Dexamethasone implant in the management of diabetic macular edema from clinician’s perspective

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Abstract: The aim of this article is to provide an overview of characteristics and principles of use of dexamethasone implant in patients with diabetic macular edema (DME). The condensed information about patient selection, dosing, and postinjection management is provided to make the clinician’s decisions easier in real-life practice. DME is a common complication of diabetes and the leading cause of visual loss in the working-age population. Inflammation plays an important role in the pathogenesis of DME. The breakdown of the blood–retinal barrier involves the expression of inflammatory cytokines and growth factors, including vascular endothelial growth factor (VEGF). Steroids have proved to be effective in the treatment of DME by blocking the production of VEGF and other inflammatory cytokines, by inhibiting leukostasis, and by enhancing the barrier function of vascular endothelial cell tight junctions. Dexamethasone intravitreal implant has demonstrated efficacy in the treatment of DME resistant to anti-VEGF therapy and in vitrectomized eyes. Data from clinical trials suggest that dexamethasone implant can be considered as first-line treatment in pseudophakic eyes. Dexamethasone implant is also the first-line therapy in patients not suited for anti-VEGF therapy, pregnant women, and patients unable to return for frequent monitoring. It has been shown that the maximum effect of dexamethasone implant on visual gain and retinal thickness occurs approximately 2 months after injection. Various treatment regimens are used in real-life situations, and reported reinjection intervals were usually <6 months. The number of retreatments needed decreased over time. Treatment algorithms should be personalized. Postinjection management and follow-up should consider potential adverse events such as intraocular pressure elevation and cataract.

Keywords: dexamethasone, diabetic macular edema, intravitreal implant, Ozurdex

Introduction
Diabetic macular edema (DME), defined as retinal thickening in the macula, is a common complication of diabetes. The global prevalence of diabetes is increasing, with diabetic retinopathy (DR) being the leading cause of visual loss in the working-age population in many countries. About one-third of patients with diabetes have signs of DR and about one-third of patients with DR have the vision-threatening disease. Whereas proliferative DR is the most common vision-threatening condition in patients with type 1 diabetes, DME is the most common cause of visual loss in patients with type 2 diabetes. 1,2 DME may affect up to 7% of patients with diabetes. The risk factors of DME development are largely similar to those for DR. 2,3

Inflammation plays an important role in the pathogenesis of DME. DR has features of chronic low-grade inflammation and is associated with significant
increases in proinflammatory cytokines within the retina and functional changes to immune cells and tissue macrophages.4–6 Many studies have shown elevated levels of proinflammatory cytokines, chemokines, growth factors, and adhesion molecules in the vitreous or aqueous humor of patients with DR and DME.7–11 These elevations in ocular levels of inflammatory mediators do not correlate with plasma levels, indicating that the inflammation is locally driven.6,11 Activated microglia and leukocytes are sources of proinflammatory mediators. Increased levels of proinflammatory mediators, including vascular endothelial growth factor (VEGF), increased leukocyte adhesion, and leukostasis lead to capillary occlusions and blood–retinal barrier breakdown. Consequent molecular alterations, such as proteins of the tight junction complex, and cytokine-induced vascular cell death contribute to increased capillary permeability.6,12

In patients with DME, liquid accumulates in intracellular and extracellular spaces. Intracellular edema (cytotoxic edema) appears earlier, and extracellular edema (vasogenic edema) appears later as a result of blood–retinal barrier breakdown.13,14 Fluid accumulation together with inflammatory, microvascular, and neurodegenerative changes leads to disruption of normal retinal architecture and loss of visual function.4,15

Steroids were used in the treatment of various ocular disorders from many years. Although the exact mechanism of steroid action on ocular tissues is not fully understood, they have proved to be effective in the treatment of DME by blocking the production of VEGF and other inflammatory cytokines, by inhibiting leukostasis, and by enhancing the barrier function of vascular endothelial cell tight junctions.16 Long-term steroid use may also have a neuroprotective effect on the retina.17–19

Systemic steroids must be administered with caution to diabetic patients because they alter glycemic homeostasis and favor hypertension. However, this seems not to be a problem in the case of their intravitreal administration. From the other side, intravitreally administered corticosteroids are associated with increased risks of cataract development and elevation of intraocular pressure (IOP).18,20,21 Also, there is a higher risk of endophthalmitis and other procedure-related complications due to the intravitreal administration of the drug.

