REVIEW

Role of implants in the treatment of diabetic macular edema: focus on the dexamethasone intravitreal implant

Zafer Cebeci
Nur Kir

Department of Ophthalmology, Istanbul Faculty of Medicine, Istanbul University, Capa, Istanbul, Turkey

Abstract: Diabetic macular edema (DME) is the leading cause of sight-threatening complication in diabetic patients, and several treatment modalities have been developed and evaluated to treat this pathology. Intravitreal agents, such as anti-vascular endothelial growth factors (anti-VEGF) or corticosteroids, have become more popular in recent years and are widely used for treating DME. Sustained release drugs appear to be mentioned more often nowadays for extending the period of intravitreal activity, and corticosteroids play a key role in inhibiting the inflammatory process in DME. A potent corticosteroid, dexamethasone (Ozurdex®), in the form of an intravitreal implant, has been approved for various ocular etiologies among which DME is also one. This review evaluates the role of implants in the treatment of DME, mainly focusing on the dexamethasone intravitreal implant.

Keywords: diabetes mellitus, diabetic macular edema, vascular endothelial growth factor, dexamethasone, Iluvien, corticosteroid

Introduction

Diabetes mellitus (DM) is a common, chronic, metabolic disease that causes micro- and macrovascular complications, and its prevalence has significantly increased worldwide, with an expectation that 592 million people will be affected by 2035.[1] Diabetic retinopathy (DR) is an important major microvascular complication of DM, and the leading cause of visual loss.[2] DR can be divided into two major stages: nonproliferative DR and proliferative DR. Nonproliferative DR can be called as early stage and microaneurysm formation is the earliest sign of DR. Intraretinal hemorrhages, hard exudates, retinal capillary nonperfusion, cotton wool spots, venous abnormalities, and intraretinal microvascular abnormalities can be found during this stage. Proliferative DR, advanced stage, is characterized by neovascularization and develops due to ischemia and release of vasoactive materials. These fragile, abnormal new vessels grow along the retina and into the vitreous, and lead to vitreous hemorrhage, tractional retinal detachment, resulting in vision loss. The most frequent cause of visual impairment in DR is due to diabetic macular edema (DME), which occurs with leakage of plasma and lipid in the macula.[3] It can occur in any of the DR stages and in any patients with type 1 and 2 DM. Prevalence of DR is higher in type 1 DM than type 2 DM, and overall, the prevalence of DR has been found to be 35.4%, with 7.2% for proliferative DR and 7.5% for DME in diabetic patients aged 20–79 years in one meta-analysis.[4] The Wisconsin epidemiological study of diabetic retinopathy (WESDR) reported the incidence of DME to be 20% in type 1 DM and 14%–25% in type 2 DM patients over a 10-year period.[5] The 25-year follow-up data in the WESDR showed that 29% of type 1

Correspondence: Zafer Cebeci
Department of Ophthalmology, Istanbul Faculty of Medicine, Istanbul University, Capa 34390, Istanbul, Turkey
Tel +90 212 414 2000
Fax +90 212 414 2026
Email zafceb@gmail.com

DM patients developed DME.[6] Although the prevalence of DM has increased, improvements in the treatment have decreased the prevalence of severe DR, including DME, in developed countries.[7,8] However, as the world population increases, diabetes and DME will remain significant global health issues.

Laser photocoagulation, pharmacotherapy with intravitreal injection of corticosteroids or anti-vascular endothelial growth factor (VEGF), and pars plana vitrectomy are options for treating DME.[9] For many years, laser photocoagulation has been used for the standard treatment of DME.[10] The Early Treatment Diabetic Retinopathy Study showed that the direct treatment of microaneurysms, with grid laser photocoagulation to diffuse leakage areas, lowers the risk of moderate vision loss in DME; however, visual acuity often remained unchanged or little improvement was reported.[10] Since then, new pharmacological therapies such as the intravitreal injection of corticosteroids and anti-VEGFs (pegaptanib, bevacizumab, ranibizumab, aflibercept) have become available. Anti-VEGF agents have been shown to be efficacious for treating DME.[11–18] However, in some patients with DME who show partial response or are refractory to anti-VEGF drugs, corticosteroids constitute another option with extended treatment intervals.

This review focuses on the dexamethasone (DEX) intravitreal implant, or Ozurdex® (Allergan, Inc., Irvine, CA, USA), for the treatment of DME.

Pathogenesis of DME

Hyperglycemia-induced biochemical pathways in DR lead to increased oxidative stress, inflammation, and vascular dysfunction, which contribute to the development of DME. The inflammatory process that triggers the breakdown of the blood–retinal barrier (BRB) plays a critical role in the pathogenesis of DME.[19,20] Mainly, inflammatory cytokines and angiogenic growth factors contribute to the impairment of BRB and the increase in vascular permeability.[21] Increased leukocytes have been detected in the retinal vasculature of diabetic patients, and leukocyte adhesion to the vascular endothelium has been shown to have negative effects on the integrity of the endothelial junction.[22,23] In an experimental model of diabetes, the adhesion of the leukocytes to the retinal vasculature was detected in 1 week.[23] Additionally, leukostasis appeared to be responsible for the increase in the vascular leakage and the breakdown of the BRB.[24,25]

In DR, the enhanced expression of the intracellular adhesion molecule (ICAM)-1, selectin, vascular cell adhesion molecules, and the platelet endothelial cell adhesion molecule were reported, and these adhesion molecules also increase leukostasis.[22,24,26] The free radicals produced by leukostasis from oxygen molecules and inflammatory cytokines help in developing DME. Furthermore, VEGF, an angiogenic and proinflammatory factor that plays an important role in vascular permeability, was found to be elevated in the vitreous fluid and retina of DR patients.[27–29] The breakdown of the BRB was also induced by increased levels of VEGF.[30,31] Phosphorylation of adherens junction protein (vascular endothelial-cadherin) and tight junction proteins (occludin and ZO-1) stimulated by VEGF results in a disruption of the barrier.[32] VEGF has been found to upregulate the expression of adhesive molecules in vitro and this leads to inflammatory cell adhesion to endothelium.[33] VEGF induces increased leukostasis in the retinal vasculature, and release of cytokines and migration by leukocytes cause BRB breakdown.[28,30] Also, intraocular levels of ischemia induced angiogenic factor (erythropoietin), and a polypeptide hormone (adiponectin) was found to be increased in diabetic patients and this could have effect in pathogenesis of DME and DR.[34,35]

Corticosteroids in DME

Corticosteroids behave in multiple ways for the treatment of DME.[36] They are potent anti-inflammatory agents and inhibit VEGF expression.[37,38] The use of systemic or intravitreal corticosteroids inhibits leukocyte adhesion via the suppression of ICAM-1 gene expression, decreasing the protein levels and inhibiting the breakdown of the BRB by decreasing the VEGF levels.[38,39] Mainly, three synthetic corticosteroids have been used in the treatment of DME: triamcinolone acetonide (TA), DEX, and fluocinolone acetonide (FA). TA is the most commonly used steroid for treating retinal diseases and is a minimally water soluble, crystalline steroid, which is injected intravitreally in a suspension form. Three formulations of TA are available for intravitreal use: Kenalog® (Bristol-Myers Squibb, Princeton, NJ, USA), Trivaris® (Allergan, Inc.), and Triesence® (Alcon, Fort Worth, TX, USA). Subtenon or intravitreal application of TA can be used for DME, but intravitreal injection has been shown to be more efficacious than subtenon injection within 3 months in a meta-analysis.[40] Different doses of TA have been used (between 1 and 25 mg) intraocularly, and the most commonly accepted dose is 4 mg/0.1 mL.[41–44] Numerous studies have been done to evaluate TA in DME and have shown effectiveness, especially in pseudophakic patients.[45–47] However, as an ocular side effect of corticosteroids, TA is associated with an increased risk of cataract progression and rise in intraocular pressure (IOP).[48–50]

DEX is a steroid which is five times more potent than TA.[51–53] The lipophilicity of DEX is less than that of TA and FA, causing less binding to the trabecular meshwork and the lens.[54] This decreases the risks of high IOP and cataract formation. The half-life of intravitreally injected DEX in the human vitreous humor is 5.5 hours, which limits the clinical use;[55] therefore, to extend the activity of DEX, an intravitreal sustained release form was developed.[56–59] Ozurdex®, a DEX implant, was the first intravitreally injectable biodegradable implant drug approved for the treatment of DME. The DEX intravitreal implant will be discussed in more detail later.

