4 months (55-57). The implantation of DEX 1 month before cataract showed reduced effectiveness after 1–2 months post-surgery, while the concomitant treatment granted better management at 3 months. This concomitant treatment might correspond well with the pro-inflammatory peak triggered by surgery and the inflammatory effect of DEX. Both treatments show good results in preventing macular edema, but further studies are needed to determine the superior choice (46).

New proposal in the treatment of diabetic retinopathy and DME

Advancements in understanding diabetic retinopathy and DME pathogenesis have significantly impacted treatment approaches. For decades, laser photocoagulation has been regarded as a standard of care but after the introduction of anti-VEGF was one of the most significant developments in ophthalmology. Soon after the very first pieces of evidence of the efficacy of monthly bevacizumab in DME (58,59). New molecules such as: ranibizumab and aflibercept and new treatment regimen such as: pro-re-nata and treat-and-extend have demonstrated the important benefits of the antiangiogenic agents (60). The introduction of intravitreal corticosteroids and long-release drug delivery systems have also provided important alternatives in the DME management (61). Despite the scientific evidence supporting the effectiveness of anti-VEGF and corticosteroids, some patients still exhibit sub-optimal responses to medical treatment. The available drugs have varying durations of the effect, with anti-VEGF showing action from 4 to 8 weeks, and DEX lasting about 4 months, but its effect diminishes after this period. New molecules are opening a new proposal of treatment based on the long durability effect. Among them, it has been presented Brolucizumab which has shown an action for 12 weeks. The most common ocular adverse events associated with the use of Brolucizumab, as reported in the Hawk and Harrier studies, were conjunctival hemorrhage, uveitis, and iritis. Although approximately 90% of uveitis and iritis cases were treated with topical corticosteroids and anti-infectives, they resolved without sequelae (62). It has just been approved for neovascular age-related macular degeneration, but a phase III randomized clinical trial is now in progress to demonstrate the possibility of using it in the DME (63). Fluocinolone acetonide in the formulation of non-biodegradable implant (Iluvien: fluocinolone acetonide intravitreal insert, Alimera Sciences Inc., Alpharetta, GA, USA), has been licensed in the United States and Europe to treat DME insufficiently responsive to previous therapies, however it seems to have a durability of 36 months. The study of new molecular targets in the cascade of the angiogenesis could be an important innovation about the creation of new molecules capable of going beyond the limitations of previous treatments. Another treatment option is represented by the port delivery system of ranibizumab, a permanent implant requiring surgical insertion at the pars plana level, ensuring drug release in the vitreous cavity (64). A new promising molecular target is represented by angiopoietin-2, which seems to show good results in the association with intravitreal injections (65). Additionally, phase I/II clinical trials are exploring the possibility of a drug delivered in the suprachoroidal space, minimizing drug levels in the anterior segment while maintaining effective levels in the retina (66).

Conclusions

During the COVID-19 pandemic, Ozurdex has shown high efficacy in managing pathologies characterized by macular edema such as: diabetic retinopathy, non-infectious posterior uveitis, CRVO, and BRVO (4). This is an important aspect as its long-lasting action allows for greater patient compliance due to extended follow-up periods, despite the lack of evidence-based clinical practice guidelines for intravitreal injections (9,11,14). Finally, it has demonstrated promising results in the management of edema after cataract surgery in patients with DME. However, there is still a debate about the better choice between the implant before or during cataract surgery (46). Intravitreal corticosteroids and long delivery systems have been an important therapeutical option of treatment showing good results. Furthermore, there is a subset of patients who do not respond completely to the treatment, indicating the need for new therapeutic targets and molecules to offer a broader range of therapeutic alternatives (61).

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Footnote

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