Nowadays, three fluorinated synthetic corticosteroids are used for the treatment of DME: triamcinolone acetonide (TA), dexamethasone phosphate (DEX), and fluocinolone acetonide (FA). They all lack mineralocorticoid activity, but they differ in glucocorticoid-receptor binding affinity and lipophilicity. Differences in binding affinities and lipophilicity may partly explain differences in their relative potencies.17,21 DEX is five times more potent than TA. It is also less lipophilic than TA and FA, causing less binding to the trabecular meshwork and the lens. Therefore, DEX has lower risks for IOP elevation and cataract formation.22

The aim of this article is to provide an overview about the characteristics and principles of use of dexamethasone implant in patients with diabetic macular edema. The condensed information about patient selection, dosing, and postinjection management should help the clinician deciding in real-life situations.

**Dexamethasone implant**

The short half-life of intravitreally injected DEX limits its clinical use. Extended-release systems have been developed to prolong drug retention in the vitreous. An extended-release biodegradable DEX implant (Ozurdex®; Allergan, Inc., Irvine, CA, USA) loaded with 700 μg of dexamethasone was the first intravitreally injectable drug implant approved for the treatment of DME.23 The rod-shaped DEX implant, approximately 0.46 mm in diameter and 6 mm in length, is injected into the eye with a special disposable injection device through pars plana (Figure 1). The biodegradable polymer matrix slowly degrades and releases DEX into the vitreous (Figure 2). It has been designed to release DEX into the vitreous for up to 6 months.

Results of several trials demonstrated the efficacy of DEX implant in improving visual acuity (VA) and reducing central retinal thickness (CRT) in patients with DME. The first report showing the efficacy of DEX implant in treating DME comes from 2007.24 The study involved 315 patients with persistent macular edema resulting from various conditions, including DME. Authors compared two...
doses of DEX (350 μg and 700 μg) with no treatment. The analysis of 171 eyes with DME showed a statistically significant difference in the proportion of eyes achieving at least a 10-letter improvement in best-corrected visual acuity (BCVA) between the 700 μg DEX implant group and the observation group at days 60 (26% vs 9%; \( p=0.01 \)) and 90 (33% vs 12%; \( p=0.007 \)). The difference between the 700 μg DEX implant group and the observation group persisted through day 180 but was no longer statistically significant (30% vs 23%; \( p=0.4 \)). A statistically significant difference in the proportion of eyes that achieved at least a 10-letter improvement in BCVA was also evident between the 350 μg DEX implant group and the observation group at day 60 (23% vs 9%; \( p=0.04 \)), but not at day 90 or day 180 (\( p=0.31 \)). There was a dose–response trend at all time points, but the differences between the 700 μg and 350 μg DEX implant groups were not statistically significant (\( p=0.14 \)). The efficacy in different patterns of DME was similar. \(^{26} \)

Macular edema: Assessments of Implantable Dexamethasone in Diabetes (MEAD) trials evaluated the efficacy and safety of DEX implant in treating DME. These were two randomized, multicenter, masked, sham-controlled, Phase III trials with identical protocols. These 3-year trials included 1,048 patients with DME, BCVA of 20/50 to 20/200 Snellen equivalent, and CRT of \( \geq 300 \) μm by optical coherence tomography (OCT). Patients were randomized into three groups. The first group was treated with 700 μg DEX implant, the second with 350 μg DEX implant, and the third received a sham procedure. Retreatment according to predefined criteria was allowed after 6 months. After 3 years, 22.2% of patients treated with 700 μg DEX implant and 18.4% of patients treated with 350 μg DEX implant gained \( \geq 15 \) letters from baseline BCVA, which was statistically significant in comparison with the sham group (12.0%; \( p<0.018 \)). The mean number of treatments received over 3 years was 4.1, 4.4, and 3.3 with the 700 μg DEX implant group, 350 μg DEX implant group, and sham group, respectively. Rates of cataract-related adverse events (AEs) in phakic eyes were 67.9%, 64.1%, and 20.4% in the 700 μg DEX implant group, 350 μg DEX implant group, and sham group, respectively. An IOP of \( \geq 35 \) mm Hg occurred in 6.6% in the 700 μg DEX implant group, in 5.2% in the 350 μg DEX implant group, but in only 0.9% in the sham group. Increases in IOP were controlled with medication or no therapy, and only two patients (0.6%) in the 700 μg DEX implant group and one (0.3%) in the 350 μg DEX implant group required trabeculectomy. \(^{27} \)

