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A New Approach for Diabetic Macular Edema Treatment: review of clinical practice results with 0.19 mg fluocinolone acetonide intravitreal implant including vitrectomized eyes

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Abstract

Purpose of Review: Fluocinolone acetonide is a synthetic fluorinated glucocorticoid. It has selective and potent agonist properties by binding to the cytosolic glucocorticoid receptor with high affinity; it is devoid of mineralocorticoid activity. Two extended-release (i.e. lasting up to 3 years) drug delivery systems containing fluocinolone acetonide (FAC) have been approved by the FDA for intravitreal use: Retisert® (Bausch&Lomb, New Jersey, USA) and Iluvien® (Alimera Sciences, Atlanta, USA). The former contains 0.59 mg of FAC, which is approved for the treatment of chronic noninfectious posterior segment uveitis. The latter contains a dose of 0.19 mg of FAC and is approved for the treatment of diabetic macular edema and here we review the results published in the clinical literature relating to its use in the treatment of diabetic macular edema (DME).

Recent Findings: The 0.19 mg FAC implant (Iluvien®) is a new approved treatment approach for DME. It is a non-biodegradable implant that continuously releases a microdose of FAC into the vitreous cavity for up to three years. It is effective in chronic DME with the added value of

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decreasing the treatment burden of multiple intravitreal injections. Recently, clinical practice studies are reporting its efficacy and safety profile (intra-ocular pressure rise and cataract), as well as its use in clinical setting not included in clinical trial such as vitrectomized eyes.

Summary: The FAc implant has demonstrated in clinical practice results that mirror the results of the clinical trials efficacy wise. Regarding its safety profile, cataract is a common complication, however, intra-ocular pressure rises may be lower than the ones reported in trials. The implant has shown effectiveness in vitrectomized eyes. An increasing evidence of real-world studies have supported utility of the implant in DME patients. It's extended-release format for up to 3 years benefits to the patient and carer as it means fewer injections and visits to the clinic.

Keywords

Diabetic macular edema; intravitreal corticosteroids; long-acting corticosteroids; diabetic retinopathy

Introduction

Diabetic macular edema (DME) is a serious manifestation of diabetic retinopathy (DR), which is the leading cause of visual loss and blindness in Western countries among the working-age population. Even though intravitreal anti-VEGF therapy has revolutionized the treatment of the disease, 40–60% of patients do not have an optimal anatomic response to treatment with vision left on the table.⁽¹⁾

A stepwise approach to treat DME is typically recommended beginning with a course of at least 3 injections of anti-VEGF. Patients who demonstrate an insufficient response to anti-VEGF can be subsequently treated with a second line therapy, although in some circumstances they can be used as a first line if they are unsuitable for anti-VEGF therapy. A non-biodegradable intravitreal implant containing 0.19 mg fluocinolone acetonide (FAc; ILUVIEN) that can last up to three years has become available for the treatment of chronic DME. In the USA, the ILUVIEN implant can be used in patients who have been previously treated with a course of corticosteroids and that did not have a clinically significant rise in intraocular pressure. It's extended-release format potentially provides therapy for up to 3 years. This provides advantages to the treating physician through the more efficient management of clinical capacity and has benefits to the patient and carer as it potentially means fewer injections and visits to the clinic.

Fluocinolone acetonide is a synthetic fluorinated glucocorticoid. It has selective and potent agonist properties by binding to the cytosolic glucocorticoid receptor with high affinity; it is devoid of mineralocorticoid activity.^(2–4)

The present review focuses on the use of this 0.19 mg FAc intravitreal implant (Iluvien®) namely its results in clinical trials and real-world conditions as well as in vitrectomized eyes.

We report results from numerous studies, particularly those referring to clinical practice, and summarize their outcomes and safety findings and compare to the results of its clinical trials.

