ILUVIEN[®] technology in the treatment of center-involving diabetic macular edema: a review of the literature

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Diabetic macular edema (DME) is one of the major causes of blindness, caused primarily by hyperglycemia and results from multiple pathological processes mostly secondary to increased levels of VEGF and other inflammatory cytokines. DME management includes control of systemic risk factors together with laser photocoagulation, frequent intraocular injections of anti-VEGF agents and steroids implants. Recent adoption of novel alternative drug delivery options has led to the development of sustained release ocular implants with longer duration of action with less injection frequency. This article will review the pharmacology and clinical data in terms of efficacy, safety and benefits of the sustained release steroid implants in treatment of DME with special emphasis on the fluocinolone acetonide ILUVIEN[®] implant.

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Background

Diabetic macular edema (DME) is a common microvascular complication of diabetes characterized by a breakdown in the blood–retinal barrier (BRB). This results in intracellular and extracellular retinal leakage from perifoveal abnormal capillary vessels and microaneurysms, and leads to thickening of the retina. Center-involving DME is a major cause of visual loss in patients with diabetes and is considered one of the leading causes of severe visual impairment in working-age population [1].

Clinically elevated blood glucose levels, high cholesterol as well as the accumulation of oxygen-free radicals and advanced glyceric end products have all been implicated in the pathogenesis of DME ultimately contributing to the increased levels of expressed VEGFA through increased retinal hypoxia. VEGFA, in turn, results in the breakdown of the BRB through rapid phosphorylation of integral protein components of the junctional complexes between the retinal pigment epithelial (RPE) cells and vascular endothelial cells [2].

Furthermore, the role of inflammation as a mediator in the pathogenesis of diabetic retinopathy (DR) and DME has been established; leukostasis (the accumulation of leukocytes on the retinal capillaries' luminal surface) is considered to be a major contributor to the BRB dysfunction through the upregulation of inflammatory cytokines such as intracellular adhesion molecule ICAM-1, IL-6, IL-8, as well as monocyte chemotactic protein (MCP-1). DR is also characterized by increased leukocyte adhesion, macrophage infiltration, complement activation and acute phase response protein expression [2,3].

Several systemic and ocular therapeutic measures have been implemented in the management of DME; intensive glyceric and blood pressure control together with fenofibrate therapy have been proven to be effective in reducing risk of retinopathy progression [4]. The role of focal/grid laser treatment was shown to reduce moderate visual loss in DME [5]; however, patients with diffuse leak with centrally involving DME fared less well.

Over the past few years, emerging pharmacological therapies have been evaluated and demonstrated favorable results in preserving or improving retinal function and vision by reducing the macular edema.

Anti-VEGF agents, such as ranibizumab, aflibercept and bevacizumab, have shown improved results when compared with laser treatment for DME, through reduction of the excess vascular permeability by acting solely on

VEGF levels though with much less influence on the other immunogenic cytokines involved in the pathogenesis of DME.

On the other hand, corticosteroids have a wider variety of effects in suppressing inflammatory processes within the pathophysiology of DME. It can also reduce vascular permeability and suppress angiogenesis with reduction in leukostasis and improvement of other physiological and structural changes such as tight junction integrity. The concept of local ocular delivery steroids became appealing to ophthalmologists which minimized the potential hazardous risks of systemic complications. Despite its potency, topical delivery of steroids does not provide significant therapeutic levels for most retinal pathologies and hence attention has been directed to intraocular use [6]. Several studies demonstrated the effects of intravitreal injection of triamcinolone acetonide (IVTA) in treatment of DME. In 2008, DRCR compared the effect of focal/grid laser treatment with four monthly repeated IVTA. At 4 months, the mean improvement of best corrected visual acuity best-corrected visual acuity (BCVA) was significantly better with IVTA compared with the laser groups; however, at the 2 years primary end point, the mean BCVA improvement of 1 ± 17 letters achieved with laser was significantly better than the IVTA groups [7]. The IVTA intraocular injections deliver high drug levels to the retina and choroid with low systemic exposure, yet the levels tend to decrease fairly quickly hence requiring frequent injections. Repeated injections in turn require frequent visits together with increased risks of infection and other intraocular complications. There has, therefore, been a need for the development of reliable sustained delivery systems to avoid frequent injections and variations in intraocular steroid concentrations [8].

Currently, three different slow-release, sustained-delivery systems for intraocular steroids have been developed with different efficacy and safety profiles.