The PLACID study was a controlled, multicenter study that randomized 253 patients with DME to 700 μg DEX implant followed by laser photoagulation or to sham injection followed by laser photoagulation. Reinjection was allowed after 6 months. Macular laser photoagulation could be performed for both groups as needed every 3 months. Patients were followed for 12 months. The percentage of patients that gained 10 letters or more in BCVA at 12 months did not differ between treatment groups, but the percentage of patients was significantly higher in the combination group at month 1 (31.7% vs 11%; \( p<0.001 \)) and month 9 (31.7% vs 17.3%; \( p=0.007 \)). Increased IOP was more common in the combination group than in the laser photoagulation group. IOP elevations \( \geq 35 \) mm Hg were observed in 4% of patients. However, surgery was not required to control IOP. Cataract-related AEs were more common among phakic patients in the combination group (22.2%) in comparison to the laser photoagulation group (9.5%). \(^{28} \)

The BEVORDEX study compared the efficacy of 700 μg DEX implant with bevacizumab. A total of 88 eyes with DME were divided into two groups, the first group receiving bevacizumab up to every 4 weeks and the second group receiving DEX implant up to every 16 weeks, both as needed (Pro Re Nata [PRN] regimen). At month 12, there was no difference between groups regarding a 10-letter visual gain (41% vs 40%; \( p=0.83 \)). However, a higher number of eyes receiving DEX
Implant lost vision, mainly due to cataract formation. Patients in both groups maintained the visual improvement (43% vs 45%; \( p=0.99 \)) at 24 months. The mean improvement in BCVA at 24 months was 6.9 letters in the DEX implant group and 9.6 letters in the bevacizumab group. At baseline, there were 26 pseudophakic eyes (29.5%): 16 in the DEX implant group and 10 in the bevacizumab group. In phakic eyes, the difference in mean BCVA change was more pronounced at 24 months, with the DEX implant group experiencing worse BCVA, most probably because of cataract formation. By 24 months, 11 of the 30 eyes treated with DEX implant (37%) and two of the 32 eyes treated with bevacizumab (6%) had cataract surgery. Patients treated with DEX implant had higher rates of increased IOP, but no glaucoma surgery was needed. Eyes treated with DEX implant received fewer injections than eyes treated with bevacizumab: in the first year 2.8 injections vs 9.1 injections and in the second year 2.2 injections vs 4.8 injections, respectively. A post hoc analysis of 68 study eyes (77%) that completed 2 years follow-up in the BEVORDEX study was carried out to determine whether early vision gains predict long-term visual outcomes. A short-term visual gain at 12 weeks strongly correlated with long-term visual gain, independent of treatment allocation or baseline lens status.

A multicenter, open-label, randomized study compared the safety and efficacy of DEX implant versus ranibizumab in patients with DME. DEX implant was administered at baseline, at month 5, and at month 10. Ranibizumab 0.5 mg was given monthly, starting from baseline visit. Injections were repeated until maximum BCVA was achieved, meaning that the patient’s BCVA was stable for three consecutive monthly assessments. If BCVA was stable, treatment could be suspended, but monthly treatment was reinitated if a decrease in BCVA occurred due to DME progression. The study included 363 eyes with DME. The mean BCVA change from baseline over 12 months was 4.34 letters with DEX implant and 7.6 letters with ranibizumab. DEX implant was noninferior to ranibizumab based on the prespecified noninferiority margin of five letters. This result was achieved with an average of 2.85 DEX implant and 8.7 ranibizumab injections. Ocular AEs were more frequent in the DEX implant group than in the ranibizumab group because of cataract formation and IOP increases. IOP increases were transient and managed with topical medication.

