Clinical utility of intravitreal fluocinolone acetonide (Iluvien[®]) implant in the management of patients with chronic diabetic macular edema: a review of the current literature

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Abstract: The first-line therapy for patients with center-involving diabetic macular edema (DME) is with intravitreal anti-vascular endothelial growth factor (VEGF) agents, with or without adjunctive macular laser treatment. However, a significant proportion of patients have persistent and recurrent edema despite repeated anti-VEGF injections. The fluocinolone acetonide (FA) 190 µg intravitreal implant has been shown in pivotal clinical trials to be efficacious for the treatment of DME and has been approved in many countries for use in patients who have not responded to first-line therapy. In this report, we have collated the latest data from the increasing number of studies to illustrate the pattern of usage of the Iluvien FA implant for DME during the current anti-VEGF era. We have shown that there is now a wealth of published evidence from real-world studies to support the clinical utility of the FA implant in achieving further resolution of edema and improving visual acuity outcomes in this challenging group of patients.

Keywords: fluocinolone acetonide, Iluvien, diabetic macular edema

Introduction

The first-line therapy for patients with center-involving diabetic macular edema (DME) is with intravitreal anti-vascular endothelial growth factor (VEGF) agents, with or without adjunctive macular laser treatment. However, a significant proportion of patients have persistent and recurrent edema despite repeated anti-VEGF injections. The fluocinolone acetonide (FA) 190 µg intravitreal implant (0.2 µg/day; Iluvien[®], Alimera Sciences, Inc., Alpharetta, GA, USA) was found to be efficacious for the treatment of DME in the landmark, pivotal Fluocinolone Acetonide in Diabetic Macular Edema (FAME) studies (FAME A and B), which were well-designed, Phase III, multicenter, randomized clinical trials designed to assess the efficacy and safety of a single injection of the FA implant over a 36-month period versus the standard of care.^{1,2} At the time the FAME studies were conducted, the standard of care was mainly laser photocoagulation. During the study, 34.8% of the control group received off-protocol treatments, such as anti-VEGF agents or intravitreal triamcinolone, compared with 13.4% in the FA implant-treated group.¹ Furthermore, 62.7% (n=235/375) of eyes receiving the FA implant were phakic at baseline and 80.0% of eyes receiving the FA implant (0.2 µg FA arm) required cataract surgery during the course of the 3-year trial.¹ These two factors have made it difficult for clinicians to translate the evidence from the FAME studies directly into their current clinical practice, especially regarding the

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role of the FA implant among the current armamentarium of anti-VEGF agents that are now well established as the first-line therapies for DME.^{3–7} Currently, there have been no studies published or planned to compare the head-to-head performance of the FA implant and anti-VEGF as first-line agents for the therapy of DME.

Recent evidences from follow-up and exploratory analyses of data from large-scale clinical trials on ranibizumab and aflibercept with or without adjuvant laser treatment have shown that a sizeable proportion of patients have persistent macular edema, which is unresponsive to anti-VEGF therapy either as monotherapy or in combination with prompt or delayed or repeated macular grid laser treatment.^{8–11} One report showed that half of the eyes treated for DME with intravitreal ranibizumab have persistent central-involved DME up to 24 weeks after initiating treatment.¹² A recent analysis of Protocol I data showed that ~40% of eyes had suboptimal early response (<5-letter improvement in best corrected visual acuity [BCVA]) at 12 weeks and the majority had suboptimal visual outcomes after 3 years of treatment.¹³ Given this limitation of anti-VEGF agents, it is fortunate that the FA implant has been licensed for the treatment of vision impairment associated with chronic DME that is insufficiently responsive to available therapies.^{14,15} This has led to an increasing usage of the FA implant for patients with DME who have responded suboptimally to therapy, although the definition of insufficient response has been quite variable in the published literature.¹⁶ As there have been no prospective studies to evaluate the role of the FA implant in the current anti-VEGF era, clinicians have to rely on a less robust evidence base and their own clinical experience to guide their utilization of the FA implant and especially on how to define insufficient response.

In this report, we aim to collate and distil the reports from an increasing number of studies, which are largely uncontrolled and retrospective, to illustrate the pattern of usage of the FA implant for chronic DME during the current anti-VEGF era and also to summarize their clinical outcomes and safety findings. All references to the FA implant used in the FAME studies relate to the low-dose and not the high-dose implant. Comparison of the FA implant with the dexamethasone implant has not been made as this is beyond the scope of this review. It is hoped that this summary will be useful for clinicians in clinical decision-making and also to enable greater confidence in justifying the use of the FA implant for chronic DME, especially when anti-VEGF agents have been ineffective in resolving the edema and when recurrent or persistent edema is causing visual decline or requiring very frequent injections.