Epidemiology

The global prevalence of DME in patients with diabetes is 6.8%(5) and 14%–25% of patients with diabetes develop DME within 10 years of initial diagnosis.(6) DME can be unilateral or bilateral. Bilateral disease has been reported in 33%–46% of the patients.(7) It has been shown that 20.1% of patients with type 1 diabetes, 25.4% with type 2 insulin-dependent diabetes, and 13.9% with type 2 insulin-independent diabetes respectively, develop DME within a 10-year time period.(6) The development of DME is responsible for the majority of visual impairment seen in type II diabetic patients.(6)

Current Treatment Strategies

Systemic Control of the Disease

DME is a chronic condition that can be difficult to manage.(8) Without treatment almost half of all patients will lose two or more lines of visual acuity within 2 years.(9) Preventing vision loss requires an interdisciplinary medical intervention. Systemic strategies include a tight glycemic control, intensive lipid and arterial pressure control. Early detection of the complications of diabetic retinopathy, in particular macular edema, is crucial for initiation of treatment.(4)

Ophthalmic Treatment Options

Current therapeutic strategies include, as first-line therapy, intravitreal injections of vascular endothelium growth factor (VEGF) inhibitors. Intravitreal corticosteroids have also been successfully used. Both pharmacologic therapies have been replacing focal/grid laser photocoagulation, the main treatment in the past.(3,4)

Macular Laser

Grid/focal laser photocoagulation were considered the standard therapy for the treatment of clinically significant DME. This therapeutic approach mostly stabilized visual acuity at the expense of the destruction of retinal tissue.(10) The results of clinical practice were variable and unsatisfactory.(11)

Anti-VEGF Therapy

More recently, anti-VEGF agents have become first-line treatment. In Phase III trials, ranibizumab(12) and aflibercept(13) have demonstrated a greater visual improvement than photocoagulation. They have been approved by the FDA for the treatment of center-involving DME. Bevacizumab is an off-label option that has been widely used due to its cost-effectiveness.(14) However, 40–60% of eyes that receive anti-VEGF injections, show an insufficient response with recurrent and persistent macular edema, even after repeated injections.(2,15–17) Anti-VEGF therapy requires frequent intravitreal injections that are difficult to transpose to clinical practice. For this reason, fewer injections are administered in clinical practice than in clinical trials, and contributes to decreased efficacy as the results of clinical trials have been difficult to replicate in regular clinical practice.(3,17)

Long acting anti-VEGF agents are not currently available as the three most frequently used anti-VEGF agents (aflibercept, bevacizumab and ranibizumab) have a short period of activity that may last from 4–8 weeks.(18)

Corticosteroids

Biochemical research has showed that the pathogenesis of DME is clearly multifactorial and that the inflammatory pathways play an important role. Patients with advanced disease exhibit many intra-ocular inflammatory markers and these findings have led to increasing interest in corticosteroid therapy.(2,15,19,20) Treatment options include triamcinolone, a biodegradable dexamethasone intravitreal implant and the non-degradable FAc implant. Even though corticosteroids are effective in treating DME, two ocular adverse events (ocular hypertension and cataract) have made it a second-line therapy.

Triamcinolone and the dexamethasone implant have a pharmacological activity that lasts 3–6 months. The FAc implant can last up to three years and therefore has a great advantage over the other treatment modalities as the need for retreatment is reduced. The implant delivers a sustained low dose of FAc into the vitreous cavity, which would maximize the efficacy while minimizing off- target effects.(2,21)

The Role of Inflammation in the Pathogenesis of Diabetic Macular Edema

DME is a multifactorial process initiated by hyperglycemia.(22) It is characterized by the breakdown of tight junctions that form the inner blood-retina barrier (BRB) leading to increased vascular permeability, allowing leakage of fluid and plasma constituents into the macula(3,16)

The main risk factor for DR is hyperglycemia.(23) Other risk factors such as duration of diabetes, high glycosylated haemoglobin levels, hypertension and hyperlipidemia are involved in DME development.(15),(24)

Chronic hyperglycemia is responsible for many changes that occur in the retinal microvasculature, typically in the structural and cellular components. (25) The loss of pericytes, microaneurysm formation and increasing ischemia due to impaired retinal blood flow. The damage to endothelial cells lead to extracellular fluid accumulation, deposition of extracellular matrix components and thickening of the capillary basement membrane. (15,25,26)

Hyperglycemia-induced biochemical pathways lead to increased oxidative stress, inflammation and vascular dysfunction.(15,23) These changes induce the release of inflammatory cytokines and pro-angiogenic growth factors, such as VEGF, angiopoietins, tumor necrosis factor (TNF) , interleukins and matrix metalloproteinases (MMPs), which contribute to BRB breakdown.(15)

