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Corticosteroids for Diabetic Macular Edema

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Abstract:

Diabetic macular edema (DME) is a chronic condition with a multifactorial pathogenesis. Vascular endothelial growth factor (VEGF) and several inflammatory mediators are upregulated in eyes with DME. VEGF inhibitors and corticosteroids have all been used successfully in the management of DME. Currently available corticosteroids include triamcinolone acetonide (TA), the dexamethasone (DEX) intravitreal implant, and the fluocinolone acetonide (FA) intravitreal implant. The response to treatment can vary substantially with each treatment modality. Some cases of DME are VEGF driven, and in others, inflammation plays a key role. Chronicity appears to favor corticosteroid treatment. There are no clear guidelines to guide switching from an anti-VEGF to a corticosteroid. Combination therapy of an anti-VEGF drug and a corticosteroid does not appear to provide additional benefit over monotherapy with either drug. The main advantage of corticosteroids over VEGF inhibitors is their longer duration of action. Vitrectomy does not affect the pharmacokinetics of the corticosteroid implants. Common adverse events of corticosteroids include cataract formation, cataract progression, and ocular hypertension. TA may cause a sterile endophthalmitis and pseudoendophthalmitis. Migration of the intravitreal DEX and FA implants into the anterior chamber can be problematic. Because of their less favorable safety profile, corticosteroids are generally used as a second-line treatment for DME. Advantages of using an intravitreal corticosteroid implant include the reduction of treatment burden and predictable pharmacokinetics even in vitrectomized eyes. Pseudophakic eyes, previously vitrectomized eyes and eyes with long-standing DME, particularly of patients who have difficulty in maintaining a monthly appointment, may benefit from primary treatment with a corticosteroid intravitreal implant.

Keywords:

Corticosteroids, dexamethasone implant, diabetic macular edema, diabetic retinopathy, fluocinolone implant, Iluvien, Ozurdex, Retisert, triamcinolone acetonide

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Introduction

Several clinical trials demonstrate that vascular endothelial growth factor (VEGF) inhibitors outperform macular laser photocoagulation (MLP) and have become first-line agents in the treatment of diabetic macular edema (DME).[1-6] Eyes treated with an anti-VEGF gain from 6 to 12 ETDRS letters depending on the baseline visual acuity.[7] Up to 40% of eyes achieve an improvement of ≥3 lines of best-corrected visual acuity (BCVA) and up to 60% gain a BCVA of ≥20/40. Very few eyes lose vision. Nevertheless, despite an intensive anti-VEGF treatment, up to two-thirds of patients exhibit persistent DME at 6 months.[8,9]

Current alternatives for eyes that have a suboptimal response to VEGF inhibitors include corticosteroids. Triamcinolone acetonide (TA) was the first widely used intravitreal medication for DME.[10] Currently available corticosteroids include TA, the dexamethasone (DEX) intravitreal implant, and the fluocinolone acetonide (FA) intravitreal implant.

Pathophysiology of Diabetic Macular Edema

A complete review of the pathophysiologic mechanisms in DME is beyond the scope of

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this paper. Other sources review this topic thoroughly.[11] Briefly, eyes with DME exhibit intraocular upregulation of a myriad of different growth factors and cytokines, such as interleukin-6, interleukin-8, interleukin-1β, monocyte chemotactic protein-1, tumor necrosis factor α, and VEGF. This translates into retinal endothelial damage, thickening of the capillary basement membrane, deposition of extracellular matrix components, and retinal microvasculature damage. Breakdown of the blood–retinal barrier ensues and extracellular fluid accumulates in the macular area.[12,13]

VEGF inhibition is not 100% effective in all patients. Despite six consecutive monthly injections of a VEGF inhibitor, 40%–60% of eyes had persistent DME.[14] This suggests that in some eyes, the main driver of DME is VEGF, whereas in other eyes, other cytokines predominate. Since several inflammatory mediators are upregulated in DME and corticosteroids have broad anti-inflammatory properties, it makes sense to use them in the management of DME.