FA is a potent steroid that has two approved sustained release forms for an extended time of action: Retisert® (Bausch and Lomb, Rochester, NY, USA) and Iluvien® (Alimera Sciences, Alpharetta, GA, USA). However, the only FA implant approved for treating DME is a 0.19 mg nondegradable FA (Iluvien®), and it was approved by the US Food and Drug Administration (FDA) in September of 2014. It has been indicated for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in the IOP. Iluvien® provides 36 months of a continuous, low-dose corticosteroid with a single injection[60–62] and has a much greater solubility than DEX, allowing the release of the drug over a longer period of time.[63] The FA implant showed benefits in patients with DME for up to 3 years.[62,64–67] However, the 3-year data from a multicenter trial showed that 4.8% of the low-dose (0.2 µg/d) group and 8.1% of the high-dose (0.5 µg/d) group needed incisional glaucoma surgery, and almost all of the phakic patients who had FA implants developed cataracts.[65]

Design and mechanism of action of the DEX implant

The DEX intravitreal implant (Ozurdex®) consists of 0.7 mg of DEX in a NOVADUR® (Styrolution; Aurora, Illinois USA) solid polymer sustained-release drug-delivery system (DDS). The NOVADUR® system contains a poly(D,L-lactide-*co*-glycolide) intravitreal polymer matrix without a preservative, which slowly biodegrades to lactic acid and glycolic acid.[68] The ocular tissues eliminate the lactic acid and glycolic acid as carbon dioxide and water. Ozurdex® comes in a sterile package with a 22 G single applicator, and insertion of rod-shaped implant (0.46 mm in diameter and 6 mm in length) was done under local anesthesia for intravitreal delivery through the pars plana.

The DEX implant had an initial phase with a high concentration of DEX followed by a lower concentration

second phase.[69] This implant showed peak levels of the drug over the 2 months after administration and continued its releasing activity at decreasing doses for 6 months.[69] Although the DEX implant is a solid, intact, one-piece drug, fragmentation could occur after intravitreal implantation.[70–72] Even the fragmented implant showed similar releasing characteristics in vivo and in a vitreous fluid animal model compared to an intact one.[73] The aqueous and vitreous levels of DEX did not differ between the fragmented and nonfragmented implants.

The FDA first approved the 0.7 mg DEX intravitreal implant (Ozurdex®) for the treatment of macular edema, secondary to retinal vein occlusion, in 2009. The first approval was followed by an indication for the treatment of noninfectious ocular inflammation, or uveitis, affecting the posterior segment of the eye. In June 2014, the FDA approved Ozurdex® for use in adult patients with DME.

Efficacy
DEX intravitreal implant (0.7 and 0.35 mg) vs sham

The efficacy of the DEX intravitreal implant for the treatment of DME has been described in several main clinical trials (Table 1). In one randomized study over 6 months, a DEX DDS Phase II trial was conducted to evaluate the efficacy and safety of 350 and 700 µg intravitreal DEX implants vs observation in patients with macular edema persisting for 90 days or longer, after laser or medical treatment.[58] The patients enrolled in this study had persistent macular edema secondary to different diagnoses, such as retinal vein occlusion, Irvine-Gass syndrome, uveitis, and nearly half with DR. The proportion of patients gaining ≥10 letters and ≥15 letters in the 700 µg DEX implant group was significantly greater than in the observation group at day 90 (primary end point), regardless of the diagnosis (35.2% vs 13.3%, $P<0.01$ and 18.1% vs 5.7%, $P=0.006$, respectively). In 2010, the DEX DDS Phase II study group analyzed the results of the subgroup of patients with DME.[74] The proportion of eyes with improved best-corrected visual acuity (BCVA) at months 2 and 3, compared to the baseline, was found to be statistically significant between the 700 µg DEX implant and observation groups (26% vs 9%, $P=0.01$ at month 2 and 33% vs 12%, $P=0.007$ at month 3). A higher proportion of eyes gaining ≥10 letters in the BCVA was also detected in the 700 µg DEX implant group compared to the observation group at month 6, but the difference was not significant (30% vs 23%, $P=0.4$). Only the data for the decrease in the central retinal thickness (CRT) from the baseline was

Table 1 Summary of main clinical trials with DEX intravitreal implant for the treatment of diabetic macular edema

Study	Phase	Number of eyes	Follow-up (months)	Treatment arms	Outcome measures	Results
Haller et al[74]	II	171	6	0.35 mg DEX implant vs 0.7 mg DEX implant vs observation	Percentage of patients gaining ≥10 letters in BCVA from baseline at day 90. CRT decreases from baseline at day 90. Percentage of patients with ≥2 levels decrease in fluorescein leakage at day 90	0.7 mg DEX implant (33.3%), and 0.35 mg DEX implant (21.1%) greater than observation (12.3%); $P=0.007$. −132.3 μm (0.7 mg) vs −30.2 μm; (observation) $P<0.001$. 36.4% (0.7 mg) vs 5.4% (observation); $P<0.001$
Boyer et al[81]	II	55	6	0.7 mg DEX implant (vitrectomized patients)	BCVA increase from baseline at month 6. Percentage of patients gaining ≥10 letters in BCVA from baseline. CRT change from baseline at month 6. Percentage of patients with fluorescein leakage in the macula	Mean +3.0 letters; $P=0.046$. 21% at month 6. Mean −38.9 μm at month 6; $P=0.004$. 96.4% at baseline vs 84.0% at month 6
Callanan et al[78]	II	253	12	0.7 mg DEX implant + laser vs laser	Percentage of patients gaining ≥10 letters in BCVA from baseline at month 12. BCVA change from baseline. CRT change from baseline. Fluorescein leakage area from baseline	27.8% (0.7 mg DEX implant + laser) vs 23.6% (laser); $P=0.453$. Greater improvement in DEX implant + laser than laser alone, in patients with diffuse DME over 12 months (AUC analysis); $P<0.001$. No significant difference between arms in mean CRT change from baseline at month 12. Mean change in leakage area decreased greater in DEX implant + laser than laser alone, in all time points; $P≤0.041$
Gillies et al[79]	II	88	12	0.7 mg DEX implant vs 1.25 mg bevacizumab	Percentage of patients gaining ≥10 letters in BCVA from baseline at month 12. Mean improvement in BCVA. CRT change from baseline	41% (DEX implant) vs 40% (bevacizumab); $P=0.99$. +5.6 letters (DEX implant) vs +8.9 letters (bevacizumab); $P=0.24$. Mean −187 μm (DEX implant) vs −122 μm (bevacizumab); $P=0.015$
Boyer et al[76]	III	1,048	36	0.35 mg DEX implant vs 0.7 mg DEX implant vs sham	Percentage of patients gaining ≥15 letters in BCVA from baseline at month 36. CRT decrease from baseline	0.7 mg DEX implant (22.2%), and 0.35 mg DEX implant (18.4%) greater than sham (12%); $P≤0.018$. Mean decrease in CRT with 0.7 mg DEX implant (−111.6 μm), and 0.35 mg DEX implant (−107.9 μm) greater than sham (−41.9 μm); $P<0.001$ (AUC analysis)

Abbreviations: AUC, area under the curve; BCVA, best corrected visual acuity; CRT, central retinal thickness; DDS, drug delivery system; DEX, dexamethasone.

described for month 3, which was significantly decreased in the 700 μg DEX implant compared to the observed patients. The same study group analyzed the different patterns of DME from the previously published trial,[58,75] and the patterns were classified as: focal, cystoid, diffuse, and cystoid–diffuse. A significant decrease in the CRT and an improvement of 10 or more letters in the BCVA were achieved at day 90 in all of the patterns of DME treated with the 700 μg DEX implant.