Diabetic patients with DR had significantly higher concentrations of inflammatory cytokines interleukin (IL)-1 β , IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), interferon gamma-induced protein-10 and VEGF in the aqueous humor, compared with nondiabetic

patients. All these cytokines, except for VEGF, correlated with the severity of diabetic retinopathy.(27)

VEGF influences the development of DME by stimulating vascular endothelial cell proliferation and increasing vascular permeability.(23) It is produced by several retinal cells in response to stimuli such as hypoxia and advanced glycation end products.(26) At early disease stages, VEGF overexpression is primarily responsible for vasogenic retinal changes and may be associated with the onset of macular edema formation.(3,20) Some data suggested that VEGF stimulates the expression of specific adhesion molecules, such as intracellular adhesion molecule –1 (ICAM-1) and vascular cell adhesion molecule –1 (VCAM-1), leading to the accumulation and adhesion of leucocytes, which are inflammatory cells.(26) Retinal leukostasis contributes to capillary non-perfusion, endothelial cell damage and vascular leakage.(4,25)

Müller cells represent the principal glial cells of the retina and act as a bridge between retinal nerves and the microcirculation. (4,23) These cells produce pigment epithelium derived growth factor (PEDF), a potent inhibitor of angiogenesis that reduces VEGF and antagonizes its action.(26) A dysfunction of Müller cells contribute to edema formation.

Corticosteroids inhibit inflammatory responses such as edema, capillary dilation, leukocyte migration, capillary and fibroblast proliferation, fibrin and collagen deposition and scar formation.(3) Corticosteroids have the ability of inhibit phospholipase A₂, via activation of lipocortins, decreasing arachidonic acid release. By blocking the arachidonic acid pathway, corticosteroids inhibit the synthesis of inflammatory mediators and prevent vasodilatation and increased capillary permeability.(28) Corticosteroids inhibit the expression of TNF- α , which is one of the crucial mediators of leukostasis, chemoattraction of monocytes, and upregulation of adhesion molecules (such ICAM-1). It also induces the expression of PEDF that has anti-inflammatory properties. (2,15) Because corticosteroids inhibit all these components of the inflammatory cascade, it is not surprising that the have been used successfully to treat DME.

Fluocinolone Acetonide - Pharmacological Properties

Two different extended-release drug delivery systems of FAc have been approved by FDA for intravitreal use: Retisert® (Bausch&Lomb, New Jersey, USA) and Iluvien® (Alimera Sciences, Atlanta, USA).

Retisert® is a nonbiodegradable implant containing 0.59 mg FAc, which is approved for the treatment of chronic noninfectious posterior segment uveitis. (23,29)

Iluvien® was approved in Europe for the treatment of vision impairment associated with chronic DME, considered insufficiently responsive to available therapies. In the USA, it was approved for the treatment of DME in patients treated with a course of corticosteroids, without clinically significant increase in intra-ocular pressure (IOP).(3,29) It is a sustained-delivery, low-dose, non-biodegradable intravitreal implant, which consists of a small (length 3.5 mm, diameter 0.37mm) cylindrical polyimide tube. It contains a central polyvinyl alcohol matrix where the FAc is embedded and contains a dose of 0.19 mg of FAc which is

released into the vitreous cavity at an initial rate of 0.25 µg/day (average rate 0.20 µg/day) and lasts up to 36 months. The implant is injected into the vitreous cavity through the pars plana using a 25-gauge needle. (2,3,16) It does not need sutures as it remains free within the vitreous cavity.

A study concerning the release kinetics of FAc showed that it reached its maximum concentrations in the aqueous one week after administration. Steady-state concentrations were reached approximately from month 6 until month 9 and then maintained through 36 months. With the exception of the first week, plasma concentrations remained below quantifiable levels during the 36 month-period. (30)

The efficacy of the FAc implant in vitrectomized eyes was not evaluated in clinical trials and its kinetics has not been studied in this condition. However, real-world clinical studies suggest that outcomes in vitrectomized and non-vitrectomized eyes are similar. It seems that the implant is also effective in these patients. This knowledge is fundamental as it is estimated that up to 20% of patients with DME may have had a prior pars plana vitrectomy. (31)(32)

The FAc implant was investigated in several trials. Efficacy and safety was examined in the FAMOUS (Fluocinolone Acetonide in Human Aqueous)(33) and FAME (Fluocinolone Acetonide for Diabetic Macular Edema) trials(34). The results of these two trials are summarized in table 1.