A small retrospective study compared the effects of DEX implant and ranibizumab in patients with symmetrical bilateral DME recalcitrant to ranibizumab. Eleven patients received DEX implant in one eye, while the contralateral eye continued to receive ranibizumab monthly for 3 months. Mean BCVA improved in 3 months from 0.415 logMAR to 0.261 logMAR in eyes receiving DEX implant and from 0.394 logMAR to 0.269 logMAR in eyes receiving ranibizumab.

The Diabetic Retinopathy Clinical Research (DRCR) network Phase II randomized clinical trial evaluated the potential benefit of adding intravitreous corticosteroid to anti-VEGF therapy. A total of 129 eyes with persistent DME, with BCVA of 20/32 to 20/320, and prior anti-VEGF therapy, were randomized to receive ranibizumab therapy alone or in combination with DEX implant. The addition of intravitreous DEX implant to continued ranibizumab therapy did not improve BCVA at 24 weeks more than continued ranibizumab therapy alone.

The CHAMPLAIN study evaluated the safety and efficacy of DEX implant in vitrectomized eyes with DME. In this prospective multicenter study, 55 previously vitrectomized eyes with treatment-resistant DME received a single DEX implant injection. The mean BCVA gain from baseline was six letters after 8 weeks and three letters after 26 weeks. At 8 weeks, 30.4% of eyes gained 10 or more letters in BCVA. Cataract progressed in two of the 12 phakic eyes (17%) and IOP increased in 16% of eyes. Only one eye had an IOP increase >35 mm Hg, and it occurred after 8 weeks. Comparison of anatomic and functional improvement after DEX implant between nonvitrectomized (34) and vitrectomized (24) eyes with persistent DME showed no statistically significant differences in BCVA and CRT during 6 months of follow-up.

Data from many real-life studies have shown that visual gains are higher in treatment-naive patients comparing to previously treated patients. This leads to the conclusion that early treatment is critical for favorable outcomes.

The official Ozurdex label in Europe recommends retreatment after approximately 6 months. However, the therapeutic effect in most eyes lasts around 4 months. Real-life studies have shown that the first reinjection interval was usually shorter than 6 months when using the PRN regimen.

Based on available data, DEX implant is an important option for treating DME. Careful patient selection, optimal dosing, and postinjection management are crucial for obtaining optimal treatment results.

Patient selection

Anti-VEGF drugs are considered the first-line therapy for DME, but corticosteroids are also an important option for treating DME patients. Corticosteroids are mostly used as a second choice due to AEs, the most frequent being an
increase in IOP and progression of cataract. In persistent DME not responding to anti-VEGF therapy, it is reasonable to switch to corticosteroids.\textsuperscript{45} There is no definite consensus regarding the definition of a nonresponder to anti-VEGF therapy. Consequently, the timing of the switch from anti-VEGF therapy to corticosteroid remains controversial. Findings from the DRCR network Protocol I and BEVORDEX clinical trials suggest that the long-term response to therapy may be predicted by the response after three anti-VEGF injections in 12 weeks.\textsuperscript{31,46} In the case of no visual and anatomical improvement after 3 to 6 anti-VEGF injections, a change of treatment should be considered,\textsuperscript{45} bearing in mind that long-standing DME, if left untreated, can lead to permanent damage to the retina.\textsuperscript{47} A recent retrospective real-life study showed that eyes with DME refractory to anti-VEGF therapy that were switched to DEX implant after three monthly anti-VEGF injections had better visual and anatomical outcomes at 12 months than those that continued with anti-VEGF therapy.\textsuperscript{48}

The use of DEX implant as a first-line therapy could be warranted in patients in whom the use of anti-VEGF treatment is contraindicated or is expected to be suboptimal: patients with a history of a major cardiovascular event, pregnant patients, patients after vitrectomy, and patients unable or unwilling to return for frequent monitoring.

