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Sustained-Release Steroids for the Treatment of Diabetic Macular Edema

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Abstract Glucocorticoids have been used for decades in the treatment of ocular disorders via topical, periocular, and more recently intravitreal routes. However, their exact mechanisms of action on ocular tissues remain imperfectly understood. Fortunately, two recently approved intravitreal sustained-release drug delivery systems have opened new perspectives for these very potent drugs. To date, among other retinal conditions, their label includes diabetic macular edema, for which a long-lasting therapeutic effect has been demonstrated both morphologically and functionally in several randomized clinical trials. The rate of ocular complications of intravitreal sustained-release steroids, mainly cataract formation and intraocular pressure elevation, is higher than with anti-vascular endothelial growth factor agents. Yet, a better understanding of the mechanisms underlying these adverse effects and the search for the minimal efficient dose should help optimize their therapeutic window.

Introduction

Systemic glucocorticoids must be administered with caution to diabetic patients because they alter the glycemic homeostasis [1, 2] inducing peripheral insulin resistance [3] together with a progressive failure of pancreatic β-cells [4]. Through binding to the vascular and kidney mineralocorticoid receptor [5, 6], they favor hypertension [7, 8], further increasing the metabolic and cardiovascular risk factors of the diabetic patients [9]. Yet, intraocular corticosteroids are paradoxically gaining momentum in the local ocular treatment of diabetic macular edema [10]. The eye being a confined environment, isolated from the systemic circulation by blood-ocular bar-

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riers, no significant systemic diffusion of corticosteroids is measured following their local administration in the vitreous, preventing from the systemic complications of glucocorticoids. Classically, the corticosteroid family is classified by the potency, the mineralocorticoid-binding affinity, and the half-life of each molecule. Yet, these classifications are translated from systemic to ocular use without evidence that the drugs maintain their pharmacologic properties in the eye, which questions the relevance of such translations. For instance, the mineralocorticoid pathway activation in the eye is not taken into account and the rate of specific ocular side effects, such as ocular hypertension, glaucoma, and cataract, are not included in the classification. The anti-edematous mechanisms triggered by glucocorticoids in the macula are complex and multi-factorial. They exert an intense, wide-spectrum anti-inflammatory action and are potent vasoconstrictors. Additionally, they regulate the expression of junction proteins in endothelial cells [11, 12] and the expression and distribution of ion channels and water channels in retinal glial Müller cells (Fig. 1a) [13]. Interestingly, dexamethasone and triamcinolone exert a specific and differential regulation of K+ inwardly rectifying channel 4.1 (Kir4.1) and Aquaporin 4 (AQP4) in retinal glial Müller cells, suggesting that the dose and type of corticosteroid may influence their anti-edematous properties [13].