Intravitreal Pharmacokinetics of Corticosteroids

TA has a 7.5-fold higher anti-inflammatory potency than cortisone.[15] An intravitreal injection of a bolus of TA follows a two-compartment model characterized by an initial burst period followed by a duration period. In the burst period, the TA concentration exponentially decreases. In the duration period, there is a steady decline of drug.[16] In nonvitrectomized eyes, the mean elimination half-life was 18.6 days compared to 3.2 days in the vitrectomized eye. A single intravitreal injection of 4 mg of TA lasts approximately 3 months in the nonvitrectomized human eye.[16,17]

DEX has a 25-fold higher anti-inflammatory potency than cortisol.[18] Because of its higher water solubility, DEX's intravitreal half-life in human eyes is only of 5.5 h.[19] An intravitreal biodegradable DEX sustained-release implant containing 700 μg of dexamethasone embedded in a poly (D, L-lactide-co-glycolide) has been developed (Ozurdex, Allergan Inc., Irvine, CA, USA). As the implant slowly releases DEX, the polymer slowly degrades into water and carbon dioxide. Eventually, the implant completely degrades.

FA has a similar anti-inflammatory potency as DEX.[18] Retisert (Bausch and Lomb, Rochester, NY, USA) is a nonbiodegradable implant that contains 0.59 mg of FA. It is sutured to the pars plana and engineered to release 0.59 μg of FA per day for the 1st month and then 0.3–0.4 μg of FA per day for up to 30 months. The main indication for Retisert has been chronic noninfectious posterior uveitis.[20] Another nonbiodegradable implant containing 0.19 mg of FA (Iluvien, Alimera Sciences, Alpharetta, GA, USA) has been commercialized and approved in several jurisdictions for eyes with DME. Unlike the Retisert implant, Iluvien is injected intravitreally via a 25-gauge needle. It is designed to release 0.20 μg FA per day with a low burst and near-zero order kinetics up to 3 years.[21]

Triamcinolone acetonide

Jonas and Söfker[10] were the first to inject 20 mg of TA intravitreally in an eye with persistent DME following MLP. The DME regressed and the patient regained vision. The visual gains were maintained for at least 5 months. In contrast, most retina specialists started using 4 mg as the dose of intravitreal TA. This decision was based mostly on the ease of use of 4 mg since the readily available commercial preparation of TA was 40 mg/mL. A dose-escalating randomized clinical trial tested doses between 2 and 13 mg of TA in eyes with DME. The effect and duration were dose dependent. However, the rise of intraocular pressure was not.[22]

A Cochrane systematic review from 2007 identified four clinical trials that studied the efficacy of intravitreal TA in a total of 183 eyes with persistent or chronic DME.[23-25] On an average, eyes gained 5.7 letters (24 months) to 14.5 letters (9 months).

Posterior sub-Tenon delivery of TA in the hopes of diminishing the possible adverse events of an intravitreal injection has been explored and deemed not worthy of further study in the management of DME.[26] Animal models have shown that suprachoroidal delivery of drugs provides more selectivity for the choroid and retina than intravitreal injections.[27] Supposedly, less TA will be delivered to the anterior segment of the eye and caused less complications. A Phase I/II clinical trial assessed the safety and efficacy of a proprietary TA that was injected in the suprachoroidal space of eyes with DME with microneedles. This study showed that multiple suprachoroidal injections were well tolerated.[28]

Dexamethasone implants

The MEAD study randomized 1048 patients to 0.7 mg DEX implant, 0.35 mg DEX implant, or sham injections. In this cohort of patients, 67% had prior MLP, 18% had intravitreal steroids, 9% had anti-VEGF, and 28% were treatment naive.[29] Patients were re-injected every 6 months if persistent DME was documented in the optical coherence tomography (OCT). Only 67% of eyes in the DEX groups completed the 3-year study. Among the patients who completed the study, the mean number of implants received was 5. At 3 years, 22.2% of eyes treated with the 0.7 mg implant had a gain of ≥3 lines of BCVA compared to 18.4% in the 0.35 mg implant group and 12% in the sham group. The DEX-treated eyes gained eight letters compared to two letters in the sham group.

