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The Role of Steroids in the Management of Diabetic Macular Edema

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Abstract
Inflammation is substantially contributing to the development and worsening of diabetic retinopathy in general and diabetic macular edema (DME) in particular, which provides the rationale to treat DME with corticosteroids. While anti-vascular endothelial growth factor (VEGF) agents are mostly chosen as a first-line treatment, there is an important role for steroids in the treatment algorithm for DME. A slow-release bioerodible dexamethasone implant and an extended-release nonbioerodible fluocinolone acetonide insert are both approved for the treatment of DME and provide the advantage of sustained drug delivery and reduced treatment burden. Steroids bare the complications of cataract progression and increase of intraocular pressure (IOP). However, with dexamethasone implant, IOP rise is well manageable with topical treatment in almost all cases. Dexamethasone implant has been shown to be effective in the treatment of naive DME as well as in eyes nonresponding to anti-VEGF agents. In these cases, early switching to steroids may be considered and has been shown to be beneficial. Fluocinolone acetonide is reserved for severe cases of chronic DME insufficiently responsive to other available therapies. Future randomized controlled trials are needed to realize the role of steroids in the current treatment algorithm of DME.

Diabetic Retinopathy – An Inflammatory Disease?

While glycemic control and systemic blood pressure are important in the prevention of diabetic microvascular complications, these do no solely account for their development [1, 2]. Inflammation has been shown to play a major role in the pathogenesis of atherothrombosis and microalbuminuria in diabetic patients [3, 4]. Lately, there is growing evidence that inflammation is important in the development and worsening of diabetic retinopathy in general [5, 6] and diabetic macular edema (DME) in particular [7–9]. Low-grade subclinical inflammation, spe-

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cifically adherent leukocytes, are responsible for the development of vascular pathologies in diabetic retinopathy. Leukostasis in retinal capillaries is an early event in the cascade of DME, causing dysfunction of the blood-retinal barrier (BRB) [10]. In an experimental setting, diabetes caused adherence and accumulation of leucocytes within the retinal vasculature and a subsequent migration of leucocytes into the neural retina [11–13]. These early microscopic changes precede any clinical signs of diabetic retinopathy.

The expression of proinflammatory cytokines, such as intracellular adhesion molecule (ICAM)-1 [14], interleukin-6 (IL-6), tumor necrosis factor (TNF), and cyclooxygenase-2, is upregulated [8], further neutrophils and monocytes are attracted, and vascular permeability deteriorates.

Experiments in diabetic rats showed that treatments with ICAM-1- or β2 integrin-neutralizing antibodies were able to suppress leucocyte adhesion, stabilize the BRB, and even prevent endothelial cell injury and its apoptosis [15–17]. Moreover, the inhibition of leucocyte adhesion via ICAM-1 and CD18 showed long-term suppression of diabetic complications [18].

A large-scale prospective clinical study combined systemic C-reactive protein, IL-6, and TNF-α levels in an inflammatory marker *Z*-score, which was found to be significantly associated with retinopathy and other systemic microvascular complications of diabetes mellitus [19].

Vascular endothelial growth factor (VEFG) has a central implication in the pathogenesis of DME. Being mainly a vasogenic factor, VEGF also has the power to trigger inflammation by inducing ICAM-1 expression, leucocyte adhesion, and monocyte migration [20–22]. In experimental settings, intravitreous injections of VEGF induced leukostasis in the retina, enhancing vascular permeability and capillary nonperfusion [20]. Leukostasis itself was accompanied by upregulation of retinal ICAM-1 expression. When bioactivity of this molecule was inhibited by a neutralizing antibody, permeability and leukostasis were strongly inhibited.

The Rationale for Use of Steroids in the Treatment of DME

Corticosteroids provide powerful anti-inflammatory and anti-edematous effects by targeting not only the synthesis of proinflammatory mediators involved in DME (IL-6, IL-8, MCP-1, ICAM-1, TNF-α, VEGF, HGF, ANGPT2, etc.) [23] but also a decrease in VEGF synthesis. Corticosteroids block the arachidonic acid pathway via phospholipase A2 inhibition and, hence, downregulate the synthesis of thromboxanes, leukotrienes, and prostaglandins. Consequently, the BRB improves, density and activity of tight junctions in the retinal capillary endothelium enhance, and retinal oxygenation ameliorates.

Müller cells are essential to maintain the homeostasis in the retina. There is growing evidence suggesting that Müller cells may be the first to be affected in DME, showing intracellular edema. Activated Müller cells release cytotoxic substances which are responsible for the recruitment of leukocytes, BRB breakdown, direct glial dysfunction, and neuronal cell death. With progression of the disease, they may become apoptotic [24]. Gliotic Müller cells not only promote but also inhibit tissue repair processes in preclinical studies [25]. The rational approach for treating DME with corticosteroids involves targeting those inflammatory processes and preventing changes in the retinal glia.