Triamcinolone acetonide was the first glucocorticoid injected into the vitreous [14, 15]. The preparations used initially were not developed nor approved for intraocular use, although there are now triamcinolone acetonide formulations that are approved for intraocular use. Due to its very high hydrophobicity, triamcinolone acetonide forms a solid crystalline aggregate in the vitreous, which allows a long-lasting effect. But, triamcinolone acetonide was never incorporated in a drug delivery system that could provide a controlled release of the drug. Moreover, a potential toxicity of triamcinolone acetonide and of the more hydrophobic dexamethasone has been observed experimentally in vitro and in vivo on retinal and vascular cells. After intravitreal administration in healthy rats and in a murine model of choroidal neovascularization, triamcinolone acetonide triggered vascular endothelial cell death. It also exerted a deleterious effect on retinal pigment epithelium and Müller cells via a caspase-independent, paraptotic process [16]. The direct application of triamcinolone acetonide on rat retinal explants confirmed its toxic effect on vascular endothelial cells through caspase-independent mechanisms [17]. Indeed, the controversy on the toxicity of glucocorticoids on the retina is mostly due to the fact that corticoids exert toxicity through nonclassical pathways, undetected by routine toxicology methods [16]. Nevertheless, the more hydrophobic, the more toxic because intracellular penetration is higher. Clinically, no prospective study was designed to assess the retinal safety of triamcinolone acetonide. But, authors have reported visual loss with
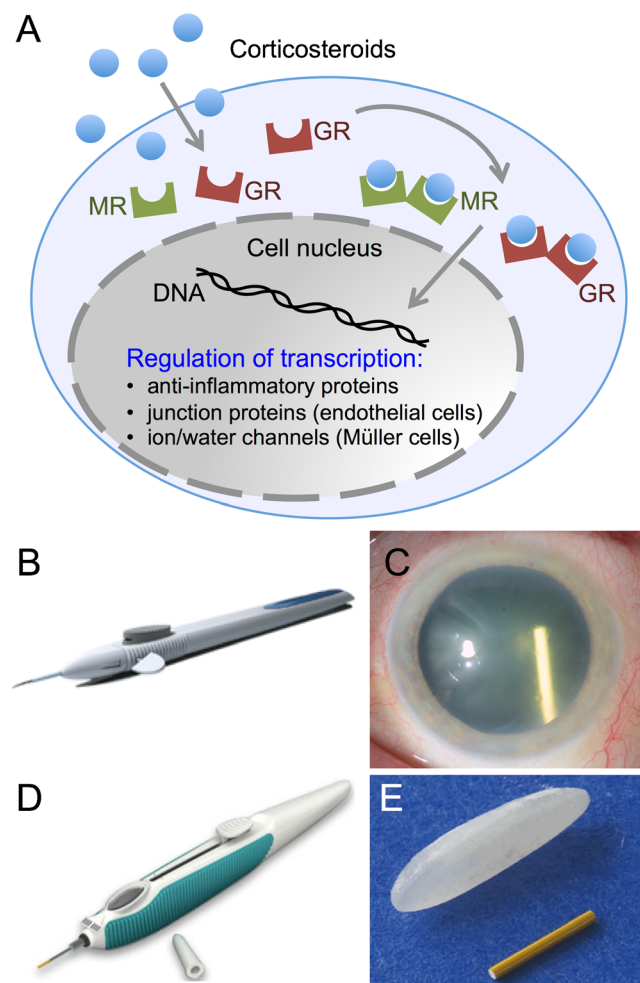
Fig. 1 **a** Schematic mechanism of corticosteroid action: after diffusion through the cell membrane, corticosteroids bind to the glucocorticoid (GR) and mineralocorticoid receptors (MR) according to their affinity profile and trigger a nuclear displacement of GR- and MR-homodimers that regulate the transcription of specific genes involved in the pathogenesis of macular edema. **b** Injection device for the dexamethasone implant (Ozurdex®). **c** Biomicroscopy photograph showing an intravitreal dexamethasone implant. **d** Injection device for the fluocinolone acetonide insert (Iluvien®). **e** Comparative photograph of the fluocinolone acetonide insert and a rice grain

electroretinographic alterations and visual field defects after repeated intravitreal triamcinolone injections [18], retinal pigment epithelium changes after accidental subretinal injection of triamcinolone [19], or optic atrophy after ILM peeling and intravitreal triamcinolone injection [20].

Recently, two drug delivery systems have been approved for the sustained intravitreal release of glucocorticoids, the dexamethasone (DEX) implant, and the fluocinolone acetonide (FAc) insert. Along with anti-vascular endothelial growth factor (VEGF) agents, they have expanded the toolbox available for retina specialists and have revolutionized the management of macular edema. However, none of them completely fulfills yet all optimal characteristics required by such therapeutic agents. This review will focus on the

pharmacological specifications ideally required from such devices, the properties of the two approved products, and the clinical evidence regarding their therapeutic action and side effects.