The longest trial using the DEX implant for DME was a 3-year, randomized, sham-controlled, Phase III study, which evaluated the efficacy and safety of 0.7 and 0.35 mg DEX implants.[76] Two identical trials conducted at the same time were combined for the analysis, and a total of 1,048 patients were randomized into groups, receiving either the 0.7 or 0.35 mg DEX implant or a sham injection. At baseline, only 27.8% of the cases did not receive any previous treatments for DME. At the end of 3 years, 57.9% of the patients completed the study, which was higher in the DEX implant groups (64.1% in the 0.7 mg DEX implant group and 66.3% in the 0.35 mg DEX implant group) and lower in the sham group due to nonefficacy (43.4%). The mean number of retreatments received by the patients was 4.1, 4.4, and 3.3, with the 0.7 mg DEX implant, 0.35 mg DEX implant, and sham injection, respectively, during the trial (retreatments with DEX implant was done ≥6 months after the most recent implant and sham group received no active treatment). As a primary outcome of gaining 15 letters or more from baseline at the final visit, a significant difference was found between the two treatment arms and the sham injection (22.2% for the 0.7 mg DEX implant, 18.4% for the 0.35 mg DEX implant, and 12% for the sham; $P \leq 0.018$). The primary outcome was also found in similar percentages for the phakic and pseudophakic patients at the end of the study. At the final follow-up, the CRT decrease from the baseline was significant in the 0.7 and 0.35 mg DEX implants compared to the sham group (mean: −111.6 and −107.6 vs −41.9 μm, respectively, $P < 0.001$). In addition, an increase in the CRT was only reported in the sham injection group after cataract surgery. VEGF levels are known to be increased in the aqueous humor 1 day after cataract surgery, decreasing to the normal levels 1 month later.[77] A decrease in the CRT was found in the treated arms after the cataract surgery, and the DEX implant provided possible protection against the inflammatory process in the treated groups that had cataract surgery.[76]

DEX intravitreal implant + laser vs laser

The PLACID study group conducted a randomized, controlled, multicenter, 12-month trial to compare a 0.7 mg DEX implant with laser photocoagulation and with laser alone in the treatment of DME.[78] Patients (n=253) with DME were initially randomized into two groups, where one group received a 0.7 mg DEX implant and the other had a sham injection. All of the patients were treated with laser photocoagulation 1 month later, and retreatment with the DEX implant was done at 6 and 9 months as needed. The laser photocoagulation was repeated at 3 month intervals as required. At least a 10 letter statistically significant increase from the baseline was obtained in a higher percentage of the patients at week 1 and months 1 and 9 in the DEX implant plus laser group. Additionally, a significant difference in the BCVA was found in a higher percentage for the DEX implant with laser at week 1 and months 1, 4, and 9 in a subgroup of the DME patients with diffuse macular capillary bed leakage. As the primary efficacy variable, there was no significant difference found for ≥10 letters of improvement from the baseline at month 12 (27.8% vs 23.6%, DEX implant + laser vs laser, respectively). The maximum increase in the BCVA was obtained 1 month after the second retreatment with the implant or sham injection (+7.9 vs +2.3 letters). Furthermore, a significant decrease in the central macular thickness was found in 4 of 8 visits, but no difference was obtained in either group at months 6 and 12 for the CRT. The change in the area of leakage measured with fluorescein angiography was significantly greater in the DEX implant group in all visits. One important finding of the study was discordance between the optical coherence tomography results and BCVA. The laser alone had an effect on reducing the edema at month 6, but the BCVA only improved in the DEX implant plus laser group at same time point. The authors concluded that the intervals for retreatment with the DEX implant were not enough because the CRT did not differ at months 6 and 12.

DEX intravitreal implant vs bevacizumab

Intravitreal bevacizumab (1.25 mg) and the DEX (0.7 mg) implant were compared in a randomized, Phase II trial called the BEVORDEX study.[79] Forty-two eyes received intravitreal bevacizumab every 4 weeks, and 46 eyes received an intravitreal DEX (0.7 mg) implant every 16 weeks, with a PRN regimen for 12 months. The primary outcome of the study was to gain ten or more letters in the BCVA at 12 months, which was achieved in 40% of the bevacizumab-treated eyes and 41% of the DEX implant-treated group ($P=0.99$). The mean CRT decrease was statistically significant between the groups, and the reduction was −122 μm in the bevacizumab group and −187 μm in the DEX implant group ($P=0.015$). The mean number of injections over 1 year was 8.6 for the

bevacizumab group and 2.7 for the DEX implant group. Finally, in the DEX implant-treated eyes, 11% lost ten or more letters of the BCVA, which was due to cataracts in 4 of 5 cases; none lost ≥ ten letters in the bevacizumab-treated eyes.

DEX in vitrectomized eyes

The pharmacokinetic profile of the 0.7 mg DEX implant in vitrectomized and nonvitrectomized eyes was studied in an animal model by Chang-Lin et al.[80] In this study, the concentration of DEX in the vitreous fluid and retina did not differ statistically significantly between the vitrectomized and nonvitrectomized eyes during each visit of 31 days of follow-up. The OZURDEX CHAMPLAIN study assessed the efficacy and safety of the 0.7 mg DEX implant in vitrectomized patients with treatment-resistant DME.[81] In this prospective, multicenter, 26-week, Phase II trial, the patients (n=55) had a mean duration of DME for 43 months and had pars plana vitrectomy 31 months prior to the study. The maximum effect for the decrease of the mean CRT was obtained at week 8, and it was statistically significantly lower than the baseline during the study (mean: −156 μm, $P<0.001$). An increase in the BCVA from the baseline was observed at week 1, and the mean gain in the letters was found to be +6.0 at week 8 and +3.0 letters at week 26. At the end of the study, 43% of the patients gained at least 5 letters, and 21% had gained at least 10 letters. A loss of ≥10 letters was observed in 11%, and loss of ≥15 letters in 7% the patients at the final visit. A slight decrease in the BCVA and increase in the CRT began at month 2, after the peak values, and continued over 6 months.

Medeiros et al[82] evaluated the effects of the DEX implant in vitrectomized or nonvitrectomized DME patients who failed to succeed with other therapies. Patients who were treated at least 3 months previously with laser photocoagulation, intravitreal triamcinolone acetonide, or intravitreal anti-VEGF received a single implant and were followed up for 6 months. Significant anatomical and functional success was achieved from the baseline at months 1, 3, and 6, after the treatment in both groups. However, no significant difference was found between the groups. Similar results for the improvement of the BCVA and CRT at 2 and 4 months after a single implant were found between the vitrectomized and nonvitrectomized eyes in the Bonnin et al[83] study. Recurrence was reported at month 4 in 79% of the eyes. Vitrectomized DME patients treated with some drugs including TA causes a challenging situation, because of the increased drug clearence.[84–87] Sustained release drugs, such as the DEX implant, provide a good treatment option in vitrectomized patients with DME.