At around 15 months, the visual improvement in the DEX-treated eyes was reduced and recovered toward the 3-year visit. This was attributed to the development of cataract around month 15 and later cataract extraction. A third of patients who were treated with the DEX implant required medication to control intraocular pressure (IOP) and 0.3% required incisional surgery to adequately control IOP. The DEX implant does not last 6 months as the manufacturer suggests. A more frequent dosing regimen may improve the visual outcomes.[30]

The RELDEX study was a retrospective review of 128 eyes that were treated with DEX implant.[31] At 3 years, the mean gain in visual acuity was 9.5 letters, 25% had a gain of ≥3 lines of BCVA, 36% had complete resolution of DME, and only 11.4% of eyes had a loss of ≥3 lines of BCVA. These outcomes were obtained with 3.6 DEX injections with a mean re-treatment time period of 7.3 months. Only 4% of eyes required rescue with an anti-VEGF drug.[31]

Treatment-naive eyes fare better with the DEX implant than previously treated eyes.[32-36] Previously treated eyes most likely have more chronic disease and as such may already have sustained irreversible damage.

Fluocinolone acetonide implants

One of the major drawbacks of anti-VEGF treatment of DME is the frequency and number of injections and office visits required to control the disease process.[14] The FA implant can release drug for up to 3 years, which translates into a reduced retreatment frequency and may lower the risk of treatment-associated endophthalmitis.[21,37] The calculated cumulative risk of endophthalmitis after 20–40 injections has been calculated to be around 1%.[38] A retrospective study reviewed 160 eyes that were switched to the Iluvien-FA implant.[37] Before the switch, eyes were being treated every 2.9 months. In contrast, after the switch, eyes were treated every 14.3 months.

The off-label use of the Retisert-FA implant was reported to be beneficial in eyes with DME that had persistent or recurrent DME despite MLP.[39] In a multicenter prospective randomized study, 196 eyes with persistent or recurrent DME were randomized to receive the Retisert-FA implant or the standard of care, which could be additional laser or observation. There was a significant improvement in visual acuity in the eyes implanted with the Retisert-FA implant up to 2 years as compared to the eyes with the standard of care. By 3 years, the differences between the groups were no longer significant, suggesting that by this time the Retisert-FA implant was already being depleted of FA.[39]

The FAME Studies randomly assigned 956 patients with DME refractory to MLP to three groups: 0.2 μg Iluvien-FA per day, 0.5 μg Iluvien-FA per day, or sham injection. Patients could receive rescue MLP 6 months after initial treatment. Eyes enrolled in this study had a mean duration of DME of 5.1 years. At 3 years, 28.7%, 27.8%, and 18.9% gained ≥15 letters, respectively. Despite 0.2 μg Iluvien-FA per day implantation, 40% of eyes required rescue MLP.[40] A subgroup analysis of this study showed that eyes with chronic DME (defined as eyes having DME for >3 years) had a greater response to the Iluvien-FA than eyes with a shorter duration of DME.[41]

In Europe, Iluvien-FA was approved for chronic DME, which was defined as persistent or recurrent DME despite prior treatment. Several European real-world studies have confirmed the functional and anatomic benefits of an Iluvien-FA 0.2 μg implant in DME eyes, with an insufficient response to an anti-VEGF or other corticosteroid. This is in contradistinction of the FAME Studies that enrolled eyes unresponsive to MLP.[42-48] An electronic medical record (EMR)-based study from the United Kingdom validated the results of the FAME Studies.[44] In this study, 345 eyes were followed for an average of 428 days. More than 75% of eyes had an insufficient response to an anti-VEGF agent. About 20% of the patients gained ≥15 letters and gained 5.1 letters from baseline. Importantly, the proportion of patients who achieved a BCVA of ≥20/40 improved from 18% at baseline to almost 40% at 24 months.[44] The Iluvien Registry Safety Study was a Phase IV study that assessed the safety and efficacy of Iluvien in Europe. Almost 600 eyes were registered. Less than a third of eyes required additional treatment for DME. The percentage of eyes gaining a BCVA of ≥20/40 doubled from 19% at baseline to 40% at month 12.[42]