Pharmacological Requirements of an Ideal Sustained-Release System

The advantages of drug delivery systems for the sustained release of corticosteroids are as follows:

– Controlled and sustained vitreous release of drug for an extended period of time—currently 3 months or more
– Reduction of the total administered dose with a potential reduction of ocular side effects
– Reduction of the frequency and cumulated number of intravitreal injections
– Improved pharmacokinetics with a flattening of concentration peaks and valleys
– Improvement of pharmacodynamic properties resulting from a controlled, stable concentration

An ideal sustained-release drug delivery system should present the following characteristics:

– Biodegradable matrix with a zero pharmacokinetic order.
– Sustained and controlled release lasting for an extended duration.
– Complete degradation of the matrix polymer when the entire drug is released.
– Biocompatibility and ocular tolerance of the matrix materials.
– Injectable device that fits in a small-gauge needle, typically 23-gauge or thinner in the light of current standards for vitreoretinal procedures.
– Once injected, the implant should induce little or no visual disturbance.
– The implant design should allow potential removal in case of excessive side effects.

Existing Steroid Sustained-Release Devices

Dexamethasone Intravitreal Implant

The dexamethasone intravitreal implant (DEX implant, Ozurdex®; Allergan, Inc., Irvine, CA) consists of a sustained-release preparation containing 0.7 mg of dexamethasone embedded in a biodegradable poly(lactic co-glycolic acid) matrix material (Fig. 1b, c). It has been designed to release dexamethasone into the vitreous for up to 6 months, with pharmacokinetics studies confirming the presence of the drug in the retina and vitreous of *Macaca fascicularis*

monkeys 6 months after injection, with peak concentrations during the first 2 months, and undetectable levels after the sixth month [21]. However, clinical efficacy is observed up to 4 months after injection in some eyes [22•].

Dimensions of the DEX implant are as follows: length, 6 mm, and diameter, 0.46 mm, allowing it to fit into a specialized 22-gauge trans-scleral injector. Intravitreal injection is performed under topical anesthetic drops, and the self-sealing incision does not require sutures.

The DEX implant has been approved by the US Food and Drug Administration (FDA) for the following indications: diabetic macular edema (DME), macular edema following branch or central retinal vein occlusion, and noninfectious posterior uveitis.

Sustained-Delivery Fluocinolone Acetonide Insert

The sustained-delivery fluocinolone acetonide (FAc) insert (Iluvien®; Alimera Sciences, Alpharetta, GA) is composed of nonbiodegradable cylindrical tubes of polymer loaded with 0.19 mg of fluocinolone acetonide. The dimensions of the insert are 3.5×0.37 mm, and it is inserted into the vitreous via a 25-gauge sutureless scleral incision using a manufactured injection device (Fig. 1d, e). It has been designed to release FAc at an initial rate of 0.25 μg/day.

Aqueous humor levels of FAc peak during the first 3 months, followed by steady-state levels through 36 months [23]. These results are consistent with reports of clinical efficacy for up to 3 years post-insertion [24••].

The FDA approved the FAc insert 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 intraocular pressure.

Main Outcomes of Clinical Trials

For more than two decades from the mid-1980s, the standard of care for DME had been focal or grid laser photocoagulation associated to a strict control of glycemia, blood pressure, and other cardiovascular comorbidities [25]. Despite its widespread use from the mid-2000s and randomized clinical trials showing that it was beneficial for DME [26–28], the glucocorticoid triamcinolone acetonide was never formulated for intravitreal use specifically for DME treatment. Therefore, focal laser photocoagulation remained until recently the only approved therapeutic option for DME [29]. In 2012, ranibizumab, an anti-VEGF monoclonal antibody fragment, became the first approved drug for the treatment of DME, based on the results from the RIDE and RISE clinical trials [30, 31••], and proved superior to triamcinolone acetonide [32•]. This context explains why controlled, randomized clinical trials evaluating steroid-releasing devices have been designed differently according to the selected control

intervention: sham, laser photocoagulation or anti-VEGF, with some trials also evaluating combinations of these treatments.

Dexamethasone Intravitreal Implant

The efficacy of the DEX implant has been assessed by several randomized clinical trials, which are summarized in Table 1.