FAMOUS trial

This phase II, prospective, randomized, interventional and multicenter clinical trial included 37 patients with persistent DME despite previous laser photocoagulation (focal/grid) therapy. Other inclusion criteria were foveal thickness ≤ 250 µm and a best corrected visual acuity (BCVA) ≥ 19 letters in Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

Patients were excluded if they had received laser therapy, steroid injection or any intraocular surgery in the prior 3 months, or intraocular injection of anti-VEGF agents in the prior 2 months. Also, exclusion criteria included glaucoma, IOP > 21 mm Hg or treatment with IOP-lowering drops and prior vitrectomy or current peripheral retinal detachment.

Subjects were randomized 1:1 to receive an intravitreal implant of a 0.2 µg/day or 0.5 µg/day.(33)

Efficacy

The study revealed excellent sustained intraocular drug release for 1 year. One week after intravitreal insertion of the 0.5 or 0.2 µg/day inserts in patients with DME, aqueous level of FA was 3.8 and 3.4 ng/ml, respectively. One month after administration of the 0.5 µg/day inserts, the mean aqueous level of FA was 3.8 ng/ml, which was significantly greater than the level (2.7 ng/ml) achieved 1 month after administration of the 0.2 µg/day inserts. Between 3 and 12 months, the mean aqueous levels of FA were not significantly different for the 2 doses.

After administration of the 0.5 µg/day implant, the mean increase from baseline in BCVA letter score at months 3, 6, and 12 was 7.5, 6.9 and 5.7 letters, respectively, whereas in the 0.2 µg/day implant the BCVA improvement at months 3, 6, and 12 was 5.1, 2.7 and 1.3 letters, respectively. (33)

Safety

Regarding safety, there was no significant change in mean IOP after administration of 0.2 µg/day, while a mild increase (2.6 mm) in mean IOP was observed in patients receiving 0.5µg/day FAcimplant. In those patients who were phakic at baseline, a significant progression of cataract occurred in 35% and 71.4% of low or high dose cases with , 14% and 29% of eyes in each group requiring cataract surgery.(33)

FAME trials

The efficacy and safety of FAc implant was assessed in the FAME A and B clinical trials. These were a pair of parallel, prospective, randomized, double-masked, sham-injection controlled, multicentre, phase III clinical trials conducted over a 36-month period.

The inclusion criteria for the study were DME with foveal thickness ≥ 250 µm despite at least one prior macular laser photocoagulation treatment and a BVCA between 19 and 68 in ETDRS letter score (Snellen range of 20/50–20/400). The exclusion criteria were similar to the FAMOUS trial.

A total of 956 patients were randomized to either sham (N=185), low-dose (0.2 µm/day; N=375) or high-dose (0.5 µm/day; N=393) implant, administered to one eye. Baseline characteristics (age, race and mean duration of diabetes) were balanced between the groups.

Patients were allowed to receive rescue focal/grid laser therapy for persistent edema any time after week 6, and it could be repeated as frequently as every 3 months. After 1 year, patients could receive a retreatment with the initially assigned drug if they had a loss in BCVA ≥ 5 letters or increased foveal thickness.

Efficacy

The primary end-point was the proportion of patients showing a BCVA improvement of ≥ 15 ETDRS letters at month 24. This goal was achieved in 28.7% and 28.6% of patients who received low or high dose implants, respectively, versus 16.2% in the sham group.(34) This was significantly greater in both groups compared with the sham group from week 3 through month 36.(34,35) By month 36, the proportion of patients who gained ≥ 15 letters were 28.7 % in the low dose and 27.8 % in the high dose groups compared with 18.9% in the sham group ($p<0.01$). (35)

In both active groups a gradual decline in the mean of BCVA letter scores between 6 and 18 months was observed (related to cataract formation); this was followed by an increase between 18–24 months (due to cataract surgery). After two years, the mean visual gain was +4.4 and +5.4 letters in the low and high dose groups, respectively, compared with +1.7 in the sham group ($p= 0.02$). (34)