The USER study demonstrated that the visual acuity, before the switch to the Iluvien-FA implant, was maintained while on the implant but with a much reduced treatment burden. However, even with the implant, one-third of eyes required additional treatment to control DME which was comparable to the FAME Studies.[37]

A cost-effectiveness analysis from the United Kingdom concluded that the Iluvien-FA implant provided good value for patients with chronic DME, particularly pseudophakic patients.[49]

Corticosteroids versus Macular Laser Photocoagulation

At 2 years of follow-up, MLP was more effective and had less adverse events than repeated injections of 1 or 4 mg of TA. Early on, the TA caused a greater improvement in BCVA than the MLP-treated eyes. However, as time

went on, the difference vanished. Subgroup analysis of only the pseudophakic eyes did not alter the results. At 2 years, the mean number of treatments for the laser arm was 2.9 compared to 3.5 and 3.2 for the 1 and 4 mg TA arms, respectively. These results were unchanged at 3 years of follow-up.[50,51]

The PLACID Study compared treatment with MLP to MLP plus the DEX implant.[52] Patients were randomized to a DEX (n = 126) or sham implant (n = 127) at baseline plus MLP at month 1. Patients could receive up to three additional MLP treatments and one additional DEX or sham implant as needed. At 12 months, there was no difference between the two arms of the study in terms of 10-letter gain, the primary outcome of the study. However, significant differences were noted at 1 week, 1 month, and 9 months. Anywhere from 22.2% to 30.3% of eyes in the combination arm gained at least 10 letters from baseline. The area under the curve (AUC) analysis demonstrated that more visual gain was achieved in the combination arm than the MLP monotherapy arm. These results are further evidence that the DEX implant lasts less than 6 months in most patients.[52] Similarly, the OZLASE Study randomized 80 eyes to combined DEX plus MLP or MLP monotherapy. The eyes in the combination arm received DEX at baseline and at 16 weeks. Thereafter, they were eligible for repeat DEX every 16 weeks or repeat MLP if re-treatment criteria were met. At 56 weeks, there was no statistical difference in the mean change in BCVA in the combination arm (−0.3 letters) and the MLP arm (+0.4 letters). The anatomic differences were statistically significant, however. The authors suggest that cataract formation in the combination arm confounded the BCVA results. In addition, the inclusion criteria of this trial only allowed patients with relatively good visual acuities to be enrolled, so there could have been a ceiling effect that affected the magnitude of improvement.[53]

Corticosteroids versus Anti-Vascular Endothelial Growth Factor

Since steroids induce cataract progression in phakic eyes, the visual results may be confounded by the development of cataract. A few comparative trials between bevacizumab and TA have been conducted. Most of these have been small retrospective studies with a relatively short follow-up.[54-56] Kriechbaum *et al*.[57] conducted a prospective comparative trial of 2.5 mg of bevacizumab versus 8 mg of TA. At 6 months, the visual gains and decrease in macular thickness were comparable between two groups. At 12 months, the visual gains were superior with bevacizumab. This was attributed to cataract formation in the TA-treated eyes.

Protocol I of the Diabetic Retinopathy Clinical Research (DRCR) network compared intravitreal TA plus immediate MLP to MLP to ranibizumab plus deferred MLP to ranibizumab plus immediate MLP.[4,58,59] Initially, the combination of TA and MLP was superior to MLP monotherapy. By 2 years, the combination of MLP and TA was similar to MLP monotherapy and inferior to both ranibizumab arms. A subgroup analysis of the pseudophakic eyes showed that by 2 years, the results were comparable to the ranibizumab arms. However, by 5 years, the ranibizumab arm was superior to the TA arm.