In the randomized, masked, phase-III "MEAD" clinical trial that included 377 participants (cohort sizes and results mentioned for all clinical trials will refer to participants who completed the study until the end of the follow-up period), the 0.7-mg DEX implant was compared to sham over a 3-year period [33••]. In a third arm, patients received DEX implants at a lower dose (0.35 mg), but this formulation was eventually not retained for commercial distribution and will therefore not be mentioned further in this review. Noticeably, inclusion criteria required that baseline visual acuities should be between 20/200 and 20/50, thus excluding patients with good baseline visual acuity levels despite edema (a common finding in DME) and patients with very low baseline levels, who have usually less recovery potential. The study population was composed of a mixed cohort of treatment-naive patients and patients refractory to other therapies. Another specificity of the study design was the prohibition of focal laser treatment in the macula in both arms during the study period. The mean average reduction in central retinal thickness (measured at the fovea) from the baseline was greater in the DEX implant group, -112 versus -42 μm ($p<0.001$). The percentage of treated patients that had gained ≥15 letters at 3 years was higher than in the sham group (22 vs 12 %, $p=0.018$). The mean visual acuity change over the 3-year period was only +3.5 letters for DEX-implanted patients, but this difference was significant compared to sham (+2.0, $p=0.023$). Although not clinically meaningful for an individual eye, it indicates a favorable distribution of visual acuity gainers over losers among treated patients. In addition, 68 % of subjects that were phakic at baseline had undergone cataract extraction at 3 years, versus 20 % in the sham group. Noticeably, patients from the DEX group received a mean of only 4.1 injections over the 3-year study period. Finally, the rates of dropout or loss to follow-up from this study were high (324 subjects out of 701 initially included in the 0.7 mg DEX and sham arms) and could affect the interpretation of the results.

Another randomized, double-masked trial compared DEX implant and laser (103 participants) versus sham and laser (94 participants), with one possible retreatment by DEX/sham at 6 or 9 months, and three possible additional laser sessions [34]. In the DEX group, a significantly greater proportion of subjects had a visual improvement ≥10 letters by 9 months, but this effect was not maintained at 12 months, suggesting that retreatment by DEX implant should be performed at intervals shorter than 6 months.

Table 1 Design and outcome of randomized clinical trials evaluating the dexamethasone intravitreal implant

Reference (study name)	Duration	Intervention	Number of eyes[a]	Frequency	Mean number of injections during study	Visual acuity outcome	Result	p Value	Morphological outcome	Result	p Value
Boyer DS et al. Ophthalmology, 2014 (MEAD)	3 years	DEX vs sham	225/152	6 months (if needed)	5.0/5.1	% Subjects who gained ≥15 letters	22 %/ 12 %	$p≤0.018$	Mean visual acuity change	-112 μm/ -42 μm	$p<0.001$
						Mean central macular thickness change	+3.5/+2.0 letters	$p=0.019$			
Gillies M, C et al. Ophthalmology, 2014 (BEVORDEX)	1 year	DEX vs bevacizumab	46/42	16 weeks 4 weeks (if needed)	2.7/8.6	% Subjects who gained ≥10 letters	41 %/ 40 %	$p=0.99$	Mean central macular thickness change	-187 μm/ -122 μm	$p=0.015$
						Mean visual acuity change	+5.6/+8.9	$p=0.24$			
Maturi RK et al. Retina, 2015	1 year	Combination: bevacizumab + DEX vs bevacizumab monotherapy	18/17	Baseline DEX: 1, 5, and 9 months 4 weeks	8/9	Mean visual acuity change	+5.4/+4.9 letters	$p=0.75$	Mean central macular thickness change	-45 μm/ -30 μm	$p=0.03$
Callanan DG et al. Ophthalmology, 2013	1 year	DEX +laser at 1 month vs sham implant + laser at 1 month	103/94	Implant: one additional at 6 months Laser: up to three additional treatments	NA	% Subjects who gained ≥10 letters	27.8 %/ 23.6 %	$p=0.453$ (but significant difference at 9 months)	Mean central macular thickness change	-70 μm/ -60 μm	$p=0.164$