DEX intravitreal implant in persistent, treatment-refractory DME

Apart from the treatment of naïve cases, persistent DME patients who have not responded to any previous treatment modality form a challenging group. Efficacy of 0.7 mg DEX implant in refractory, persistent DME, who were initially treated with other modalities (laser, intravitreal anti-VEGF, TA), was reported in several studies with case series to larger number of participants.[88–97] One retrospective, interventional case series study evaluated the single injection of a 0.7 mg DEX implant in 58 patients with persistent DME.[92] Significant improvements from the baseline in the BCVA and CRT were observed at months 1, 3, and 6. The effect of DEX was evaluated for 4 months in patients with chronic DME who were unresponsive to a minimum of three bevacizumab injections.[94] Only the values at month 1 for the BCVA and at months 1, 2, and 3 for the CRT showed significant differences from the baseline. A similar study was done by Totan et al,[96] which evaluated 0.7 mg DEX implant in bevacizumab persistent DME. They found improvement in BCVA and CRT during the 3 months postinjection, but both anatomic and functional outcomes regressed between 3 and 6 months.

Zhioua et al[95] performed a retrospective study to assess the efficacy of a 0.7 mg DEX implant in DME patients who failed to respond to at least 6 monthly consecutive intravitreal ranibizumab injections. During the study period of 9 months, the BCVA and CRT were significantly improved at months 1, 3, 6, and 9 from the baseline values, and only one patient required a second DEX implant. A comparison between the refractory and treatment-naïve cases treated with a 0.7 mg DEX implant was conducted by Escobar-Barranco et al.[98] Their study was conducted during a 6-month period, and 80% of the naïve and 69.4% of the refractory patients required one or two additional DEX implants, with additional laser photocoagulation sessions. Both groups showed better BCVAs from the baseline in the follow-up period, while the naïve cases gained more letters than the refractory patients in all of the visits. The total macular volume and CRT showed similar values during the study, and both were significantly decreased from the baseline values. Apart from the other studies, retreatment with the implant was done starting at 3 months, and the median time for the reinjection was 4 months. Retreatment was needed in a higher percentage of the refractory patients (80% in refractory vs 69.4% in naïve patients).

A subgroup analysis of the naïve and nonnaïve cases among nonvitrectomized eyes was conducted in the Bonnin et al[83] study, in which the naïve eyes showed better outcomes in the BCVA than the nonnaïve eyes, and the CRT did not differ between the groups. A multicentric study from France also assessed naïve and nonnaïve DME patients in subgroup analysis, and improvement in BCVA was obtained in two groups, but significant difference was found only at month 4 (71.3 letters, naïve vs 60.5 nonnaïve; P=0.005).[99] Both the naïve and nonnaïve patients showed anatomical responses to the DEX implant, but irreversible impairment of the retinal tissue in the refractory cases might result in less visual acuity gain than in the naïve patients. The authors concluded that, according to the better BCVAs in the naïve cases, treatment with the implant in the earlier stages of DME might be more advantageous.[98]

Overall, the studies showed improvements for the BCVA and CRT from the baseline in some of the visits, but significant data were not obtained for exactly the same time points. This disparity might be a result of the variances in the duration of the DME in the patients, the metabolic control status, baseline BCVA, and CRT.

There is no consensus on the best treatment choice for any of the intravitreal drugs used for DME. Anti-VEGF medications are considered to be the first-line therapies for DME, especially in phakic cases. However, in partial responders to anti-VEGF treatment or in pseudophakic patients, combination therapies are gaining more interest for achieving better anatomical and functional results as well as for reducing the injection numbers. A combination of triamcinolone with anti-VEGF agents for the treatment of DME has been assessed in the literature.[100–105] However, adding triamcinolone to the anti-VEGF drugs did not have a significant difference on the efficacy during the long-term follow-up.

Maturi et al[106] conducted a 12-month, randomized, controlled study to evaluate the effects of a 0.7 mg DEX implant combined with bevacizumab compared to bevacizumab monotherapy in the DME patients who had previously responded poorly to bevacizumab. The average number of bevacizumab injections was six in the combination group and nine in the bevacizumab only group; however, the combination group needed an average number of 2.1 DEX implant treatments. The first implant was injected at month 1, and additional implants were injected at months 5 and 9. At the end of 1 year, an increase in the BCVA was reported in the two groups, but did not significantly differ between the groups. The combination group had a significantly reduced CRT from the monotherapy group from baseline at the final visit (−45 μm in combination group vs −30 μm in bevacizumab group, P=0.03). Also, CRT was significantly decreased from baseline at month 12 in patients who received the combination therapy to one eye and monotherapy to the other (−92 vs −2 μm, respectively, P=0.048).

In major clinical trials, the patients usually receive retreatments with implants in predetermined intervals of a minimum of 6 months.[76,78] This might contradict the real-life experience for the retreatment time as well as the maximum BCVA gain. The effects of repeated intravitreal DEX implants for DME were assessed in 15 eyes of 12 patients,[107] where the participants received at least two implants during an "as needed" regimen during the follow-up. Overall, 7 eyes received 3, 3 eyes had 4, and 3 eyes had 5 implants, and the duration for the retreatment ranged between 4 and 21 months. An improvement in the BCVA and a decrease in the CRT were obtained after all of the repeated injections. Seven eyes had a rebound effect of an increase in the CRT that was higher than the baseline, after an early response to treatment; however, all of these eyes showed positive responses to the retreatment. The anatomical responses after the first and second implants were found to be more successful than the functional improvements.

To determine the exact time for retreatment with the DEX implant, Panozzo et al[108] also applied an "as needed" regimen for 20 eyes with DME. The retreatment interval ranged between 3 and 7 months, with a mean of 5.3 months for naïve cases, and 5 months for nonnaïve cases, and more of the naïve cases needed retreatment at months 6 and 7 (P<0.05). As the DEX implant begins to be used more commonly for DME, the best intervals between the treatments will be defined.

Safety
IOP increase
The most common concern about the intraocular use of corticosteroids is the increase in the IOP.[48–50] The elevated IOP appeared to be lower in the DEX implant studies than in the patients treated with the FA implant and TA;[109] however, there is no prospective trial that compares the safety of the three synthetic corticosteroids. An IOP increase was observed in 40% of the patients treated with 4 mg of TA for DME over 2 years, in which IOP-lowering medication was needed in 37% of the patients, 4.8% of the cases required incisional glaucoma surgery, and 1.3% needed selective laser trabeculoplasty over 3 years in the DME patients treated with a low-dose (0.2 μg/d) FA implant.[65,110]

During the PLACID study, the DEX implant plus laser group had more frequent IOP increases than the laser

only group.[78] At least a 10 mmHg increase from the baseline was found in 15.2% of the patients receiving the DEX implant plus laser vs 1.6% in the laser only treatment; 16.8% of the patients had IOPs ≥25 mmHg in the DEX implant plus laser arm. At month 12, none of the eyes had IOPs of 25 mmHg or higher, and surgery was not required for controlling the IOP.