The Retisert® implant is a nonbiodegradable device surgically implanted in the vitreous cavity through a pars plana incision; the device provides sustained delivery of 0.59 mg fluocinolone acetonide (FAc) with initial release rate of approximately 0.6 µg/day. In the USA, it is approved for the treatment of chronic noninfectious posterior uveitis [9]. The device was previously tested for patients with DME, and though there were signs of benefits in DME, there were concerns regarding high rate of increased intraocular pressure (IOP) requiring filtering surgery [10].

Ozurdex® is a biodegradable and bioerodible implant containing 0.7 mg of dexamethasone (DEX). DEX is a less potent glucocorticoid receptor agonist as compared with triamcinolone acetonide, hence requiring slow release delivery systems. It is delivered intravitreally with a 22-gauge applicator through a shelved injection technique to ensure a self-sealing wound. The implant utilizes a Novadur solid polymer delivery system containing a poly-D,L-lactide-co-glycolide polymer matrix that slowly degrades to lactic acid and glycolic acid enabling extended release of DEX over a 6-month period. In the UK, the steroid implant has the NICE approval for use in patients with central or branch retinal vein occlusion, noninfectious posterior uveitis as well as pseudophakic patients with DME [11].

The ILUVIEN® sustained-release FAc device is an injectable nonbioerodible intravitreal insert designed for sustained release of FAc for up to 36 months. FAc is a potent glucocorticoid receptor agonist, with low water solubility and high lipophilicity [12]. The implant is a cylindrical tube, 3.5 mm long and 0.37 mm in diameter, made from the same polymer used for many intraocular lens haptics. It contains 0.19 mg of FAc in a polyvinyl alcohol (PVA) matrix and is inserted into the vitreous cavity through a 25-gauge needle. One end of the tube is coated with the PVA and the other end with silicone adhesive. The PVA end is permeable and controls the release of the FAc into the vitreous chamber. It has been engineered to provide a release rate of 0.2 µg/day. The drug is released into the vitreous through hydration of the PVA matrix that consists of water, FAc and PVA. Once hydration occurs, FAc that is perfused throughout the matrix slowly leaches out of the tube through diffusion [12]. In UK, the ILUVIEN implant is approved for the treatment of persistent and/or recurrent DME insufficiently responsive to other therapies, whereas in the USA, it is approved for 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.

This article will focus on update data on the pharmacokinetics and pharmacodynamics as well as the clinical data related to the use of the ILUVIEN FAc sustained-release device.

FAc (6a,9-Difluoro-11β,16a, 21-tetrahydroxypregna-1,4-diene-3, 20-dione cyclic 16,17-acetal with acetone) is a medium potency synthetic fluorinated glucocorticoid previously used as a dermal anti-inflammatory product has also been shown to reduce the expression of VEGF (Figure 1) [12].

Pharmacokinetics data

In an experimental study on cultured human RPE cells (APRE-19 cells), FAc was shown to inhibit VEGF expression via glucocorticoid receptor activity. In addition, FAc inhibited proliferation of the APRE-19 cells. The drug also

Figure 1. Fluocinolone acetonide chemical structure.
The highlighted fluorine atom is not present in either triamcinolone acetonide or dexamethasone.

inhibited angiogenesis induced by TNF- α in chick chorioallanotic membrane assays in a dose-dependent manner. FAc is considered to reduce retinal oedema through its anti-inflammatory effects as inhibition of edema, fibrin deposition, capillary dilatation, leukocyte migration, capillary and fibroblast proliferation, collagen deposition and scar formation [12].

The ocular and systemic pharmacokinetics of FAc were evaluated following administration of ILUVIEN intravitreal implants in rabbit eyes over 24 months. The FAc intravitreal implant was administered to rabbits in three doses (0.2, 0.5 and 1.0 $\mu\text{g/day}$). The concentration of FAc was measured in the plasma and ocular tissues with a validated methodology at various points of time through the 24-month period [12]. All plasma samples were found to be below the limit of quantification (200 pg/ml), hence there were no quantifiable systemic exposure to FAc following intravitreal administration of the FAc ILUVIEN 190 μg implant or higher doses, and therefore no further systemic pharmacokinetics analysis were performed.