In the FAME trials, the mean central retina thickness (CRT) measured at baseline was 451, 461, 485 μm in the sham, low-dose and high-dose groups, respectively, representing severe edema. The FAc implant was associated with rapid reductions in CRT after one week, supporting the action of FAc. (34,35) The difference between active groups and sham remained significant over 24 months. At the primary end point, CRT was 340, 293, 308 μm in the sham, low-dose and high-dose groups, respectively.(34) CRT continued to decrease through 36 months, although there was no significant differences between the groups at 36 months.(35)

In a post-hoc analysis of the FAME trial, both dosages demonstrated statistically significant improvements in mean DR severity score compared with sham treatment as well as a slower progression to proliferative disease when it occurred.(36)

Safety

Cataract surgery was more frequent in the treated group at the end of month 24, (41.1% of patients on the low-dose group, 50.9% on the high-dose group, and in 7% of the sham group, which corresponded to 74.9%, 84.5%, and 23.1% of the patients in each of the groups)(34) In both treatment groups, visual acuity decreased between 6 and 18 months and then increased after the surgery. (34,35) In order to exclude potential confounding effects of cataract formation, the authors compared the mean change in BCVA between pseudophakic eyes and phakic eyes at baseline. In both implant groups, patients who were pseudophakic at baseline showed a mean gain of 7 letters in their ETDRS score, between baseline and week 6 that remained stable until month 24. Additionally, the visual benefit was similar in patients who underwent cataract surgery during the trial compared to those who were already pseudophakic at baseline. (34) However, in phakic eyes treated with the low-dose implant and that did not have cataract surgery by month 36, the visual acuity reduced 6 letters in BCVA score.(35)

Over 36 months, the IOP-related adverse events occurred in 37.1% and 45.5% of patients of low or high dose groups, respectively, compared to 11.9% of the sham group. Laser trabeculoplasty was carried out in 2.5%, 1.3% and 0% of high dose, low-dose or sham groups, respectively, while incisional glaucoma surgery was performed in 8.1%, 4.8% and 0.5% of these groups, respectively.(35)

Real world outcomes

An increasing number of real world clinical studies have been conducted. The evidence generally supports the FAME trial. A synthesis of the available evidence of real world outcomes is detailed in Table 2.

Prospective studies

There is limited data available from open-label, prospective, phase 4 studies. The study by Massin et al. was the first real-world study to assess the effectiveness of the implant in chronic DME patients considered insufficiently responsive to laser only (group 1) or laser and anti-VEGF treatment (group 2). This study included 16 patients corresponding to 17

eyes. At baseline, mean visual acuities were 47.7 letters in group 1 and 44.8 letters in group 2 and the mean CRT was 550.6 μm and 701 μm , respectively. The macular edema rapidly decreased in both groups, with a reduction in CRT of 299 μm ($p < 0.01$; group 1) and 251 μm ($p = 0.016$; group 2) at 12 months. Treated eyes had visual gains of 5.6 letters ($p = 0.141$; group 1) and 0.9 letters ($p = 0.865$; group 2). The mean area under the curve from baseline to last visual acuity for pseudophakic eyes was 4.2 and 9.5 letters in groups 1 and 2, respectively. The implant was well tolerated in all patients, and high IOP was reported in 3 eyes (18%). These adverse events were controlled by topical treatment. This study confirmed the efficacy of the FAc implant in patients with severe macular edema insufficiently responsive to laser and anti-VEGF. Moreover, considering safety results and once that better outcomes were obtained in group 1 compared with group 2, this study supported an earlier use of the FAc implant in the DME treatment pathway in selected patients. (22)

The study by Figueira et al (RESPOND) had similar results regarding the safety and efficacy of the implant. It included 12 patients who had prior anti-VEGF injections and some of them had associated laser or steroid therapies. A single eye of each patient was treated. At baseline, the mean BCVA was 48.8 ± 10.9 letters and the mean CRT was $650.5 \pm 140.9 \mu\text{m}$. At month 12, pseudophakic eyes ($n=8$) showed greater improvements in visual acuity than phakic eyes ($n=4$), as well as greater reduction in macular edema. The mean BCVA variation was +3.7 letters ($p = 0.255$), corresponding to +6.8 ($p = 0.058$) and -2.5 letters ($p = 0.715$) in pseudophakic and phakic eyes, respectively. A significant decrease of macular edema was observed over the 12 month-period ($-292.83 \mu\text{m}$, $p = 0.003$), with rapid reduction seen at week 1. An increase in IOP over 25 mmHg occurred in 2 patients and both were controlled with topical therapy. (20)