The BEVORDEX Study compared 42 eyes that were treated with intravitreal bevacizumab to 46 eyes that received a 0.7 mg DEX implant.[60] Eyes in the bevacizumab group were re-injected every 4 weeks, whereas eyes in the DEX implant were re-injected every 16 weeks. At 12 months, there was no difference in either group achieving a ≥10-letter gain from baseline. However, the eyes treated with the DEX implant experienced a greater decrease in central macular thickness (CMT) with fewer injections.[60] Furthermore, the DEX implant was more efficient than bevacizumab in eliminating hard exudates from the center of the fovea.[61] At 2 years, the bevacizumab-treated eyes received an average of 14.6 injections with a mean re-treatment interval of 71 days, whereas the eyes in the DEX implant arm were injected an average of 5.6 times with a mean re-treatment interval of 145 days.[62] Despite the increased treatment burden with bevacizumab, the improvement of vision-related quality of life outcomes in both groups was similar.[63]

A noninferiority, multicenter, 12-month randomized study compared the DEX implant and ranibizumab.[64] Eyes randomized to the DEX implant were injected at baseline and months 5 and 10. Eyes randomized to ranibizumab were injected monthly until maximal visual acuity was obtained (the patient's BCVA was stable for 3 consecutive monthly visits). Rescue MLP was available for both groups. A noninferiority margin of five letters was chosen. At 12 months, the mean gain in the DEX arm was 4.34 letters compared to 7.60 letters in the ranibizumab arm. Since the lower limit of the 95% confidence interval of the difference between both arms was – 4.74 letters, it was concluded that the DEX implant was noninferior to ranibizumab. There were more adverse events in the DEX arm, due to IOP elevation and cataract, compared to the ranibizumab arm. The DEX arm received on average 2.85 injections compared to 8.7 ranibizumab injections.

A comparison of the visual outcomes of the FAME Studies and the ranibizumab plus deferred MLP arm of Protocol I of the DRCR network using the AUC analysis showed that ranibizumab plus deferred MLP was more effective than the Iluvien-FA 0.2 μg per day implant.[65]

The AUC of the Iluvien-FA implant was depressed because of the development of cataract in phakic eyes during the 12–18-month time period. A subgroup analysis of pseudophakic eyes revealed that there was no significant difference between the ranibizumab-treated eyes and the Iluvien-FA treated eyes. In 3 years, eyes received 14 injections of ranibizumab compared to 1.3 injections of the Iluvien-FA implant. Major limitations of this study were that the data were derived from two different clinical trials with entirely different populations. It must be borne in mind that none of the eyes enrolled in FAME were treatment naive. In addition, Protocol I did not specifically look at chronicity of DME.

Switching from Anti-Vascular Endothelial Growth Factor to Corticosteroids

A major difficulty in assessing the literature with respect to the effectiveness of the different treatment modalities is the lack of a consistent definition of what constitutes refractory DME. A *post hoc* analysis of Protocol I of the DRCR network found that the response to ranibizumab after the initial 3 monthly injections was associated with the long-term outcome.[66] Approximately 40% of eyes that started treatment with monthly ranibizumab had persistent DME at 6 months. Eyes with <5-letter gain after three injections showed limited additional improvement for 3 years. At 3 years, despite continuing injections, only 29% of these eyes achieved >10 letters improvement in BCVA. Based on these data, some have recommended switching after the 3rd consecutive monthly anti-VEGF injection if DME persists. Switching studies must be interpreted with caution. Most of these are poorly designed and lack a control group which makes it impossible to know if the improvement was related to regression to the mean, time effects, or secondary to the new drug.[67]