In a 12-month BEVORDEX trial, the eyes that experienced IOPs higher than 25 mmHg at least once during the visits were all in the DEX implanted eyes (26%) vs none in the bevacizumab group.[79] The eyes with increased IOPs were managed with observation or topical IOP-lowering medications. Furthermore, the 3-year MEAD study reported that the percentages of IOP ≥25 mmHg at any visit were 32%, 27.4%, and 4.3% in the 0.7 and 0.35 mg DEX implant and sham groups, respectively, and that one patient from the 0.7 mg and 0.35 mg DEX implant groups required a trabeculectomy.[76] In years 2 and 3, as well as after the retreatments, the incidence of IOP-related AE did not increase. No cumulative effect of DEX on the IOP was determined during the study.

In combination therapy with bevacizumab, 28.5% of the patients had IOPs of >21 mmHg, and all were controlled with topical medications.[106] Even in the repeated implants which were all controlled with medication, 1 of 15 eyes developed IOP increases after the second injection, and 1 of 7 eyes developed them after the third injection, with a mean increase time of 1–3 months after the injection.[107] An IOP increase was found in 20% of the 15 eyes that received at least two implants, and all of them were treated with anti-glaucomatous medications.[107]

Cataract

One of the other major adverse effects of concern for corticosteroids was the development or progression of cataracts in phakic patients. In the studies with shorter than 6 months of follow-up, it is not feasible to assess the cataract progression. The phakic patients in the DRCR.net trial showed that 51% of the patients in the TA group needed cataract surgery over 2 years.[110] However, 80% of the patients receiving a low-dose (0.2 µg/d) FA implant required cataract surgery during the 3-year follow-up in the FAME study.[65] In a comparative study of the DEX implant plus laser versus laser alone, the cataract progression in the phakic eyes was significantly higher in the DEX implant group (22.2% vs 9.5%; *P*=0.017) at 12 months, but the surgery rates did not differ between the groups.[78] In the BEVORDEX study, the increases in the cataract ≥2 grades were 13% and 4.8%, and 6.5%, and 2.4% of the patients

required surgery for cataracts in the 0.7 mg DEX implant and bevacizumab groups, respectively.[79]

The 3-year data from the MEAD study showed that the incidence of cataracts in the phakic patients was 67.9%, 64.1%, and 20.4% in the 0.7 and 0.35 mg DEX implants and sham injection groups from the baseline, respectively, and the surgical requirement for cataracts was 59.2%, 52.3%, and 7.2%, respectively.[76] In the DEX implant groups, 75% of the patients had cataract surgery between 18 and 30 months, and these findings support the fact that short-term studies are insufficient to evaluate the cataract progression and that retreatments might also increase the progression.

Others

Conjunctival hemorrhages due to injection procedure is one of the frequent adverse ocular events, in addition to the rise in the IOP and cataracts in some of the studies.[78,79,81,106] Despite the frequency, conjunctival hemorrhages are usually resolved without complications. Ocular adverse events, such as retinal tears, retinal detachment, endophthalmitis, and hypotony, appeared in <2% of the patients.[76] Eye pain, vitreous hemorrhages, and floaters were also reported as an adverse ocular event.[76,78,79]

Systemic adverse events

In contrast to the local ocular adverse events related to steroids, systemic adverse event rate increases are most often reported in the trials using anti-VEGF for DME, contributing to chronic VEGF inhibition.[16–18] In most of the studies with the DEX implant, no significant systemic adverse events (SAEs) were reported;[78,106] however, most of these studies included a small sample size and were continued for less than 1 year. The most common SAEs in the treatment arms of one 3-year randomized, Phase III study were cellulitis (1.4%) in the 0.7 mg DEX implant group, congestive heart failure (2.6%) in the 0.35 mg DEX implant group, prostate cancer (1.4%) in the male patients, and cerebrovascular incident (1.1%) in the sham group.[76] The 3-year data showed that cardiac disorders were nearly the same between the 0.7 mg DEX implant and sham groups, but higher in the 0.35 mg DEX implant group (5.7% in the 0.7 mg DEX implant arm, 9.6% in the 0.35 DEX implant arm, and 5.6% in the sham arm).[76] Cerebrovascular incidents were found in 1.2%, 0.9%, and 1.1% of the 0.7 mg DEX implant, 0.35 mg DEX implant, and sham groups, respectively.[76] Death was reported in all of the treatment arms of the MEAD study, but none of the deaths were related to the treatment.[76]

In the BEVORDEX study, three patients received both interventions, one in either eye, and had SAEs, one had a myocardial infarction and two had cerebrovascular incidents.[79] Even in the repeated treatments, no systemic adverse events were reported.[107] The intravitreal 0.7 mg DEX implant seems to have a favorable systemic safety profile, and may help physicians who experience difficulties in using anti-VEGF agents because of systemic concerns.

Quality of life

For patients with existing life-long systemic diseases, such as diabetes, additional visits for ocular pathologies among their examinations at other clinics constitute a treatment burden. These patients are most likely to prefer fewer injections and visits in DME treatments. Anti-VEGF agents are known to have better outcomes in the quality of life than in laser therapy.[111–113] However, no such analyses for the quality of life indices have been reported for intravitreal steroid implants. Although it was not statistically significant, the patients who had bevacizumab in one eye and an implant in the other eye preferred the DEX implant.[79] The National Eye Institute Visual Functioning Questionnare-25 scores improved after treatment with the injection of the DEX implant.[81] Sustained release drugs may be more appropriate in selected cases to decrease the frequency of visits, injections, and the cost of therapy.

Conclusion

DME continues to be a major problem in diabetic patients. As the prevalence of diabetes increases, the treatment modalities for DME are also evolving, and nowadays, there are multiple treatment options available. Laser photocoagulation is used nowadays for noncenter involving DME and in combination therapies with pharmacological agents to increase the treatment response. Anti-VEGF agents are currently used as the first-line of treatment for DME, particularly in phakic patients. But in some patients with DME who did receive anti-VEGF, complete response was not shown even after multiple injections. Inflammation plays an important role in DME and leads to BRB breakdown, resulting in macular edema.[19,20] Pharmacological agents targeting the inflammatory process constitute a valuable option for treating DME.[9,19,114,115] Corticosteroids have a potent anti-inflammatory and anti-edema effect. A synthetic corticosteroid, DEX implant, is in clinical use for the treatment of DME in a form of sustained release DDS to extend the duration of action. Clinical trials have shown the efficacy and safety of DEX implants for the management of DME, without significant systemic side effects. The intravitreal 0.7 mg DEX implant gives ophthalmologists an alternative treatment strategy in DME to reduce the treatment burden and to increase the therapeutic efficacy, especially in pseudophakic eyes without the risk of glaucoma. It also helps those with persistent DME despite numerous anti-VEGF treatments, in patients with anti-VEGF contraindicated due to systemic concerns, and in combination therapies with laser and intravitreal anti-VEGF. In addition, head-to-head clinical trials between anti-VEGFs and the DEX implant will improve our knowledge of the efficacy and safety. The best treatment option in DME should be tailored to individual cases and should be defined according to the disease and patient characteristics.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract*. 2014;103(2):137–149.
2. Fong DS, Aiello LP, Ferris FL 3rd, Klein R. Diabetic retinopathy. *Diabetes Care*. 2004;27(10):2540–2553.
3. Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic macular edema. *Curr Diab Rep*. 2012;12(4):346–354.
4. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35(3): 556–564.
5. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. *Ophthalmology*. 1995;102(1):7–16.
6. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. *Ophthalmology*. 2009;116(3):497–503.
7. Cugati S, Kifley A, Mitchell P, Wang JJ. Temporal trends in the age-specific prevalence of diabetes and diabetic retinopathy in older persons: population-based survey findings. *Diabetes Res Clin Pract*. 2006;74(3):301–308.
8. Klein R, Klein BE. Are individuals with diabetes seeing better? a long-term epidemiological perspective. *Diabetes*. 2010;59(8):1853–1860.
9. Das A, McGuire PG, Rangasamy S. Diabetic macular edema: pathophysiology and novel therapeutic targets. *Ophthalmology*. 2015; 122(7):1375–1394.
10. Early Treatment Diabetic Retinopathy Study research group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol*. 1985; 103(12):1796–1806.
11. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. *Arch Ophthalmol*. 2012;130(8):972–979.
12. Elman MJ, Ayala A, Bressler NM, et al; Diabetic Retinopathy Clinical Research Network. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. *Ophthalmology*. 2015;122(2):375–381.
13. Do DV, Nguyen QD, Khwaja AA, et al; READ-2 Study Group. Ranibizumab for edema of the macula in diabetes study: 3-year outcomes and the need for prolonged frequent treatment. *JAMA Ophthalmol*. 2013;131(2):139–145.