Anti-VEGF drugs detected in the systemic circulation after they had been injected intravitreally could be associated with an increased risk for systemic AEs in patients with a history of a major cardiovascular event.\textsuperscript{49,50} Although systemic concentrations were low, concerns have been raised regarding systemic anti-VEGF drug levels after intravitreous treatment, their potential impact on plasma free-VEGF levels, and possible association with an increased risk for systemic AEs. A meta-analysis assessing the risk in anti-VEGF-treated DME patients revealed that high-risk patients with DME that received monthly anti-VEGF treatment over the course of 2 years possibly have an increased risk of vascular-related death and cerebrovascular accidents.\textsuperscript{51} Although their findings were inconsistent with those from major clinical studies with lower drug exposure, the authors of two different meta-analyses suggested that cumulative exposure to anti-VEGF might be an independent risk factor for a major cardiovascular event.\textsuperscript{51,52}

Progression of diabetic retinopathy during pregnancy can be dramatic. It occurs at approximately double the rate of nonpregnant women.\textsuperscript{53} Lack of documented experience and concerns about potential fetal side effects\textsuperscript{54} make the implementation of VEGF inhibition controversial. Consequently, anti-VEGF therapy is generally not offered to pregnant patients. Because of the destructive nature of laser photocoagulation treatment, DEX implant may be considered a better choice for pregnant women with DME. DEX implant seems to have minimal systemic exposure.\textsuperscript{55} In addition, glucocorticoid medication is accepted in pregnancy for a range of clinical indications.\textsuperscript{56} Data from retrospective observational case series on pregnant women with DME and treated with corticosteroids showed a prompt response to treatment without a clinically significant IOP increase. Given the durability of the DEX implant, on average one implant per patient was needed. That made cataract formation less likely.\textsuperscript{57}

For patients after vitrectomy, removal of the vitreous humor leads to increased diffusion of molecules, such as oxygen and cytokines, including angiogenic cytokines (VEGF), to and from the retina.\textsuperscript{58} Even though a recent DRCR network trial showed that previous vitrectomy did not influence the outcomes of intravitreal anti-VEGF therapy,\textsuperscript{59} many studies reported accelerated diffusion and clearance of various drugs from the vitreous cavity in vitrectomized eyes. It made intravitreal pharmacotherapy less effective.\textsuperscript{60–64} To overcome the faster clearance of drugs in vitrectomized eyes, an implant with sustained drug release may be the best solution. In the CHAMPLAIN study, intravitreal treatment with DEX implant favorably improved VA and reduced DME in vitrectomized eyes with long-standing DME.\textsuperscript{35} A retrospective study compared improvements in BCVA and foveal thickness in vitrectomized and nonvitrectomized eyes with DME. During 6 months follow-up, there were no significant differences between the two groups.\textsuperscript{37}

DEX implant can be offered as a first-line option for patients unable or unwilling to come for monthly anti-VEGF injections. However, these patients still require IOP monitoring.

The lens status assessment is a key element before starting treatment with DEX implant. Pseudophakic patients are good candidates for DEX implant. Phakic patients should be informed about the risk of cataract progression and a potential need for surgery. Although visually significant cataract formation is unlikely to develop early after initiating treatment with DEX implant, its incidence increases after the first year of therapy.\textsuperscript{27,29} In the MEAD study, over 75% of the cataract surgeries in the DEX implant groups were performed between 18 and 30 months. Cataract extraction significantly improved vision.\textsuperscript{27,29,30,65}
With the aim of achieving optimal treatment results, personalized treatment with a thorough evaluation of patients’ general health and eye, in particular, is important. Predictive biomarkers help in assessing the most likely response to a particular treatment.66 Predictors of favorable treatment response with high vision gain were subretinal fluid, intraretinal cysts, and/or vitreomacular adhesion at baseline.67–69 On the other hand, disorganization of the inner retinal layers, disruption of the ellipsoid zone, and/or external limiting membrane, and a thin subfoveal choroid at baseline were predictors of poor VA after therapy.45,70–72 Hyperreflective spots (HRSs) were associated with poorer visual outcome in DME patients treated with DEX implant.73 The presence of a higher number of HRS and subretinal fluid may indicate a prevalent inflammatory component in DME.69,74 In a patient subgroup with a higher number of HRS, better morphological and functional outcomes were observed if treated with DEX implant73–76 compared to anti-VEGF treatment.74 A reduction of HRS and better morphological and functional outcomes after treatment with DEX implant in patients with DME73–76 were found in the patients’ subgroup with a higher number of HRS in comparison to anti-VEGF treatment.74