Despite the benefits shown by VEGF inhibition in eyes with DME, there are several barriers to treatment. In many parts of the world, particularly in developing countries, anti-VEGF therapy for DME is not sustainable. Pharmacological treatments are expensive and represent an important economic burden.[68] Multiple visits also impose a burden on the caretakers and patients themselves. Since current anti-VEGF drugs are short acting, they need to be injected frequently. To obtain the best results, patients need to be injected and monitored intensively, particularly during the first 2 years.[4,14] Patients in the real world were monitored less frequently and received fewer injections when compared to patients in clinical trials. Under-treatment is a real issue.[69-72] Advantages of using an intravitreal implant include the reduction of treatment burden.

Combination of Anti-Vascular Endothelial Growth Factor plus Corticosteroid

Monotherapy with corticosteroids or anti-VEGF drugs results in a suboptimal response in up to 60% of eyes.[14] Given the multifactorial nature of DME, some have proposed combination therapy to search for possible synergies. A Cochrane review identified eight randomized clinical trials that compared a combination of a corticosteroid plus an anti-VEGF with anti-VEGF monotherapy.[73] Most of these trials compared TA plus bevacizumab to bevacizumab monotherapy. One study compared the DEX implant plus bevacizumab to bevacizumab monotherapy[74] and another one DEX implant plus ranibizumab to ranibizumab monotherapy.[75] In both of these two studies, the combination arm received the DEX implant every 4 months whereas anti-VEGF was injected monthly as needed. The superior anatomic results in the combination arm did not translate to superior visual outcomes, which were similar between the two arms.[74,75] Based on the current evidence, the addition of a corticosteroid does not appear to add additional benefits to anti-VEGF monotherapy and may add potential complications.

Previous Vitrectomy

Vitrectomy causes a more rapid drug clearance from the vitreous cavity as illustrated by the significant reduction in the mean half-life of TA from 18.6 days in nonvitrectomized eyes compared to 3.2 days in vitrectomized eyes.[16] Corticosteroid intravitreal implants release drugs at a constant rate and provide predictable pharmacokinetics even in vitrectomized eyes.[45,76] The DEX implant improved vision and macular thickness with a peak effectiveness between 8 and 13 weeks in vitrectomized eyes with DME.[76] Another study reported that there were no differences in the anatomic and functional outcomes between previously vitrectomized eyes to nonvitrectomized eyes with chronic refractory DME that were injected with a single Iluvien-FA implant.[45]

Diabetic Retinopathy Severity Score and Diabetic Retinal Neurodegeneration

Worsening in the diabetic retinopathy severity score (DRSS) correlates with the development of proliferative diabetic retinopathy (PDR) and visual loss.[77,78] A *post hoc* analysis of the FAME Studies concluded that sustained release of Iluvien-FA into the vitreous cavity of eyes with DME slows development of PRD and progression of diabetic retinopathy.[79]

Interpretation of DRSS improvement merits caution.[80] In a retrospective review of 18 eyes that underwent

3 consecutive monthly anti-VEGF injections, ultra-widefield color photographs and fluorescein angiograms were compared at baseline and 1 month after the last injection. The DRSS score improved by ≥1 step in 61% of eyes. Despite this improvement, the corresponding fluorescein angiograms in these same eyes showed that there was no reperfusion in the areas lacking perfusion. Eyes with DRSS improvement may still be at high risk of developing PDR.[80]

Corticosteroids may slow down diabetic retinal neurodegeneration. The pre- and post-Iluvien-FA injection OCTs at 3-month intervals of 130 patients were compared.[81] The inner neuroretinal thickness was used as a surrogate marker of retinal neurodegeneration. The rate of thinning of the area 1.5–3 mm from the center of the fovea slowed down after Iluvien-FA implantation.