Following the administration of the 0.2 $\mu\text{g/day}$ ILUVIEN Implant, the FAc levels peaked in most ocular tissues at days 2, or 8 and reached approximate steady levels by month 3 and then gradually faded over the 24 months period. FAc was present at relatively high levels in the important tissue relevant for posterior segment diseases such as the choroid/RPE, and retina as well as the lens, and iris/ciliary body at 2 years. Lower levels were observed in the vitreous cavity. Aqueous FAc levels were below the lower limit of quantification at most time points. This was explained in part to be due to less sensitive measurements methods used for the study [13].

In humans, the aqueous levels of FAc after administration of low dose 0.2 $\mu\text{g/day}$ FAc insert (ILUVIEN, Alimera Sciences, Inc. Alpharetta, GA, USA) was studied as part of the FAMOUS Phase II randomized clinical trial. The highest mean levels were noted at 1 week after administration. The mean ($\pm$ standard deviation) and median aqueous FAc levels were 2.17 ± 0.93 and 2.16 ng/ml, respectively. At 6 and 9 months after insertion, the median and mean FAc levels remained at approximately 1 ng/ml. At 12 months, this declined slightly to 0.70 ± 0.37 and 0.88 ng/ml, respectively. The concentration of aqueous FAc leveled between 12 and 36 months. The FAc levels reached 0.55 ± 0.45 and 0.6 ng/ml at month 36. The steady-state FAc level achieved with the ILUVIEN implant remained in the range of 0.5–1.0 ng/ml and sustained over the 36 months period. Furthermore, plasma levels of FAc in patients treated with ILUVIEN were below the limit of detection (<100 pg/ml) at all times during the study. These results provided firm understanding to underpin the results of clinical efficacy trials [6].

Clinical efficacy

The effect of ILUVIEN on patients with DME was initially evaluated in Phase II clinical trials where the 0.2 $\mu\text{g/day}$ implant reduced macular edema – as measured by the retinal central point thickness and macular volume – and improved visual acuity over 18 months period [12].

The clinical efficacy of FAc 0.2 $\mu\text{g/day}$ ILUVIEN intravitreal implant has been evaluated in the FAME clinical trials (randomized, double masked, 36 months, Phase III trials) [14,15]. Patients with DME of central retinal thickness (CRT) more than 250 μm following treatment with at least one macular laser treatment were invited for the study, with BCVA between 19 and 68 ETDRS letters. Patients with previous history of anti-VEGF treatment, glaucoma and previous vitrectomy were excluded from the study. Enrolled patients were randomized to 0.2 or 0.5 $\mu\text{g/day}$ FAc implants or sham injections. The primary study end point was percentage of patients achieving BCVA of more than 15 letters gain at month 24. Results at 36 months were also recorded. Patients demographics were balanced at baseline between the treatment groups, the majority of patients were phakic with over 40% of patients reported to have cataract.

At 24 months, the mean change in BCVA was +4.4 ETDRS letters with 28.7% of patients achieving ≥ 15 letters gain versus 16.2% in the sham group. The visual improvement started as early as 3 weeks postinjection and was maintained throughout the study. Nevertheless, a gradual decline was noted between month 6 and 18 owing to the development of cataractous changes, and improved later following cataract extraction. The proportion of patients achieving driving standard vision was significantly higher in the 0.2 $\mu\text{g}/\text{day}$ ILUVIEN implant group as compared with sham (31 vs 22%). The mean change in BCVA letter score from baseline was significantly higher in the FAc ILUVIEN implant group as compared with sham group, achieving 4.4 and 5.3 letters at 24 and 36 months, respectively. At 24 months, the BCVA letter gain was significantly higher in the pseudophakic group as compared with the phakic group (7.1 vs 2.8, respectively).

At 36 months, the visual improvement effect was sustained for patients completing the FAME study, 33% of patients in the ILUVIEN 0.2 $\mu\text{g}/\text{day}$ arm had ≥ 15 letters improvement from baseline BCVA versus 21.4% in the sham group. The mean change in letter gain was 8.1 versus 3.2 letters in the respective treatment groups.

The visual improvement noted in the FAME study subjects receiving the ILUVIEN implant treatment reflected a corresponding improvement in the CRT of these patients. There has been a steady decrease in the macular central point thickness CPT in these patients with significant severe DME with a baseline CPT of 451–485 μm . At 24 months, 51% of the FAc implant group achieved a mean CPT of ≤ 250 μm compared with 40% in the sham group. At 36 months, there was no notable difference in CPT between the two groups.