Not all patients are good candidates for DEX implant treatment. Absolute contraindications are advanced or uncontrollable glaucoma, communication with the anterior chamber, drug hypersensitivity, and local infection. Excluding a potential risk of active infection before considering therapy with DEX implant is necessary.

Dosing of DEX implant
The official Ozurdex label in Europe23 recommends retreatment after approximately 6 months. However, the therapeutic effect of DEX implant in most eyes is usually shorter than 6 months. To optimize treatment with DEX implant, the duration of the therapeutic effect must be taken into account.

Data from the PLACID study showed that the highest increase in BCVA from baseline was achieved 1 month after DEX implant injection. The maximum increase from baseline was 7.9 letters in the 7th month in patients retreated with DEX implant in the 6th month.28 Similarly, in the MEAD study, the highest increase in BCVA was noted 1.5 months after injection. Because the reinjection of DEX implant was not allowed before 6 months, marked fluctuations in BCVA and CRT were observed, particularly in the first year. Fluctuations in BCVA and CRT became smaller in the 2nd and 3rd years.27,77 The peak effectiveness of DEX implant in vitrectomized eyes with DME was seen from 2 to 3 months after injection.35 Other studies also reported the maximum increase in BCVA within 2 months after DEX implant injection.39,78–80

Several real-life studies have shown similar results regarding the number of retreatments during the first year and a mean duration between retreatment intervals. In a retrospective multicenter analysis of 79 eyes with DME treated with DEX implant and followed for at least 1 year after the first injection,38 72% of eyes did not require any additional treatment during the follow-up period. However, 21.5% of eyes required additional treatment before 6 months. The Chart Review of Ozurdex in Macular Edema study (CHROME) evaluated real-world use, efficacy, and safety of DEX implant in eyes with macular edema resulting from diabetes, retinal vein occlusion, and uveitis. The study included eyes receiving two or three DEX implant injections. The mean time to the first and second DEX implant reinjection in DME eyes was 5.8 ±0.5 months and 5.6±1.0 months, respectively.41 Aknin and Melki reported that 47% of patients needed one, two, or three additional DEX implant injections in the follow-up period of 18 months, with a mean reinjection interval of 5.6 months.81 Data from three studies in France showed consistent results regarding the use of DEX implant in DME patients with an average of 2.4 injections per year and 4.9 months interval between retreatments.82 Escobar-Barranco et al reported a median time of 4 months for the first and the second reinjection.39 Matoniti et al observed that patients that received the second injection before the 5th month benefited from 9.9 letters more of visual gain at 12 months compared to patients retreated later than at the 5th month. At the baseline, there were only 0.6 letters of difference between these subgroups.83 Similarly, Sarao et al reported a difference of 0.11 logMAR in BCVA after 6 months in favor of the group of DME eyes treated with the PRN regimen in comparison to the group of DME eyes that received DEX implant only at baseline. The mean number of injections in the PRN group was 1.6 in 6 months.80 A recent systematic review of real-world studies done by Bucolo et al showed that the average mean retreatment time was 5.3±0.9 months. Retreatment was considered on a PRN basis at any time or starting from the 3rd or 4th month.84 The idea of a fixed regimen with a shorter interval of reinjections was evaluated in a prospective, multicenter, randomized clinical
trial. The mean change in BCVA with 5-month fixed dosing of DEX implant was noninferior to the OCT-guided PRN regimen, which might be an option in simplifying treatment protocols for DME patients.84