Adverse Events of Intravitreal Corticosteroids

Ocular hypertension

Up to 50% of eyes that are injected with a corticosteroid will develop a hypertensive response.[82,83] After a follow-up of 5 years, 9% of eyes that had multiple injections of TA required a trabeculectomy.[84]

The IOP response with the DEX implant has been reported.[85-87] At 12 months, 13% of eyes that received two DEX implants had an increase of ≥10 mmHg in IOP from baseline after the first injection and 15% after the second injection. An additional 10% of eyes were started on IOP lowering medications after the second treatment. In general, the IOP elevations were transient and controlled with medication.[85] The MEAD Study reported that over 40% of eyes required initiation of a topical ocular hypotensive agent and 0.3% of eyes required incisional glaucoma surgery.[87] In these trials, the DEX implant was administered no more than every 6 months; however, in the current clinical practice, the DEX implant may be injected every 3–4 months.[85-87] In a retrospective case series of 260 eyes that were treated with the DEX implant every 3 or 4 months, 26% and 7.7% developed an IOP greater than 25 and 35 mmHg, respectively.[88]

During the 4 years of the Retisert-FA implant study, an elevation in IOP ≥30 mmHg was reported in more than 60% of eyes implanted with the Retisert-FA compared to 6% of eyes that did not have an implant. A third of all patients who were treated with the Retisert-FA implant developed uncontrolled ocular hypertension, which required glaucoma filtration surgery or explantation of the device.[39]

Because of this high rate of uncontrolled ocular hypertension with the Retisert-FA implant, the Iluvien-FA implant was designed. In the FAME Studies, 18.4% of eyes that were injected with the 0.2 μg Iluvien-FA per day implant developed an IOP higher than 30 mm compared to 4.3% of eyes treated with the sham injection and 22.9% of the 0.5 μg Iluvien-FA per day implant. Incisional glaucoma surgery was performed in 0.5%, 4.8%, and 8.1% of eyes in the sham, 0.2 μg Iluvien-FA per day implant, and 0.5 μg Iluvien-FA per day implant, respectively.[89] Because of this high risk of ocular hypertension, the Food and Drug Administration requires a prior course of corticosteroid without a significant rise in IOP in eyes that are deemed candidates of the Iluvien-FA implant. The glucocorticoid receptor binding affinity for TA, FA, and DEX is all very similar, so one could use TA or DEX to predict the IOP response for the Iluvien-FA implant.[90] If the eye develops a substantial elevation in IOP with the corticosteroid challenge, the eye is deemed not suitable for the Iluvien-FA implant. A subanalysis of the FAME Studies compared eyes that had received a steroid challenge before their Iluvien-FA implant to those that did not.[89] In eyes that did not develop a rise in IOP with a corticosteroid before Iluvien implant, none of the eyes developed a rise in IOP following Iluvien implant. Several studies confirmed these findings.[37,44] An EMR-based study from the UK reported that 14% of eyes required ocular hypotensive therapy; 7.2% had an IOP ≥30 mmHg; and 0.3% underwent glaucoma surgery. In this same study, 10% and 4.3% of eyes without a steroid challenge and without an IOP elevation event required glaucoma topical treatment and developed an IOP ≥30 mmHg, respectively.[44] The IRSS Study showed that 8.3% of eyes developed an IOP ≥30 mmHg and 2% of eyes required incisional glaucoma surgery.[43]

Cataract

The most common adverse event of intravitreal corticosteroids is steroid-induced cataract. Since DME is a chronic condition that requires multiple intravitreal injections, practically all phakic eyes will develop cataract. After 5 years of follow-up of a study that compared TA to placebo, 71% of phakic eyes underwent cataract extraction.[84] In the MEAD Study, 60% of phakic eyes underwent cataract surgery.[29] After 4 years, more than 90% of phakic eyes that had a Retisert-FA implant underwent cataract extraction compared to 20% of eyes that did not have the implant.[39] In the FAME Studies, 75%, 85%, and 23% of the phakic eyes receiving the 0.2 μg Iluvien-FA per day, 0.5 μg Iluvien-FA per day, and sham injection underwent cataract removal, respectively.