Further analysis was undertaken on the FAME phakic subjects receiving the 0.2 mg/day ILUVIEN implant to evaluate the efficacy and safety of the FAc implants in these patients who underwent cataract extraction before or after receiving the implant. BCVA after 36 months was comparable between the two groups, although patients that underwent cataract extraction following the implant tended to have numerically higher values. These data therefore emphasize the benefits of using the ILUVIEN implant in phakic eyes as well as in pseudophakic eyes [16].

Moreover, in the FAME study, subjects receiving the ILUVIEN FAc implant experienced favorable effects on their underlying DR. Time for first development of proliferative DR PDR events was significantly delayed in subjects treated with FAc. This effect was noted to be statistically significant as early as 6 months and persisted throughout the study follow-up period. In total, 28.6% of the sham control group experienced a PDR event as compared with 16.2% in the 0.2 $\mu\text{g}/\text{day}$ ILUVIEN implant group, 14.1% subjects in the sham group received panretinal photocoagulation PRP as compared with 7.2% in the ILUVIEN group. The effect on delayed PDR progression was noted in all subgroup analysis of patients with persistent and/or recurrent DME or pseudophakic patients [17].

The FAc treatment has also demonstrated statistically significant improvements in the DR severity grades as compared with sham group from month 6 and all through to month 36 of follow-up. Fewer eyes treated with the FAc implant worsened by two-or-more or by three-or-more DR severity study DRSS steps from baseline and through to months 36 as compared with the sham group. Similarly, more eyes receiving the FAc implant treatment improved by two-or-more or three-or-more DRSS steps from baseline to month 36 as compared with sham group, and reaching statistically significant levels for the FAc 0.2 $\mu\text{g}/\text{day}$ ILUVIEN implant group in patients with persistent and/or recurrent DME [17].

Further retrospective analysis of the FAME study data examined the relationship between short-term and long-term changes in visual acuity in the study subjects. Patients from the FAME clinical trials, who received the ILUVIEN implant were categorized by their visual acuity change at week 6 postinjection to those with <5 letter improvement, 5–9 letter improvement and ≥ 10 letters gain from baseline. At 36 months, patients were similarly categorized to those who improved (≥ 5 letters), were stable (<4 letter change), and others who worsened (≥ 5 letters worsening). The authors concluded that most patients (85.7%) treated with FAc 0.2 $\mu\text{g}/\text{day}$ implant experienced improved or stable BCVA over 36 months and that the BCVA gains at week 6 may be predictive of BCVA gains at month 36. Even for patients who did not experience significant improvement in BCVA at week 6, there was still a high percentage (79.1%) that experienced stable or improved BCVA at Month 36 [18].

Clinical efficacy: real-life studies

Following the publication of the FAME clinical trials results, several real-life reports have appeared in the literature reflecting the increased use of the FAc 0.2 $\mu\text{g}/\text{day}$ ILUVIEN implant in routine clinical practice for persistent and/or recurrent DME insufficiently responding to other treatment modalities. These studies reported various efficacy and safety results with different follow-up periods.

Figure 2. The effect of fluocinolone acetonide ILUVIEN® implant in short-standing versus long-standing persistent and/or recurrent diabetic macule edema.

Figure extracted from [20] <http://theophthalmologist.com/issues/1017/the-chronic/>

Interim results (from the European ILUVIEN Registry Safety Study IRISS) were presented at the European Society of Retina Specialists in Barcelona in 2017 [19]. IRISS is a 5 years observational open label study from the UK, Germany and Portugal involving 593 eyes from 563 patients. The study reported that in patients with 2 years of follow-up, visual acuity stabilized or improved in around three out of four cases [19]. Interestingly, in a subgroup analysis of the persistent and/or recurrent DME patients, the earlier use of ILUVIEN (i.e., in short-standing DME) was associated with better VA outcomes and fewer IOP-related events than was observed in patients with long-standing persistent and/or recurrent DME (Figure 2) [20].

Further results emerged from a UK retrospective audit of Medisoft electronic medical records EMR of 345 eyes collected from 14 clinical sites with a mean follow-up period of 428 days. The mean best recorded visual acuity improved from 51.9 letters at baseline to 56.4 letters at 18 months and 57.2 letters at 24 months. The percentage of eyes achieving vision stability or improvement was 78.7% at 12 months, increasing to 86.7% at 24 months. The proportion of patients with 6/12 increased from 18.1% at baseline to 39.6% at 24 months [21].