Another observational, multicentre study was conducted in UK and included 57 patients who had an insufficient response to prior anti-VEGF or steroid treatment. The implants were administered following an appropriate washout period, and following cataract surgery in phakic eyes. Of the 57 patients included in the study, only 22 completed 12 months of follow-up. An improvement in BCVA and CRT was observed 3 months after the implant insertion with a sustained effect through the 12 month-period. The mean increase in BCVA from baseline (52.7 ETDRS letters) was +5.8, +6.7 and +5.1 letters after 3, 6 and 12 months. The mean change from baseline CRT (452 μm) was -102 μm , -117 μm and -126 μm at months 3, 6 and 12. A subset of patients in this study had been submitted to previous vitrectomy ($n=25$). These eyes had a mean reduction in CRT of 156 μm and a visual gain of 3.9 letters at month 12. Increases in IOP were manageable with IOP-lowering medication (6 patients) and did not appear to affect visual outcomes. The mean change from baseline was +2.4 mmHg and +3.7 mmHg at 3 and 12 months, respectively. Implant migration into the anterior chamber occurred in 2 eyes, both previously vitrectomized and with a posterior capsule defect related to this procedure. In both eyes the implants were retrieved from the anterior chamber and reinserted into the vitreous cavity. (37)

Retrospective studies

Retrospective data from several cases series and case reports are available.

A case series published by Schmit-Eilenberger in 2015 highlights the type of patients that were being selected for treatment with the implant. 15 eyes from 10 patients, either phakic (n=5) or pseudophakic (n=10), all with chronic DME which was unresponsive to intravitreal anti-VEGF agents and in many cases, intravitreal triamcinolone and dexamethasone implants. 7 eyes had prior vitrectomy. At the last follow-up visit, the BCVA letter score had improved in 11 eyes (73.3%), remain unchanged in 2 eyes (13.3%), and slightly decreased in 2 eyes (13.3%).(38)

Similar outcomes were also seen in the consecutive case series published by Elaraoud et al of 22 patients who received an implant over an 8-month period. 3 months after treatment, the mean reduction in CRT was 148.9 μ m and the mean gain in visual gain was 6.4 letters. (39)

Additionally, Elaraoud et al also reported 6- and 12-month outcomes of a series of patients receiving bilateral implants for chronic DME.(8,19) Clinical improvement was established in these series, with a visual gain of 10.5 letters and CRT reduction of 357.9 μ m from baseline to month 12.(19)

Another case of a bilateral implant was reported by Bertelmann and Schulze in a 30-year-old man with type 1 diabetes, who had undergone photocoagulation and anti-VEGF therapies in both eyes without resolution. The patient received an FAc implant in the left eye and seven months later received one in the right eye. This case provides a direct comparison between the response to the FAc implant (left eye) versus anti-VEGF (right eye). During the first 7 months, the left eye showed rapid and sustained improvements in visual acuity and CRT, differently from that observed in right eye. After an implant was inserted in the right eye, a clear improvement in BCVA and CRT occurred which was similar to the outcomes of the left eye.(40)

The studies referred above gave support to the use of FAc implants as a feasible and effective choice in bilateral cases.(8,19,40)

In the FAME trials vitrectomy was an exclusion criteria. The study by Meireles et al was a multi-center study that reported the outcome of a single injection of the FAc implant in vitrectomized eyes that were previously treated with anti-VEGF and steroids. It included 26 eyes and the majority of them were pseudophakic (25eyes). Baseline, mean BCVA was 43.1 $\pm$ 16 letters, while mean CRT was 542 μ m $\pm$ 245. Significant changes were found after administration of the implant, with a mean change of +11.7 letters (p<0.001) and -233.5 μ m in CRT (p<0.001). The mean change in IOP from baseline to the last visit was +1.4mmHg, with 8 patients requiring IOP-lowering medications. 2 patients with previously capsular tear, had anterior migration of the implant, both were surgically reinserted without additional complications. (41) These results support those previously reported by Elaraoud et al in 5 vitrectomized eyes from a group of 22. In that study, visual acuity improved +7.2 letters and CRT decreased -176.8 μ m after 3 months. The data above suggests effectiveness of the implant in vitrectomized patients with an acceptable safety profile. (39,41)