DEX dexamethasone implant (0.7 mg), *DME* diabetic macular edema

[a] The reported number of participants refers to those who stayed in the study until the end of the follow-up period

In the head-to-head single-masked, comparative, randomized "BEVORDEX" trial of DEX implant (46 subjects) versus the anti-VEGF antibody bevacizumab (42 subjects) [22•], both treatments achieved to improve visual acuity by 10 letters or more after 12 months in a similar proportion of subjects (40 and 41 %, respectively). A greater decrease in central macular thickness was observed in the DEX arm (−187 vs −122 μm, $p=0.015$). Yet, five patients from the DEX group had a decrease in visual acuity, versus none from the bevacizumab group, a finding explained by the higher rate of cataract development in DEX-treated patients. Eventually, a mean of 2.7 DEX-implant injections versus 8.6 bevacizumab injections were performed over 12 months.

Next, a therapy combining bevacizumab at baseline and DEX implant at 1 month plus DEX implant re-injection at 5 and 9 months if needed (18 patients) has been evaluated versus bevacizumab monthly monotherapy (17 patients), in a randomized, single-masked design over 12 months [35]. There was a significant visual improvement in both groups from baseline but no difference in final visual acuities between groups. However, the mean central macular thickness reduction was greater in the combination group (−45 vs −30 μm $p=0.03$). In this group, the injection sparing effect was limited since patients received an average of eight additional injections compared to nine in the bevacizumab monotherapy group.

Interestingly, the efficacy of a single DEX implant over a 6-month period has been reported in vitrectomized eyes [36, 37], although the absence of vitreous gel may have reduced the half-life of the drug within the vitreous cavity.

Sustained-Delivery Fluocinolone Acetonide Insert

Due to its more recent introduction and the longer study durations required, fewer studies have evaluated to date the FAc insert as compared to the DEX implant. Randomized clinical trials evaluating the FAc insert are summarized in Table 2. In the randomized, double-masked "FAME" trial [24••] evaluating the FAc insert (releasing 0.25 μg/day) (209 patients) against sham (112 patients), a gain in visual acuity ≥15 letters was observed in 33 % of FAc-treated subjects compared to 21 % of sham-treated subjects after 3 years. Regarding the anatomical response, there was a significant decrease in central retinal thickness in the FAc-treated group compared to sham at 1 year, but no significant difference between the groups after 3 years.

A post hoc analysis of the previous study showed that the proportion of patients that gained ≥15 letters of visual acuity was significantly greater in patients with DME of more than 3-year duration treated by FAc versus sham, but such a difference was not observed in those with DME that lasted less than 3 years at the time of treatment [38••]. Other baseline characteristics did not differ between both groups.

Table 2 Design and outcome of randomized clinical trials evaluating the fluocinolone acetonide insert

Reference (study name)	Duration	Intervention	Frequency	Number of eyes[a]	Mean number of injections during study	Visual acuity outcome	Result	p Value	Morphological outcome	Result	p Value
Campochiaro PA et al. Ophthalmology, 2012 (FAME)	3 years	FAc insert vs sham	Baseline	209/112	1/1	% Subjects who gained ≥15 letters	33 %/21.4 %	$p=0.03$	Mean central macular thickness change	280 μm/ 280 μm	$p>0.05$
Cunha-Vaz J et al. Ophthalmology, 2014 (FAME, post hoc analysis)	3 years	FAc insert vs sham (post hoc analysis: DME of <3 years and ≥3-year duration before inclusion)	Baseline	209/112	1/1	% Subjects who gained ≥15 letters	Chronic DME (≥3 years):13 %/34 %, Nonchronic DME (<3 years): 22.4 %/27.8 %	$p<0.001$ / $p>0.05$	Mean central macular thickness change	Chronic DME ≥3 years: −187 μm/− 160 μm Nonchronic DME: −173 μm/ 116 μm	$p=0.14$ / $p=0.03$

FAc fluocinolone acetonide (0.25 μg/day), DME diabetic macular edema

[a] The reported number of participants refers to those who stayed in the study until the end of the follow-up period

Adverse Effects

The most common ocular adverse effects of corticosteroids are secondary cataract formation and intraocular pressure rise. Both effects have been observed after topical and intraocular corticosteroids administration [39].