Protocol P of the DRCR studied eyes that underwent cataract extraction in the presence of DME.[91] Approximately two-third of eyes received some type of DME treatment preoperatively, intraoperatively, or postoperatively. Sixty percent of eyes had an improvement of ≥2 lines of BCVA, 30% remained within

two lines of baseline BCVA, and 10% lost ≥2 lines. In addition, only 63% of eyes had a BCVA of ≥20/40. These results are comparatively worse than those routinely seen in modern cataract surgery.[91] In contrast, the MEAD Study reported that eyes that developed cataract regained the visual loss after cataract extraction.[29] Unlike Protocol P, the eyes that developed cataract in MEAD had their DME controlled as evidenced by the OCT measures of the CMT.

Infectious endophthalmitis, pseudoendophthalmitis, and sterile endophthalmitis

Intravitreal TA may cause endophthalmitis, pseudoendophthalmitis, and sterile endophthalmitis. Infectious endophthalmitis has been reported to occur up to 0.87%.[92] Sterile endophthalmitis has been defined as an inflammatory reaction to any of the components of TA. Its incidence has been reported to be between 1.6% and 5.3%.[93] Pseudoendophthalmitis refers to the phenomenon when TA crystals migrate from the vitreous to the anterior chamber and layer inferiorly resembling a hypopyon. The endophthalmitis rate following a DEX implant has been reported to be between 0% and 1.3%.[29,85,86,94] In the US, the rates of endophthalmitis between intravitreal anti-VEGF agents and corticosteroids were almost 7 times higher with corticosteroids than with anti-VEGF agents.[95]

Rarely, corticosteroids can induce a state of relative immunosuppression inside the vitreous cavity that may lead to opportunistic infections such as cytomegalovirus retinitis.[96-99] The incidence of viral retinitis following an intravitreal injection of TA was 0.41%. The incidence climbed to 0.9% in patients with medical immunocompromising comorbidities such as diabetes mellitus, patients receiving multiple injections, and patients with a prior history of viral retinitis.[96]

Anterior-Chamber Migration

Both the DEX and FA implants have been reported to migrate into the anterior chamber, which can potentially lead to corneal endothelial decompensation, edema, and ocular hypertension.[43,100,101] The incidence has been estimated between 4.8% and 5.9% in previously vitrectomized eyes.[101,102] Risk factors associated with anterior-chamber migration include prior vitrectomy in combination with iris defects, zonular dehiscence, and an open or defective lens capsule. Corneal decompensation results from either direct mechanical trauma or toxicity from any of the implant components. If the eye presents with corneal edema, it is imperative to remove the implant as soon as possible to avoid permanent corneal decompensation. Removal of the DEX implant may be tricky. It is beyond the scope of this review to describe in detail the surgical maneuvers to remove these implants. These are nicely summarized elsewhere.[100,101]

Intralenticular injection

The DEX implant has been injected accidentally into the crystalline lens rather than into the vitreous cavity.[103] Cataract forms secondary to mechanical trauma and corticosteroid effect on the crystalline lens.

Conclusion

VEGF and inflammatory mediators are pharmacological targets of eyes with DME. The response to treatment can vary substantially. Some cases of DME are VEGF driven, and in others, inflammation plays a key role. Chronicity appears to favor corticosteroid treatment. Currently, there is still no evidence of synergism between an anti-VEGF drug and a corticosteroid. The main advantage of corticosteroids over VEGF inhibitors is their longer duration of action. Vitrectomy does not affect the pharmacokinetics of the corticosteroid implants. Common adverse events of corticosteroids include cataract formation, cataract progression, and ocular hypertension. Because of their less favorable safety profile, corticosteroids are generally used as a second-line treatment for DME. Pseudophakic eyes, previously vitrectomized eyes and eyes with long-standing DME, particularly of patients who have difficulty in maintaining a monthly appointment, may benefit from primary treatment with a corticosteroid intravitreal implant.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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