14. Schmidt-Erfurth U, Lang GE, Holz FG, et al; RESTORE Extension Study Group. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. *Ophthalmology*. 2014;121(5):1045–1053.

15. Massin P, Bandello F, Garweg JG, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. *Diabetes Care*. 2010;33(11):2399–2405.

16. Nguyen QD, Brown DM, Marcus DM, et al; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012; 119(4):789–801.

17. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology*. 2014; 121(11):2247–2254.

18. Wells JA, Glassman AR, Ayala AR, et al; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372(13):1193–1203.

19. Rangasamy S, McGuire PG, Das A. Diabetic retinopathy and inflammation: novel therapeutic targets. *Middle East Afr J Ophthalmol*. 2012; 19(1):52–59.

20. Semeraro F, Cancarini A, dell'Omo R, Rezzola S, Romano MR, Costagliola C. Diabetic retinopathy: vascular and inflammatory disease. *J Diabetes Res*. 2015;2015:582060.

21. Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. *Surv Ophthalmol*. 2009;54(1):1–32.

22. McLeod DS, Lefer DJ, Merges C, Lutty GA. Enhanced expression of intracellular adhesion molecule-1 and P-selectin in the diabetic human retina and choroid. *Am J Pathol*. 1995;147(3):642–653.

23. Del Maschio A, Zanetti A, Corada M, et al. Polymorphonuclear leukocyte adhesion triggers the disorganization of endothelial cell-to-cell adherens junctions. *J Cell Biol*. 1996;135(2):497–510.

24. Miyamoto K, Khosrof S, Bursell SE, et al. Prevention of leukostasis and vascular leakage in streptozotocin-induced diabetic retinopathy via intercellular adhesion molecule-1 inhibition. *Proc Natl Acad Sci U S A*. 1999;96(19):10836–10841.

25. Miyamoto K, Hiroshiba N, Tsujikawa A, Ogura Y. In vivo demonstration of increased leukocyte entrapment in retinal microcirculation of diabetic rats. *Invest Ophthalmol Vis Sci*. 1998;39(11):2190–2194.

26. Nozaki M, Ogura Y, Hirabayashi Y, Saishin Y, Shimada S. Enhanced expression of adhesion molecules of the retinal vascular endothelium in spontaneous diabetic rats. *Ophthalmic Res*. 2002;34(3):158–164.

27. Adamis AP, Miller JW, Bernal MT, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol*. 1994;118(4):445–450.

28. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med*. 1994;331(22):1480–1487.

29. Pe'er J, Folberg R, Itin A, Gnessin H, Hemo I, Keshet E. Upregulated expression of vascular endothelial growth factor in proliferative diabetic retinopathy. *Br J Ophthalmol*. 1996;80(3):241–245.

30. Aiello LP, Bursell SE, Clermont A, et al. Vascular endothelial growth factor-induced retinal permeability is mediated by protein kinase C in vivo and suppressed by an orally effective beta-isoform-selective inhibitor. *Diabetes*. 1997;46(9):1473–1480.

31. Qaum T, Xu Q, Joussen AM, et al. VEGF-initiated blood-retinal barrier breakdown in early diabetes. *Invest Ophthalmol Vis Sci*. 2001; 42(10):2408–2413.

32. Antonetti DA, Barber AJ, Hollinger LA, Wolpert EB, Gardner TW. Vascular endothelial growth factor induces rapid phosphorylation of tight junction proteins occludin and zonula occluden 1. A potential mechanism for vascular permeability in diabetic retinopathy and tumors. *J Biol Chem*. 1999;274(33):23463–23467.

33. Melder RJ, Koenig GC, Witwer BP, Safabakhsh N, Munn LL, Jain RK. During angiogenesis, vascular endothelial growth factor and basic fibroblast growth factor regulate natural killer cell adhesion to tumor endothelium. *Nat Med*. 1996;2(9):992–997.

34. Semeraro F, Cancarini A, Morescalchi F, et al. Serum and intraocular concentrations of erythropoietin and vascular endothelial growth factor in patients with type 2 diabetes and proliferative retinopathy. *Diabetes Metab*. 2014;40(6):445–451.

35. Costagliola C, Daniele A, dell'Omo R, et al. Aqueous humor levels of vascular endothelial growth factor and adiponectin in patients with type 2 diabetes before and after intravitreal bevacizumab injection. *Exp Eye Res*. 2013;110:50–54.

36. Schwartz SG, Flynn HW Jr, Scott IU. Intravitreal corticosteroids in the management of diabetic macular edema. *Curr Ophthalmol Rep*. 2013;1(3).

37. Nauck M, Karakiulakis G, Perruchoud AP, Papakonstantinou E, Roth M. Corticosteroids inhibit the expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells. *Eur J Pharmacol*. 1998;341(2–3):309–315.

38. Edelman JL, Lutz D, Castro MR. Corticosteroids inhibit VEGF-induced vascular leakage in a rabbit model of blood-retinal and blood-aqueous barrier breakdown. *Exp Eye Res*. 2005;80(2):249–258.

39. Tamura H, Miyamoto K, Kiryu J, et al. Intravitreal injection of corticosteroid attenuates leukostasis and vascular leakage in experimental diabetic retina. *Invest Ophthalmol Vis Sci*. 2005;46(4): 1440–1444.

40. Qi HP, Bi S, Wei SQ, Cui H, Zhao JB. Intravitreal versus subtenon triamcinolone acetonide injection for diabetic macular edema: a systematic review and meta-analysis. *Curr Eye Res*. 2012;37(12):1136–1147.

41. Chieh JJ, Roth DB, Liu M, et al. Intravitreal triamcinolone acetonide for diabetic macular edema. *Retina*. 2005;25(7):828–834.

42. Chuang LH, Yeung L, Wang NK, et al. Secondary ocular hypertension after intravitreal injection with 2 mg or 4 mg of triamcinolone in retinal vein occlusion. *J Ocul Pharmacol Ther*. 2010;26(4):325–328.

43. Jonas JB, Spandau UH, Kamppeter BA, et al. Repeated intravitreal high-dosage injections of triamcinolone acetonide for diffuse diabetic macular edema. *Ophthalmology*. 2006;113(5):800–804.

44. Jonas J, Kreissig I, Sofker A, Degenring R. Intravitreal injection of triamcinolone for diffuse diabetic macular edema. *Arch Ophthalmol*. 2003;121(1):57–61.