Corticosteroid Agents

This paper will discuss 3 of the most commonly used corticosteroid agents: triamcinolone acetonide (TA), dexamethasone (DEX) implant, and fluocinolone acetonide (FA) implant.

Triamcinolone Acetonide

Prospective clinical trials have shown its efficacy in the treatment of DME [26–28]. The DRCR.net reported the use of intravitreal TA for DME in protocol I evaluating 3 different treatment schemes: intravitreal 0.5 mg ranibizumab plus prompt or deferred focal/grid laser; or 4 mg intravitreal TA combined with focal/grid laser compared with focal/grid laser alone [29]. Pseudophakic patients treated with TA faired similarly to the ranibizumab-treated group in terms of visual outcome and anatomical results after 2 years of follow-up. The mean elimination half-life of TA in the vitreous of a nonvitrectomized eye was 18.6 days, in contrast to a much shorter duration in a vitrectomized eye, 3.2 days [30]. As every drug that does not have a reservoir and does not work as a long-lasting drug, TA needs to be given as repeated injections, which raises the risk for complications, i.e., cataract formation and glaucoma. Uncontrolled increased intraocular pressure (IOP) might lead to glaucoma surgeries. That is why 2 sustained-release drugs (DEX implant and FA devices) were developed.

DEX Implant

DEX is a potent anti-inflammatory agent; its potency is twice that of FA and 5-fold more than that of TA [23]. Due to its high water solubility, DEX needs to be delivered in a sustained-release system to provide vitreous drug levels over time.

DEX implant (Ozurdex®; Allergan Inc., Irvine, CA, USA) is commercially available as a sterile, preloaded single-use applicator. It is inserted into the vitreous cavity with a 22-G needle via the pars plana and contains 0.7 mg of DEX. The biodegradable implant contains polylactic acid-co-glycolic acid polymers which degrade into carbon dioxide and water after slow release of DEX. Pharmacokinetic studies of DEX implant showed an initially high rate of DEX release over the first 2 months after injection, followed by a decrease in release until 6 months [31]. Intravitreal administration of DEX implant provides a high initial drug concentration with a maximum at 60 days, followed by a prolonged period of low concentration, similar to drug levels achieved with pulse corticosteroid treatment. In contrast to TA, the pharmacokinetics of the DEX implant were not significantly different in vitrectomized and nonvitrectomized animal eyes [32]. This can be explained by the fact that DEX implant does not require the vitreous as a substrate to work due to its own environment, i.e., the slow-release device.

The efficacy and safety of DEX implant has been shown in two 3-year multicenter, randomized, masked, sham injection-controlled phase III clinical trials (MEAD study) [33]. Minimum treatment intervals between repeated DEX implants were 6 months, and patients received on average 4–5 treatments over the study period. A larger portion of patients treated with DEX implant achieved a significant improvement in best corrected visual acuity (BCVA) (22.4 vs. 12.0%, $p < 0.002$) and a statistically significant reduction in central macular thickness (112 vs. 42 μm, $p < 0.001$) compared to patients in the sham group. The registration trial for Ozurdex® (MEAD), included mainly phakic patients (75%) with long-standing DME (mean duration 23 months) who were previously treated by macular laser photocoagulation in 65.8%, other corticosteroids in 16.5%, or anti-VEGF injections in 7.1%. Only 25% of the patients were treatment naive. In phakic eyes, mean BCVA improvement was substantial until the time of report of cataract, and improvement in vision from baseline was restored after cataract surgery. Furthermore, DEX implant is the only drug which was prospectively investigated in a group of vitrectomized eyes with DME: the CHAMPLAIN study showed an improvement of 6 and 3 letters at 8 and 26 weeks, respectively, after a single DEX implant. At 8 weeks, 30.4% of patients gained ≥10 letters [34].

In a recent multicenter, open-label, 12-month, randomized, parallel-group study, DEX implant met the a priori criterion for noninferiority to ranibizumab in improvement of BCVA over 12 months [35]. Both DEX implant and ranibizumab were well tolerated and improved BCVA in patients with DME. Noninferiority was achieved with an average of 2.9 DEX implant injections and 8.7 ranibizumab injections per patient with a more significant reduction in central macular thickness using DEX implant (122 vs. 187 μm, $p = 0.015$).

Similarly, the 24-month results of the BEVORDEX study identified no significant difference in the proportion of eyes with a 10-letter gain in VA between bevacizumab and DEX implant treatment, with both agents providing good improvements [36]. The burden of injections was significantly greater with bevacizumab (mean 9.1 vs. 2.8).

As treatment frequency may be set at shorter intervals than in the MEAD trial, real-life studies are of great importance in case of DEX implant. Several large-scale studies have been showing the efficacy with improvement in BCVA and decrease in retinal thickness [37–39], even in eyes with DME refractory to anti-VEGF [38, 40–42]. There was a trend to use DEX implant in DME eyes not responding to anti-VEGF treatments. Several papers have shown not only the benefits of using DEX implant in naive DME as a first-line option [38, 43], but also the advantages of early switching in patients not responding to anti-VEGF [42].