In total, 64.3% of eyes in the EMR audit required no additional treatment for DME following the FAc 0.2 µg/day ILUVIEN implant. When needed, additional treatments were administered and included macular laser treatment (6.4%) and additional intravitreal treatment (32.2%; mostly anti-VEGF agents). Nevertheless, visual outcomes were similar for patients regardless of if they received additional intravitreal treatment or not.

In addition, more case series results have been presented. In a combined analysis of case reports of 28 eyes from UK and Germany, Quhill [20] reported a mean change of BCVA of +14 letters in patients receiving the FAc 0.2 µg/day ILUVIEN implant after a mean follow-up period of 13 weeks (range: 1–57 weeks) with 32% of patients gaining ≥ 15 letters. The corresponding CRT decreased from 465 µm at baseline to 298 µm [22].

Vitrectomy is a treatment option for tractional DME, its effect mediated through releasing of the vitreomacular traction, increasing the retinal oxygenation as well as suppressing a number of the pro-permeability inflammatory cytokines in the vitreous cavity. However, the effect of vitrectomy on the duration of action and clinical efficacy of intravitreal drugs is still debatable. In FAME clinical trials, vitrectomized eyes were excluded from the study leading to paucity of clinical trial data. Experience of the ILUVIEN efficacy in vitrectomized eyes comes from reported real-life data. A retrospective study reported results of 26 vitrectomized eyes in 25 patients treated with FAc 0.2 µg/day ILUVIEN implant from 6 centers in 4 different European countries. The implant was injected 24.2 months on average following vitrectomy in these eyes with a mean postinjection follow-up period of 255 days. The study reported a mean change in BCVA of +11.7 ETDRS letters (range: -19 to +40 letters) ($p \leq 0.0004$) together with a mean change in central foveal thickness of -233.5 µm (range: -678 to +274 µm) ($p \leq 0.0001$). Considering the study results, the ILUVIEN implant can be suggested as an effective treatment option in real-life practice for patients with DME in vitrectomized eyes with insufficient response to other treatment modalities [23].

Furthermore, the first European report of real-life clinical outcomes after 3 years of treatment with the FAc 0.2 µg/day ILUVIEN implant [24] were recently presented as a poster at the Association for Research in Vision and Ophthalmology in Baltimore in 2017. The poster included results of 39 eyes (32 patients) from 8 centers in Germany. In total, 73% of patients were pseudophakic and 68.4% had prior vitrectomy. The results demonstrated a sustained response of the ILUVIEN implant with visual stability achieved in 89% of patients with 41% of patients achieving ≥ 10 letters gain.

Adverse effects

The most common reported adverse effects associated with the use of intraocular steroids are cataract formation and elevated IOP. In the FAME trials, after 36 months follow-up, 81.7% of phakic patients who received FAc 0.2 µg/day ILUVIEN implant developed cataractous changes with 80% requiring cataract extraction around 18 months postimplantation.

In total, 37% of patients in the FAc 0.2 µg/day ILUVIEN implant group in FAME trials had an increase in the IOP versus 11.9% in the sham group. IOP elevation of >30 mmHg were significantly more frequent in the ILUVIEN implant arm as compared with the sham arm (18.4 vs 4.3% of patients).

IOP elevation was treated mainly with medications (38.4% in the FAc 0.2 µg/day ILUVIEN implant group versus 14.1% in the sham group). Incisional IOP surgical intervention was required only in a small group of patients (4.8 vs 0.5%, respectively) and trabeculoplasty was required in only 1.3 and 0.0%, respectively [15].

Adverse events: real-life studies

Further real-life experience results were reported by the Medisoft audit group regarding the IOP elevation with the FAc 0.2 µg/day ILUVIEN implant [21]. In their study, they reported an increase of mean IOP of 3.1 mmHg from baseline during the first 12 months following implantation. At the last observation, 13.9% of patients required IOP-lowering agents (including patients who changed existing or received additional IOP-lowering medication following the ILUVIEN implant or those requiring new treatment initiation). In total, 7.2% of patients experienced an IOP elevation of 30 mmHg, with only a single patient requiring an IOP-lowering surgical intervention. The study reported an overall 'reported' incidence of glaucoma of 1.2%.