The mean number of injections per year decreases with time and, conversely, mean time to retreatment increases. In the RELDEX study, the mean number of DEX implant injections over 3 years was 3.6, and the mean time to retreatment was 7.3 months over 3 years. In the first year, the mean number of injections was 1.5 and the mean time to retreatment was 5.7 months. In the second year, the mean number of injections was 1.4 and in the third year, it decreased to 1.1. Conversely, in the second year, the mean time to retreatment was 7.5 months and in the third year it lengthened to 10 months.65

Injection and reinjection criteria somewhat vary between different studies and real-life situations. According to recent guidelines for the management of DME,45,85 corticosteroids are mostly a second-line treatment in patients with DME. Patients should be switched from anti-VEGF therapy to corticosteroid treatment if there is less than a 50% reduction from baseline in the excess macular thickness after three- to four-monthly anti-VEGF injections, or if their BCVA has not improved to 20/40 or after three- to six-monthly injections because of edema.86 In the MEAD study, patients were eligible for treatment if, among other criteria, BCVA was between 34 and 68 letters (20/200–20/50) and CRT was ≥300 μm. Retreatment eligibility criteria were ≥6 months from the most recent study treatment and residual edema with CRT >225 μm. A study protocol amendment in 2010 revised the anatomic criterion such that patients with CRT >175 μm or with evidence of intraretinal cysts or regions of retinal thickening within or outside the central retinal subfield seen on OCT were eligible for retreatment.27 In the PLACID study, eyes were required to have BCVA between 34 and 70 letters and CRT ≥275 μm. Retreatment was allowed after 6 months if CRT was ≥250 μm.28 Criteria in real-life situations can be more variable. Some real-life studies used a change in BCVA of five or more letters and/or a change in CRT of 50 or more μm42 or a change in BCVA of at least 10 letters and/or an increase in CRT of at least 150 μm.86 Regardless of the exact criteria for retreatment, it is essential to evaluate the functional and anatomic response to treatment when deciding on retreatment. If there is a functional and anatomic improvement after the treatment, it should continue until maximum possible improvement. If there is no functional and anatomic response, a tractional component may maintain edema, and vitrectomy should be considered. If there is a good anatomical response, but no or little functional improvement, this means that DEX implant is working, but structural changes in the retina, neuropathy, or cataract progression render functional improvement impossible. In such cases, the exact cause of the lack of functional improvement should be determined to make an optimal decision regarding subsequent treatment options.86

Based on current knowledge, it can be assumed that early retreatment may lead to better overall visual gain and fewer retreatments afterward. It seems that in most patients the first retreatment should be 4 to 5 months after the first DEX implant injection to achieve optimal results. Treatment algorithms should be personalized. From this perspective, the PRN regimen seems to be the most appropriate because it allows an individualized approach.

Postinjection management
Postinjection management and follow-up should consider potential AEs. In addition to IOP increase and cataract formation, other rare but potentially serious AEs such as retinal detachment, retinal tear, necrotizing retinitis, or endophthalmitis can develop. A recent meta-analysis reported the average time to development of viral retinitis to be 4 months, with cytomegalovirus as the most frequently observed agent.87

Despite the very low risk of endophthalmitis associated with DEX injection in DME patients,27,88 consequences may be devastating in terms of VA. The summary of product characteristics (SmPC) for Ozurdex (DEX implant)23 instructs administration of topical broad-spectrum antimicrobial drops following intravitreal DEX implant injection for 3 days after each injection. The use of antibiotic drops as a preventive method is mostly part of routine practice before and after different intraocular procedures.89–91 However, the application of povidone-iodine to the ocular surface before injection has been shown to be the only useful prophylactic measure supported by clinical trials.92 Furthermore, it has recently been shown that antibiotics do not offer protection against the risk of developing endophthalmitis after the intravitreal administration of anti-VEGF drugs and rates of endophthalmitis may be even higher in patients using topical antibiotics.93,94 An increasing proportion of resistant bacteria on the ocular surface may result in an increased risk of developing antibiotic resistant ocular infections.95 Due to repeated doses of topical antibiotics for long periods, patients receiving
intravitreal therapy may be at higher risk. Two recent meta-analyses evaluated the incidence of endophthalmitis after treatment with various intravitreal injections associated with the use of topical antibiotics. The results supported the possibility that antibiotics are not required in the prophylaxis of endophthalmitis when administering intravitreal injections, or may even be associated with a higher incidence of endophthalmitis. According to recent EURETINA expert consensus recommendations, perioperative antibiotics for intravitreal injections cannot be considered the standard of care because there is no evidence of endophthalmitis prevention. Instead, patients should be monitored regularly following the injection to allow early treatment if endophthalmitis occurs. The first biomicroscopy is advised between 2 and 7 days post application. Patients should be instructed to report any symptoms suggestive of ocular infection or other AEs.