45. Sutter FK, Simpson JM, Gillies MC. Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment: three-month efficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial. *Ophthalmology*. 2004; 111(11):2044–2049.

46. Gillies MC, Sutter FK, Simpson JM, Larsson J, Ali H, Zhu M. Intravitreal triamcinolone for refractory diabetic macular edema: two-year results of a double-masked, placebo-controlled, randomized clinical trial. *Ophthalmology*. 2006;113(9):1533–1538.

47. Gillies MC, Simpson JM, Gaston C, et al. Five-year results of a randomized trial with open-label extension of triamcinolone acetonide for refractory diabetic macular edema. *Ophthalmology*. 2009; 116(11):2182–2187.

48. Rhee DJ, Peck RE, Belmont J, et al. Intraocular pressure alterations following intravitreal triamcinolone acetonide. *Br J Ophthalmol*. 2006;90(8):999–1003.

49. Roth DB, Verma V, Realini T, Prenner JL, Feuer WJ, Fechtner RD. Long-term incidence and timing of intraocular hypertension after intravitreal triamcinolone acetonide injection. *Ophthalmology*. 2009;116(3):455–460.

50. Yamashita T, Uemura A, Kita H, Sakamoto T. Intraocular pressure after intravitreal injection of triamcinolone acetonide following vitrectomy for macular edema. *J Glaucoma*. 2007;16(2):220–224.

51. London NJ, Chiang A, Haller JA. The dexamethasone drug delivery system: indications and evidence. *Adv Ther*. 2011;28(5):351–366.

52. Edelman JL. Differentiating intraocular glucocorticoids. *Ophthalmologica*. 2010;224(Suppl 1):25–30.

53. Gan IM, Ugahary LC, van Dissel JT, van Meurs JC. Effect of intravitreal dexamethasone on vitreous vancomycin concentrations in patients with suspected postoperative bacterial endophthalmitis. *Graefes Arch Clin Exp Ophthalmol*. 2005;243(11):1186–1189.

54. Thakur A, Kadam R, Kompella UB. Trabecular meshwork and lens partitioning of corticosteroids: implications for elevated intraocular pressure and cataracts. *Arch Ophthalmol*. 2011;129(7):914–920.

55. Enyedi LB, Pearson PA, Ashton P, Jaffe GJ. An intravitreal device providing sustained release of cyclosporine and dexamethasone. *Curr Eye Res*. 1996;15(5):549–557.

56. Hainsworth DP, Pearson PA, Conklin JD, Ashton P. Sustained release intravitreal dexamethasone. *J Ocul Pharmacol Ther*. 1996; 12(1):57–63.

57. Zhang L, Li Y, Zhang C, Wang Y, Song C. Pharmacokinetics and tolerance study of intravitreal injection of dexamethasone-loaded nanoparticles in rabbits. *Int J Nanomedicine*. 2009;4:175–183.

58. Kuppermann BD, Blumenkranz MS, Haller JA, et al; Dexamethasone DDS Phase II Study Group. Randomized controlled study of an intravitreous dexamethasone drug delivery system in patients with persistent macular edema. *Arch Ophthalmol*. 2007;125(3):309–317.

59. Kuno N, Fujii S. Biodegradable intraocular therapies for retinal disorders: progress to date. *Drugs Aging*. 2010;27(2):117–134.

60. Schwartz SG, Flynn HW Jr. Fluocinolone acetonide implantable device for diabetic retinopathy. *Curr Pharm Biotechnol*. 2011; 12(3):347–351.

61. Sanford M. Fluocinolone acetonide intravitreal implant (Iluvien®): in diabetic macular oedema. *Drugs*. 2013;73(2):187–193.

62. Campochiaro PA, Hafiz G, Shah SM, et al; Famous Study Group. Sustained ocular delivery of fluocinolone acetonide by an intravitreal insert. *Ophthalmology*. 2010;117(7):1393–1399.e3.

63. Jaffe GJ, Ben-Nun J, Guo H, Dunn JP, Ashton P. Fluocinolone acetonide sustained drug delivery device to treat severe uveitis. *Ophthalmology*. 2000;107(11):2024–2033.

64. Campochiaro PA, Brown DM, Pearson A, et al; FAME Study Group. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology*. 2011; 118(4):626–635.

65. Campochiaro PA, Brown DM, Pearson A, et al; FAME Study Group. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology*. 2012;119(10):2125–2132.

66. Pearson PA, Comstock TL, Ip M, et al. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. *Ophthalmology*. 2011; 118(8):1580–1587.

67. Cunha-Vaz J, Ashton P, Iezzi R, et al; FAME Study Group. Sustained delivery fluocinolone acetonide vitreous implants: long-term benefit in patients with chronic diabetic macular edema. *Ophthalmology*. 2014;121(10):1892–1903.

68. Ozurdex® (0.7 mg dexamethasone) [package insert]. Irvine, CA: Allergan Inc.; 2009.

69. Chang-Lin JE, Attar M, Acheampong AA, et al. Pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone intravitreal implant. *Invest Ophthalmol Vis Sci*. 2011;52(1):80–86.

70. Rishi P, Mathur G, Rishi E. Fractured Ozurdex™ implant in the vitreous cavity. *Indian J Ophthalmol*. 2012;60(4):337–338.

71. Roy R, Hegde S. Split Ozurdex implant: a caution. *Can J Ophthalmol*. 2013;48(1):e15–e16.

72. Bourgault S, Albiani D. Re: Split Ozurdex implant: a caution. *Can J Ophthalmol*. 2013;48(3):218–219.

73. Bhagat R, Zhang J, Farooq S, Li XY. Comparison of the release profile and pharmacokinetics of intact and fragmented dexamethasone intravitreal implants in rabbit eyes. *J Ocul Pharmacol Ther*. 2014;30(10):854–858.

74. Haller JA, Kuppermann BD, Blumenkranz MS, et al; Dexamethasone DDS Phase II Study Group. Randomized controlled trial of an intravitreous dexamethasone drug delivery system in patients with diabetic macular edema. *Arch Ophthalmol*. 2010;128(3):289–296.

75. Kuppermann BD, Chou C, Weinberg DV, et al; Dexamethasone DDS Phase II Study Group. Intravitreous dexamethasone effects on different patterns of diabetic macular edema. *Arch Ophthalmol*. 2010;128(5):642–643.

76. Boyer DS, Yoon YH, Belfort R Jr, et al; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121(10):1904–1914.

77. Patel JI, Hykin PG, Cree IA. Diabetic cataract removal: postoperative progression of maculopathy: growth factor and clinical analysis. *Br J Ophthalmol*. 2006;90(6):697–701.

78. Callanan DG, Gupta S, Boyer DS, et al; Ozurdex PLACID Study Group. Dexamethasone intravitreal implant in combination with laser photocoagulation for the treatment of diffuse diabetic macular edema. *Ophthalmology*. 2013;120(9):1843–1851.

79. Gillies MC, Lim LL, Campain A, et al. A randomized clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular edema: the BEVORDEX study. *Ophthalmology*. 2014; 121(12):2473–2481.

80. Chang-Lin JE, Burke JA, Peng Q, et al. Pharmacokinetics of a sustained-release dexamethasone intravitreal implant in vitrectomized and nonvitrectomized eyes. *Invest Ophthalmol Vis Sci*. 2011;52(7):4605–4609.

81. Boyer DS, Faber D, Gupta S, et al; Ozurdex CHAMPLAIN Study Group. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. *Retina*. 2011;31(5):915–923.