Compared with FAME clinical trials results, the Medisoft group reported an incidence of IOP increase ≥ 10 mmHg in 24.4% of patients by 18 months with rate of IOP elevation above 30 mmHg of 13.4%. In the FAME studies for patients with persistent and/or recurrent DME, these rates were 24.9 and 10.5%, respectively, at the equivalent time points. At 18 months, the reported incidence of glaucoma was 2.4 with 22.0% of eyes requiring emergent IOP-lowering medication, whereas in the FAME study, glaucoma incidence was reported at 1.4% at the same time point with 26.3% of eyes requiring IOP-lowering agents.

Of note, in treated patients in the Medisoft EMR audit who had prior steroid use with no reported IOP elevation event, 0% reported any emergent IOP-lowering medication or had an IOP elevation above 30 mmHg following the ILUVIEN implantation. On the other hand, both events were common in patients with prior IOP elevation whether steroid related or not.

Interim analysis from the ongoing IRIS trial showed that in 593 patients, with mean duration of follow-up of 471 days, 76.7% of patients required no emergent IOP-lowering agents. In total, 11% of patients had an IOP increase of ≥ 10 mmHg and 8.3% had an IOP elevation of ≥ 30 mmHg [19]. The IRIS trial also revealed that visual acuity stabilized or improved rapidly after the FAc 0.2 µg/day ILUVIEN implantation was administered and sustained over a 2-year period.

Real-life data of IOP elevation in vitrectomized eyes were reported by Meireles *et al.* [23]. In their retrospective study of 26 eyes with prior vitrectomy, a mean IOP change of 1.4 mmHg was noted between baseline and last visit (range: -9.0 to +8.0 mmHg) after a mean follow-up period of 255 days, with 8 eyes (30.7%) initiated or continued on IOP-lowering medications.

Real-life data from the UK relating to cataract formation following the FAc 0.2 µg/day ILUVIEN implantation is limited as the treatment is approved for use in the National Health Service in pseudophakic DME eyes. This is based on guidance by The National Institute for Health and Care Excellence [25] and not the marketing authorization, which allows the FAc 0.2 µg/day ILUVIEN implant to be used irrespective of lens status [26].

Other ocular adverse effects have been reported with the FAc 0.2 µg/day ILUVIEN implant in the FAME trials [27] and through real-life audits. In total, 15% of patients receiving the ILUVIEN implant reported eye pain (vs 14% [treatment vs the sham group, respectively]), conjunctival hemorrhage (13 vs 11%), posterior capsular

Figure 3. Myodesopsia and the number of ILUVIEN® implants. Consequences of multiple implants in terms of patients experiencing floaters in the FAME trials.
Alimera sciences: data on file.

opacification (9 vs 3%), eye irritation (8 vs 6%), vitreous detachment (7 vs 7%) and myodesopsia (21 vs 9%). Interestingly, the impact of myodesopsia was not affected by the number of implants (Figure 3).

In vitrectomized eyes, migration of the FAc 0.2 µg/day ILUVIEN implant into the anterior chamber has been reported in a number of cases [28,29], due to the presence of posterior capsular tears related to previous complicated cataract procedures. The implant was shown to be repositioned and reinserted into the vitreous cavity without compromising the implant integrity [28]; however, it needs to be put in consideration when the ILUVIEN implant is planned in eyes with previous disruption of the posterior capsule [26].

Cost-effectiveness

Untreated DME is one of the leading causes of blindness in patients of working age in industrial countries [30]. Apart from its devastating consequences, the financial impact of blindness is enormous at individual as well as society levels. In the UK, an evidence review in 2013 estimated the annual cost of blindness to reach over £5 billion [31]. Current approved therapies for management of DME include frequent anti-VEGF injections, shorter acting steroid implants as well as the long acting sustained release FAc 0.2 µg/day ILUVIEN implant. In their recent study, Quhill and Beiderbeck [32] developed a cost analysis model comparing the 3-year cost of DME management with either a single FAc ILUVIEN implant or 14 anti-VEGF injections [33] in both phakic and pseudophakic eyes. Their model took into consideration the drug costs, costs of administering the drug, monitoring patients, as well as additional interventions required and the management of adverse events.