Protocol U by the DRCR.net aimed to compare continued ranibizumab injections alone with ranibizumab plus DEX implant in eyes with persistent DME [44]. This phase 2 randomized clinical trial included eyes after at least 3 anti-VEGF injections before a run-in phase, which included additional 3-monthly ranibizumab injections before receiving the study drug. The authors concluded that the combination therapy with DEX implant caused a greater reduction in retinal thickness; the addition of DEX implant did not improve visual acuity at 24 weeks more than continued ranibizumab therapy alone. However, the study design has some limitations which might have biased the outcome. There was no definition of "persistence of DME": edema could have been improved significantly but still be defined as persistent. For eligibility, monthly treatment was not mandatory, and patients might have been undertreated before inclusion. Moreover, it should be noted that there was a subgroup of patients with baseline BCVA <20/50 who experienced a greater gain in vision with combination therapy compared to continued ranibizumab injections (+6.2 vs. +3.3 letters). As there were only 27 patients in each group, the difference did not reach statistical significance.

The main side effects of DEX implant are cataract development and IOP increase. In the MEAD trial, 27.7% of patients treated with 0.7-mg DEX implant experienced an increase of ≥10 mm Hg; in 6.6% IOP reached ≥35 mm Hg. While 41.5% needed IOP-lowering medications, only 2 patients treated with DEX implant underwent incisional surgery. Data from real-life studies show an increase of IOP in 10–17% of patients, well managed with topical treatment [38, 43].

FA Implant

FA is commercially available as a sustained-release system in a 25-G inserter, lasting up to 36 months in the vitreous. In contrast to DEX implant, FA implant has not the potential to be bioerodible. The Fluocinolone Acetonide for Diabetic Macular Edema (FAME) studies evaluated the use of 2 different FA doses (0.2 vs. 0.5 μg/day) compared to sham injections. A total of 953 DME eyes were randomized 1:2:2 [45, 46]. At 36 months, a significantly higher percentage of patients in both FA groups gained 15 or more letters in vision compared to patients in the sham group ($p = 0.018$). In contrast to TA and DEX implant, the incidence of side effects was higher after FA treatment. Almost all phakic patients in the FA groups developed cataract over 36 months. However, visual outcome after cataract surgery was comparable to pseudophakic patients. Furthermore, the development of uncontrolled IOP after TA was higher, and the incidence of incisional glaucoma surgery at month 36 was 4.8% in the low-dose group and 8.1% in the high-dose insert group. The FDA approved ILUVIEN® (FA intravitreal implant) 0.19 mg 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 IOP. The results from the FAME trial have been confirmed by real-life studies [47–49].

Diabetic Retinopathy Modification

The pathogenesis of diabetic retinopathy development and progression is complex and multifactorial. Vitreous VEGF levels have been shown to correlate with disease severity to be associated with diabetic retinopathy progression [50]. While the efficacy of anti-VEGF treatment in modifying diabetic retinopathy disease progression is well established [51–54], the role of corticosteroids has been less explored. However, the potential effect of intravitreal steroids can be well explained by the contribution of proinflammatory cytokines and chemokines to the disease development and retinal ischemia [5, 55, 56].

An exploratory analysis of the protocol I by the DRCR.net revealed that intravitreal TA has the potential to reduce the risk of diabetic retinopathy progression [57, 58]. Querques et al. [59] showed a reduction in peripheral retinal ischemia in DME eyes after treatment with intravitreal DEX after a short follow-up of 12 weeks. Lately, the authors of this review published the DRProDEX study which provides long-term evidence that DEX implant not only delays progression of diabetic retinopathy and proliferative diabetic retinopathy development, but also improves diabetic retinopathy severity over 24 months [60]. A post hoc analysis of the FAME trials showed delay in progression of proliferative diabetic retinopathy after treatment with FA intravitreal implant for DME [61].

Recommendations

Anti-VEGF agents are widely used as a first-line option for DME, but it has been proven that DEX implant can be used for patients with naive DME and not only for refractory cases. In cases not responding to monthly anti-VEGF injections, switching to DEX implant should be done early in order to allow optimal treatment outcomes [62]. Furthermore, there are special populations in which corticosteroids should be chosen as first-line therapy:

- Patients who have a recent history of a cardiovascular event
- Pregnancy
- Inability or not willing to adhere to monthly treatments
- DME in eyes undergoing cataract surgery.

In patients proven to be nonsteroid responders suffering from chronic DME that is not responsive to other treatments, FA can be given. TA should be used only in cases who do not have the possibility to receive the approved agents, as it needs to be reinjected frequently and causes more increase in IOP and cataract.

In conclusion, intravitreal corticosteroids provide substantial anatomical and functional improvement with sustained release in both naive and refractory DME. Further prospective studies are needed to determine their role in the treatment algorithm of DME. A well-designed head-to-head prospective trial is needed to determine the optimal treatment in this customized era.

Disclosure Statement

The authors declare no conflict of interest.

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