82. Medeiros MD, Alkabes M, Navarro R, Garcia-Arumí J, Mateo C, Corcóstegui B. Dexamethasone intravitreal implant in vitrectomized versus nonvitrectomized eyes for treatment of patients with persistent diabetic macular edema. *J Ocul Pharmacol Ther*. 2014;30(9):709–716.

83. Bonnin S, Dupas B, Sanharawi ME, et al. Efficacy of dexamethasone intravitreal implant for the treatment of diabetic macular edema. *Eur J Ophthalmol*. 2015;25(5):448–453.

84. Chin HS, Park TS, Moon YS, Oh JH. Difference in clearance of intravitreal triamcinolone acetonide between vitrectomized and nonvitrectomized eyes. *Retina*. 2005;25(5):556–560.

85. Schindler RH, Chandler D, Thresher R, Machemer R. The clearance of intravitreal triamcinolone acetonide. *Am J Ophthalmol*. 1982; 93(4):415–417.

86. Beer PM, Bakri SJ, Singh RJ, Liu W, Peters GB 3rd, Miller M. Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection. *Ophthalmology*. 2003; 110(4):681–686.

87. Gisladottir S, Loftsson T, Stefansson E. Diffusion characteristics of vitreous humour and saline solution follow the Stokes Einstein equation. *Graefes Arch Clin Exp Ophthalmol*. 2009;247(12):1677–1684.

88. Zucchiatti I, Lattanzio R, Querques G, et al. Intravitreal dexamethasone implant in patients with persistent diabetic macular edema. *Ophthalmologica*. 2012;228(2):117–122.

89. Rishi P, Rishi E, Kuniyal L, Mathur G. Short-term results of intravitreal dexamethasone implant (OZURDEX(®)) in treatment of recalcitrant diabetic macular edema: a case series. *Oman J Ophthalmol*. 2012; 5(2):79–82.

90. Pacella E, Vestri AR, Muscella R, et al. Preliminary results of an intravitreal dexamethasone implant (Ozurdex®) in patients with persistent diabetic macular edema. *Clin Ophthalmol*. 2013;7:1423–1428.

91. Zalewski D, Raczyńska D, Raczyńska K. Five-month observation of persistent diabetic macular edema after intravitreal injection of Ozurdex implant. *Mediators Inflamm*. 2014;2014:364143.

92. Dutra Medeiros M, Postorino M, Navarro R, Garcia-Arumí J, Mateo C, Corcóstegui B. Dexamethasone intravitreal implant for treatment of patients with persistent diabetic macular edema. *Ophthalmologica*. 2014;231(3):141–146.

93. Sorkin N, Loewenstein A, Habot-Wilner Z, Goldstein M. Intravitreal dexamethasone implant in patients with persistent macular edema of variable etiologies. *Ophthalmologica*. 2014;232(2):83–91.

94. Lazic R, Lukic M, Boras I, et al. Treatment of anti-vascular endothelial growth factor-resistant diabetic macular edema with dexamethasone intravitreal implant. *Retina*. 2014;34(4):719–724.

95. Zhioua I, Semoun O, Lalloum F, Souied EH. Intravitreal dexamethasone implant in patients with ranibizumab persistent diabetic macular edema. *Retina*. 2015;35(7):1429–1435.

96. Totan Y, Güler E, Gürağaç FB. Dexamethasone intravitreal implant for chronic diabetic macular edema resistant to intravitreal bevacizumab treatment. *Curr Eye Res*. Epub 2015 Jan 22.

97. Alshahrani ST, Dolz-Marco R, Gallego-Pinazo R, et al; KKESH International Collaborative Retina Study Group. Intravitreal dexamethasone implant for the treatment of refractory macular edema in retinal vascular diseases: results of the KKESH International Collaborative Retina Study Group. *Retina*. Epub 2015 Jun 15.

98. Escobar-Barranco JJ, Pina-Marín B, Fernández-Bonet M. Dexamethasone implants in patients with naïve or refractory diffuse diabetic macular edema. *Ophthalmologica*. 2015;233(3–4): 176–185.

99. Guigou S, Pommier S, Meyer F, et al. Efficacy and safety of intravitreal dexamethasone implant in patients with diabetic macular edema. *Ophthalmologica*. 2015;233(3–4):169–175.

100. Faghihi H, Roohipoor R, Mohammadi SF, et al. Intravitreal bevacizumab versus combined bevacizumab-triamcinolone versus macular laser photocoagulation in diabetic macular edema. *Eur J Ophthalmol*. 2008;18(6):941–948.

101. Soheilian M, Ramezani A, Obudi A, et al. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. *Ophthalmology*. 2009;116(6):1142–1150.

102. Synek S, Veselý P. Intravitreal Bevacizumab with or without triamcinolone for refractory diabetic macular oedema. *Coll Antropol*. 2011;35(3):841–845.

103. Marey HM, Ellakwa AF. Intravitreal bevacizumab alone or combined with triamcinolone acetonide as the primary treatment for diabetic macular edema. *Clin Ophthalmol*. 2011;5:1011–1016.

104. Lim JW, Lee HK, Shin MC. Comparison of intravitreal bevacizumab alone or combined with triamcinolone versus triamcinolone in diabetic macular edema: a randomized clinical trial. *Ophthalmologica*. 2012; 227(2):100–106.

105. Soheilian M, Garfami KH, Ramezani A, Yaseri M, Peyman GA. Two-year results of a randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus laser in diabetic macular edema. *Retina*. 2012;32(2):314–321.

106. Maturi RK, Bleau L, Saunders J, Mubasher M, Stewart MW. A 12-month, single-masked, randomized controlled study of eyes with persistent diabetic macular edema after multiple anti-VEGF injections to assess the efficacy of the dexamethasone-delayed delivery system as an adjunct to bevacizumab compared with continued bevacizumab monotherapy. *Retina*. 2015;35(8):1604–1614.

107. Scaramuzzi M, Querques G, Spina CL, Lattanzio R, Bandello F. Repeated intravitreal dexamethasone implant (Ozurdex) for diabetic macular edema. *Retina*. 2015;35(6):1216–1222.

108. Panozzo G, Gusson E, Panozzo G, Dalla Mura G. Dexamethasone intravitreal implant for diabetic macular edema: indications for a PRN regimen of treatment. *Eur J Ophthalmol*. 2015;25(4):347–351.

109. Kiddee W, Trope GE, Sheng L, et al. Intraocular pressure monitoring post intravitreal steroids: a systematic review. *Surv Ophthalmol*. 2013;58(4):291–310.

110. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology*. 2008;115(9):1447–1449.

111. Mitchell P, Bressler N, Tolley K, et al; RESTORE Study Group. Patient-reported visual function outcomes improve after ranibizumab treatment in patients with vision impairment due to diabetic macular edema: randomized clinical trial. *JAMA Ophthalmol*. 2013; 131(10):1339–1347.

112. Bressler NM, Varma R, Suñer IJ, et al; RIDE and RISE Research Groups. Vision-related function after ranibizumab treatment for diabetic macular edema: results from RIDE and RISE. *Ophthalmology*. 2014;121(12):2461–2472.

113. Virgili G, Parravano M, Menchini F, Evans JR. Anti-vascular endothelial growth factor for diabetic macular oedema. *Cochrane Database Syst Rev*. 2014;10:CD007419.

114. Russo A, Costagliola C, Delcassi L, et al. Topical nonsteroidal anti-inflammatory drugs for macular edema. *Mediators Inflamm*. 2013; 2013:476525.

115. Zhang X, Zeng H, Bao S, Wang N, Gillies MC. Diabetic macular edema: new concepts in patho-physiology and treatment. *Cell Biosci*. 2014;4:27.