The model based its assumptions that patients would require average 14 anti-VEGF injections over 3-year period with needed frequent monitoring visits versus single FAc 0.2 µg/day ILUVIEN implant needed for the same period with quarterly monitoring visits with the assumption of 25% of these patients requiring anti-VEGF injection top-up each year to maintain optimal efficacy. The model estimated the cost of £14,273 for anti-VEGF treatment over 3-year period versus £8205 for FAc implant in pseudophakic eyes and £8932 in phakic eyes (which allowed for the additional cost of cataract extraction surgery in the majority of steroid-treated phakic patients). The greatest savings for FAc implant were reported in years 2 and 3 [32].

Based on the calculations for England, it is estimated that there are on average 7500 patients with diabetes with persistent and/or recurrent DME that have experienced a suboptimal response to previous treatments and therefore are potentially eligible for treatment with the ILUVIEN implant. The total potential savings to NHS England that can be generated with FAc treatment for these individuals (phakic and pseudophakic) could reach £41.8 million.

In the USA, a Markov model-based cost-effectiveness analysis predicted the cost efficacy of the FAc ILUVIEN implant relative to sham injection in the treatment of DME from a US healthcare payer plus caregiver perspective, based on a willingness-to-pay threshold of \$US 50,000 per quality-adjusted life-year gained [34].

Quality of life

In addition to potential financial savings, treatment with the sustained release FAc 0.2 µg/day ILUVIEN implant could have substantive effects on the patients' quality of life [35]. Previous studies showed that over half of patients with diabetes with DME have an average of 19.1 appointments with healthcare professionals, accounting for around 20 h per patient over a 6 months' period. Each injection appointment, including travel time would add 4.5 h extra burden for each patient, together with the associated anxiety reported by 75% of patients, which would definitely reflect on the compliance of patients to the treatment and its vigorous regimen. Therefore, an attempt to maintain stable vision over a longer period of time with fewer injections and less monitoring visits could help to improve patients' compliance as well as their quality of life [36].

Conclusion

The sustained release FAc 0.2 µg/day ILUVIEN implant is an approved recommended treatment modality for patients with persistent and/or recurrent DME insufficiently responsive to other treatments. The implant provides stable and sustained visual gains over a period of 36 months. The clinical efficacy of the drug was demonstrated in the FAME clinical trials and firmly supported by real-life data emerging from different groups and centers. Emerging real-life data demonstrates the effectiveness and tolerability of the ILUVIEN implant in routine clinical practice and shows that it is an important therapeutic option for patients with DME with a suboptimal response to anti-VEGF agents and laser treatments. The implant was shown to have a predictable side effect profile with a reduced risk of IOP-related events emerging in those patients who do not have a history of elevated IOP through steroid treatment or otherwise.

The ILUVIEN treatment modality provides stable vision to patients with DME with a reduced number of monitoring and follow-up visits and a reduced injection burden and with the added potential benefit of improving patient compliance and quality of life. This overall reduction in visit and treatment burden can mean the opening up of clinic capacity and additional time available for managing more complex patients with diabetes and providing treatment on a wider scale.

Executive summary

Background

- Diabetic macular edema is a common microvascular complication of diabetes, and the role of inflammation in its pathogenesis is established.
- Local pharmacological therapies for DME include anti-VEGF as well as steroid therapies. Corticosteroids have a wider variety of effects in suppressing the inflammatory process within DME pathogenesis. ILUVIEN® is a sustained release fluocinolone acetonide device approved for the treatment of DME.

Clinical efficacy

- The clinical efficacy of ILUVIEN was evaluated in the FAME studies. At 24 months, the mean change in BCVA was +4.4 ETDRS letters with 28.7% of patients achieving ≥15 letters gain. At 36 months, the visual improvement effect was sustained with 33% of patients achieving ≥15 letters improvement.

Clinical efficacy: real life studies

- Real life studies supported the FAME trial findings; results from European IRISS study and UK retrospective Medisoft audit demonstrated visual stability and improvement in patients treated with ILUVIEN. The favorable effect was also reported in patients with prior vitrectomy.

Adverse events

- The most common reported adverse effects associated with ILUVIEN are cataract formation and elevated intraocular pressure. Compared with the FAME trial findings, real-life experiences were similar reporting an overall glaucoma incidence of 2.4%.

Cost-effectiveness & quality of life

- Potential savings to NHS England that can be generated with ILUVIEN treatment for patients with DME could reach £41.8 million. Quality of life improvements can also be achieved by fewer injections and less monitoring visits than other alternative treatments hence potentially improving compliance.

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The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Author's contribution

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Company review

In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

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