Pessoa et al. retrospectively compared the efficacy of the implant in vitrectomized (n=24) and non-vitrectomized eyes (n=19). There were no statistically significant differences between the groups regarding visual gains and changes in CRT. Regarding IOP, both groups

had similar increases in mean IOP over the study period (+1.6 and +0.8 mmHg respectively). (31)

The ILUVIEN Clinical Evidence study in the UK (ICE-UK) assessed the real-world effectiveness of the implant for DME in the clinical practice.(42,43) Retrospective cohort studies were conducted in order to evaluate both the efficacy and safety (intraocular pressure) in clinical practice(43), to compare retinal thickness before and after treatment(42) as well as visual and anatomical outcomes between study and fellow eyes.(44) An overall significant improvement in visual acuity was observed over the 12 month-period, with a total of 44%, 33% and 18% of people achieving an improvement in ETDRS score of 5, 10 and 15 letters, respectively. IOP-lowering therapy was required in 15% of treated eyes.(43) In addition, a significant and sustained reduction in CRT was observed in the 12 months following treatment, with a reduction of 10%, 25% and 50% being observed in 65%, 50% and 21% of treated eyes, respectively.(42) Changes in visual acuity, central foveal thickness and intraocular pressure following the FAc implant differed significantly between study and fellow eyes, over the 12-month period. When compared to fellow eyes, which had worsening of visual acuity, study eyes not only improved visual outcomes but also CRT. Only study eyes showed an increase in intraocular pressure. (44)

Audits

The ILUVIEN Registry Safety Study is an ongoing, European multicentre, open-label, observational study collecting real-world data on the safety and effectiveness of the implant. (45) It has data from the UK, Germany and Portugal. It evaluated 593 eyes with chronic DME. The major results reported were 3.7 ETDRS letter gains at month 12. There is no data regarding macular thickness changes. The authors report that patients with short term chronic DME had greater visual gains and that 1/3 of eyes achieved a visual acuity equal or greater than 20/40. Three quarters of the patients did not require IOP lowering drops and 69% of patients did not need further treatments for DME during the study period.

Another UK study from the Medisoft Audit Group concerning safety outcomes, with a particular focus on IOP-related adverse events, was conducted using data provided from 14 clinical sites and collected using an electronic medical record system.(46) A total of 345 eyes were included. Medical management was not required in the majority of the patients with IOP increase. In fact, at last observation only 13.9% of eyes required IOP-lowering drops, whereas 7.2% had IOP elevation >30 mmHg and 0.3% required glaucoma surgery. Moreover, no adverse events were seen in the group of patients that were previously treated with steroids without no IOP-related events. The mean visual change in this study was +6 ETDRS letters. (46)

Conclusions

The FAc implant is an effective option for patients with DME, in particular in cases with persistent and recurrent edema despite multiple anti-VEGF and/or corticosteroids injections. For this challenging group of patients, the implant has been a valuable therapy, for being

clinical effective but also by reducing the treatment burden. Almost 70% of patients in a large observational trial did not need additional treatments.

The FAME trials reported efficacy and safety of the implant for DME and there is evidence that the implant can lead to improvements in mean DR severity score. Evidence from real world studies have shown similar outcomes to those obtained from clinical trials (FAME and FAMOUS), with patients treated with the implant achieving visual gains and reduction of edema. This is not surprising as the treatment performed is similar to the one performed in the trials. This is important because it is difficult in clinical practice to keep the very frequent anti-VEGF injections that are necessary to mirror clinical trial results.

Consistently with the expected adverse events, cataract formation and IOP elevation are common. The majority of treated phakic eyes developed cataracts and underwent surgical extraction, but visual benefits in these patients were similar to baseline pseudophakic eyes.

In real-world practice, the incidence of IOP elevation after the implant were slightly lower than in the FAME trials, and in most cases, manageable with IOP-lowering medication. However, IOP is an important issue that should not be forgotten in these patients.

A stepwise approach to treat DME is typically recommended beginning with a course of at least 3 injections of anti-VEGF. For patients who still demonstrate an insufficient response even after switching to another anti-VEGF and pseudophakics are good candidates to first receive IVTA or dexamethasone implant to gauge IOP and anatomic response. If minimal pressure response to IVTA, patient expressing a strong preference for reduced frequency of injections, transportation issues and poor compliance with appointments FA implant is a good option (figure 1).