An increase in IOP is mostly seen 45 to 60 days following intravitreal injection of DEX implant. However, a check for perfusion of the optic nerve head is advised immediately after the injection and tonometry should be performed within 30 min following the application. Regular monitoring of IOP is required afterward, and any elevation needs proper management. Increases in IOP are not typically observed at the safety visits within 3 weeks after DEX implant treatment. The MEAD study revealed that both mean IOP and the prevalence of IOP elevations were highest at 1.5 to 3 months after injection. These results suggested the need for a follow-up visit at 6 to 8 weeks postinjection, and IOP mostly returned to baseline levels by 6 months after injection. According to data from the SAFODEX study, which monitored IOP increase in eyes treated with DEX implant due to macular edema of various origin, there was a small percentage of patients in whom the IOP increase already occurred at 8 days and 1 month. A small percentage of late responders has also been reported in which the first increase in IOP was diagnosed at the third injection or later.

There is no evidence that repeated DEX implant injections over time have any cumulative effect on IOP increase. The IOP increase observed in the first eye appears to be a good indicator of the expected IOP in the second eye in patients that receive bilateral injections of DEX implant. In patients with glaucoma or ocular hypertension at baseline, tolerance to IOP increase seems to be poor. According to the SAFODEX study results, there were 50% and 100% of high responders to DEX implant in those treated with dual or triple therapy at baseline, respectively. However, compared to uveitic patients or patients with retinal vein occlusion, DME patients seem to have a better pressure tolerance profile.

A two-step algorithm was proposed by an expert panel of European ophthalmologists for monitoring and managing corticosteroid-induced IOP increase in patients with DME. The first step is risk stratification before treatment and the second step describes monitoring and treatment after steroid administration. During follow-up, patients developing an IOP increase should have baseline and periodic imaging and visual field testing. IOP-lowering medications are proposed only when IOP is >25 mm Hg or if diagnostic tests suggest glaucoma is developing. The panel agreed that there is no need for a specific management protocol for IOP increase induced by corticosteroid therapy compared to other causes of increased IOP.

Recently, Spanish ophthalmologists proposed a protocol for managing and monitoring DME patients. This protocol is based on therapeutic response and potential IOP increase. According to this protocol, the first postinjection checkup should be performed 6 to 8 weeks after each injection and the second postinjection checkup on week 16 after the initial injection. If the therapeutic effect persists for 4 months, the patient may be monitored every 4 to 8 weeks to evaluate the further need for therapy. If there is a recurrence of edema in week 16, but BCVA is still stable, the patient can receive another injection or the injection is postponed for 4 weeks to reevaluate the situation. If there is a recurrence of edema and worse BCVA in week 16, the patient should receive another injection. If there is a considerable worsening of edema and BCVA, shortening the interval between postinjection check-ups and a reinjection interval at 3 months should be considered. Based on the patient’s progress, reinjection intervals can be adjusted and gradually increased.

Conclusion
Based on data from clinical trials and real-life clinical experience, DEX implant is a valuable option in treating DME patients. It provides similar rates of visual improvements as anti-VEGF therapy, but with fewer injections. AEs are manageable. Management and monitoring protocols serve as a guide to a personalized treatment with the aim of optimizing clinical results and reducing the burden of treatment.

Patient consent
Patient consent has been obtained for the publication of images.
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