Despite its frequency, the mechanisms of steroid-induced lens opacification, most frequently posterior subcapsular, are not fully understood. It can develop after ocular but also systemic steroid treatment, and several possible pathways have been advanced [40]. Transcriptional changes may occur in lens epithelial cells, which express the nuclear glucocorticoid alpha receptor [41]. An imbalance in intraocular cytokines and growth factors affecting the lens homeostasis has also been suggested [42].

Corticosteroid-induced ocular hypertension results from an elevated resistance to aqueous outflow. Postulated mechanisms include: microstructural changes in the trabecular meshwork, deposition of precipitated substances in the trabecular meshwork, and inhibition of trabecular phagocytosis by endothelial cells contributing to this accumulation of substances [43].

Finally, a direct in vitro toxicity of corticosteroids on retinal vascular endothelial cells has been observed via autophagy, caspase-dependent and caspase-independent cell death, and direct DNA damage [17]. However, no acute retinal damages have been observed after intraocular steroids administration.

Dexamethasone Intravitreal Implant

Variable rates of cataract formation after DEX implant injection have been reported in the prospective studies described above, and range from 13 to 50 % after 1 year [22•, 34, 35], and 68 % after 3 years [33••]. In the trial by Boyer et al. with the longest study period, the rate of cataract extraction was 59 % after 3 years in the DEX implant group versus 7 % in the sham group.

In this trial, intraocular pressure rise over 25 mmHg at any visit was observed in 32 % of patients. Intraocular-pressure-lowering medication was prescribed in 42 % of subjects, but trabeculectomy was required in only 0.6 % of cases. Other trials with follow-up of 1 year reported the occurrence of intraocular pressure rise over 25 mmHg in 17–26 % of cases [22•, 34].

Sustained-Delivery Fluocinolone Acetonide Insert

In patients who received the FAc insert, cataract formation was observed in 82 % over a 3-year period, with cataract extraction performed in 80 % of FAc-implanted subjects versus 27 % of sham-treated subjects [24••].

Among patients from this prospective cohort, 38 % of subjects required intraocular-pressure-lowering medication

[24••]. Incisional glaucoma surgery was performed in 4.8 % of FAc-treated subjects as compared to 0.5 % of sham-treated subjects. Noticeably, the effect of FAc on intraocular pressure is likely to be dose-related, since a higher proportion of patients receiving the device releasing FAc 0.5 µg/day underwent cataract or glaucoma surgery (87 and 8 %, respectively).

Conclusion

Corticosteroids are among the most widely used classes of drugs in ophthalmology. With the advent of sustained-release devices, steroids are now also approved for the treatment of macular edema of various origins, including diabetic macular edema. Glucocorticoids and mineralocorticoids are expressed in retinal cells and in retinal pigment epithelial cells [44], and the expression of these receptors can be modulated in pathological states, as demonstrated in animal models [45]. When released in a sustained manner by intravitreal drug delivery systems, both dexamethasone and fluocinolone acetonides have a favorable effect on the course of diabetic macular edema. Yet, these long-lasting formulations have different pharmacological properties and side effect profiles. These differences can be, in part, explained by their different binding affinity to the glucocorticoid and mineralocorticoid receptors, subsequently leading to differential transcriptomic effects. Playing with these differential affinities, new steroids could be investigated that would optimize the clinical efficacy and reduce side effects. Among future optimization of these devices, the administered dose could be adapted to the disease state and a built-in, programmed dose tapering could reduce rebound effects.

These controlled-release ocular drug delivery systems have opened new applications for glucosteroids in ophthalmology, even though their mechanisms of action are not fully understood. They remain the object of intense investigations, in order to optimize this promising treatment strategy and expand it to other causes of macular edema.

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