In conclusion, clinical practice findings have corroborated the results of clinical trials and supported the value of the FAc implant as a treatment option for chronic DME.

Real-world data has shown that the implant is an option in bilateral cases and in vitrectomized eyes. Also, it has been proposed that an earlier use of the implant may have better functional results, particularly those who did not respond to first-line therapy and known to be tolerant to corticosteroids. Eyes treated with the implant have been eyes with poor responses and probably have a poor visual potential. This may have limited the visual results obtained in these studies.

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Figure 1. Flow chart highlighting the position of the FAc implant in current clinical practices.

Pseudophakics are better candidates for intravitreal corticosteroids.

Patients with poor response to anti-VEGF may receive IVTA or dexamethasone implant to gauge IOP and anatomic response. If minimal pressure response, patient expressing a strong preference for reduced frequency of injections, transportation issues and poor compliance with appointments, a FAc implant is a good option

Table 1.

Summary of randomized clinical trials with the 0.19 mg FAc implant.

Study	Study Design	Follow-up (months)	Study groups	Eyes (N)	BCVA change (ETDRS letters)	Mean CRT change (µm)	IOP related adverse events(%)	Incisional Glaucoma Surgery
FAMOUS trial(33)	RCT	12 months	0.2µg	20	+1.3	-97.8µm	0	0
			0.5µg	17	+5.7	-119.3µm	35%	5.9%
FAME trial(34)	RCT	36 months	Sham *	185	+2.0	-142µm	11.9%	0.5%
			0.2µg	375	+5.3	-181µm	37.1%	4.8%
			0.5µg	393	+5.3	-185µm	45.5%	8.1%

* Patients in the sham group of the FAME trial could be treated with rescue macular laser therapy. 60.7% of patients in this sham group were treated with laser therapy

RCT: Randomized Clinical Trial. N: Number; BCVA: Best Corrected Visual Acuity; CRT: Central Retina Thickness.

Summary of real life studies that evaluated the outcomes of the use of the 0.19 mg FAc implant. IOP lowering drops refers to patients that started new IOP lowering drops after the implant insertion. N: Number; BCVA: Best Corrected Visual Acuity; CRT: Central Retina Thickness; NR: Not Reported; DME: Diabetic Macular Edema; Anti-VEGF: Anti-vascular Endothelial Growth Factor

Table 2.

Study	Study Design	Description of DME study cohort*	Eyes (N)	Follow-up (months)	Change in BCVA (baseline) (ETDRS letters)	Change in CRT (baseline) (µm)	IOP lowering drops (%)
Massin P, et al. 2016 (22)	Prospective	Unresponsive to laser	7	12	+5.6 (47.7)	-299 (573)	14.3
		Unresponsive to laser and anti-VEGF	10		+0.9 (44.8)	-251 (701)	20
Figueira J, et al. 2017 (20)	Prospective	Pseudophakic	4	12	+6.8 (48.8)	-293 (651)	100
		Phakic	8		-2.5 (48.8)		12.5
El- Ghrably I, et al. 2017(37)	Prospective	Vitrectomized	12	12	+3.9 (52.7)	-156 (452)	41.7
		Non-vitrectomized	10		+6.2 (52.7)	-96 (452)	20
Schmit-Eilenberger VK, et al. 2015(38)	Case Series	Unresponsive to DME therapy	15	9	+12 (70)	-206 (509)	13.4
Elaraoud I, et al. 2016 (39)	Retrospective	Pseudophakic eyes	22	3	+6.4 (50.7)	-149 (631)	4.5
Elaraoud I, et al. 2016 (19)	Retrospective	Bilateral chronic DME	10	12	+10.5 (44.5)	-358 (645)	0
Meireles A, et al. 2017 (41)	Retrospective	Vitrectomized eyes	26	8.5	+11.7 (43.1)	-234 (542)	30.8
Bailey C, et al. 2017 (46)	Retrospective	Unresponsive to DME therapy	345	24	+5.3 (51.9)	-95.7 (451.2)	13.9
Chakravarthy U, et al. (45)	Observational	DME that persists or recurs	593	12	+3.7 (51.9)	NR	23.3

* , All eyes were treated according to the indication (i.e. DME that persisted or recurred despite therapy).