General mechanisms of action of corticosteroids in DME

The pathogenesis of DME has been the focus of several review articles published in recent years. Multiple inflammatory and neurodegenerative pathways have been implicated. The major component underlying the development of macular edema is believed to be the presence of chronic, low-grade inflammation of the retinal microvasculature contributing eventually to the breakdown of tight junctions that form the blood–retinal barrier, which, in turn, increases retinal vascular permeability. Corticosteroids inhibit prostaglandin and leukotriene synthesis and interfere with other pathways, including intercellular adhesion molecule-1, interleukin-6, VEGF- α , and stromal cell-derived factor-1.^{17–20} Corticosteroids also decrease paracellular permeability and increase tight junction integrity by directly restoring tight junction proteins to their appropriate location at the cell border and by increasing the gene expression of those proteins.^{21,22}

Formulation and pharmacokinetics of the FA implant

FA has an empirical formula of $C_{24}H_{30}F_2O_6$ and is a small molecule with a molecular weight of 452.49 Da.²³ It is formulated as a sustained-delivery, low-dose, intravitreal, non-bioerodible implant, which consists of a cylindrical polyimide tube measuring 3.5 mm in length and 0.37 mm in diameter and containing 190 μ g of FA as the active ingredient. The implant is injected through the pars plana into the vitreous cavity using a 25-gauge applicator in the same manner as in the intravitreal injection and can be done in the office setting.²⁴ After the injection, there is a slow release of the drug from one end of the polyimide cylinder. The dose of 190 μ g releases the drug at a rate of 0.2 μ g per day. The release kinetics of FA implants have been studied in humans and rabbits, and the corticosteroid maximum concentration in the aqueous found with FA implants were found to be several orders of magnitude lower than either triamcinolone or the bioerodible system releasing dexamethasone (Ozurdex®; Allergan)²⁵ and also lower than the aqueous maximum concentration level of commonly used corticosteroid eye drops such as Pred Forte 1% (mean C_{max} between 669.9 and 1,130 ng/mL vs 2.17 ng/mL for the FA implant).

FAME trial – efficacy

The efficacy of the FA implant was evaluated in the FAME trial.^{1,2} Patients were randomized to either a sham injection (n=185), a low-dose (0.2 μ g/day; n=375), or a high-dose (0.5 μ g/day) FA implant (n=393). Patients could receive

rescue laser photocoagulation during the study if there was persistent macular edema. After 1 year, they could receive a second treatment if their vision decreased or foveal thickness increased. Clinicians could use off-protocol therapies such as intravitreal anti-VEGF injections or intravitreal triamcinolone in patients at their discretion and those patients treated with off-protocol medications were not withdrawn and where possible their actual final outcome measures were analyzed. The primary end point was a gain of ≥ 15 letters at 24 months with follow-up to 36 months.^{1,2} At month 36, the proportion of patients gaining ≥ 15 letters was 18.9% in the FA implant group versus 21.4% in the sham group ($P=0.030$). Foveal thickening was also markedly reduced in the FA-treated group after the first follow-up visit (week 1) and a sustained reduction was maintained through to month 36.^{1,2}

FAME trial – safety

The FAME studies reported that by the end of the 3-year follow-up period, phakic patients who received the FA implant developed cataracts in 81.7% versus 50.4% in the sham group and 80% required cataract surgery versus 27.3% in the sham group. This high rate of cataract formation was attributed to the effect of FA in the treated group and to the off-protocol use of other short-acting steroids such as triamcinolone particularly in the control group.¹

Cataract formation is a well-known side effect of steroid use. While 80% of phakic patients in the FA implant group developed cataract, the overall visual benefit after cataract surgery was similar to that in pseudophakic patients. This was demonstrated in a post hoc analysis of the FAME studies data in chronic and non-chronic DME in patients who underwent cataract extraction before or after receiving the implant.²⁶ In this analysis, the BCVA after 36 months was comparable in both groups. In addition, most patients who underwent cataract surgery experienced a net gain in BCVA from pre-surgery baseline and from original study baseline. When only those patients who had cataract surgery after receiving the implant were evaluated, patients with chronic DME were numerically more likely to gain a ≥ 15 -letter improvement than those with non-chronic DME (42.3% vs 27.5%). These results demonstrated that patients who had cataract surgery after receiving the FA implant experienced long-term visual gains that were no worse and possibly better than outcomes observed in patients who were already pseudophakic when they received the FA implant. These results could be attributed to a possible protective effect of corticosteroid therapy from postoperative macular edema when administered prior to cataract surgery. These data, therefore, provide some

evidence for the use of the FA implant in phakic and in pseudophakic eyes.^{26,27}

In the FAME studies, raised intraocular pressure (IOP) was managed with IOP-lowering drops in 38.4% of patients in the FA implant group versus 14.1% in the sham control group. In terms of timing of IOP events, the onset of ocular hypertension began within 2–4 weeks with a maximum at 24–48 weeks and a return to baseline at 9–12 months.^{1,2,28} In a small number of cases (1.3%), laser trabeculoplasty was used to manage raised IOP in the FA-treated group. Incisional surgery was also used to manage raised IOP and was performed in 4.8% of patients in the FA implant group versus 0.5% in the sham group.

In the FAME trial, patients who had prior corticosteroid could be enrolled into the study only if they did not have an IOP response; that is, they were not steroid responders. Given this selection criterion, another post hoc analysis on the FAME data set by Parrish et al reported that among the 72 patients receiving FA implant, who received prior corticosteroid (and therefore would have been non-steroid responders), none required IOP-lowering surgery.²⁹ In contrast, out of 294 patients who did not have prior intravitreal corticosteroid (and therefore had not had their steroid response status confirmed), 18 (6.1%) required IOP-lowering surgery ($P=0.030$).²⁹ This highlights the potential value of knowing if patients have a strong IOP response to corticosteroid therapy and is reflected in the approved US indication of FA implant for only those eyes that have not had any clinically significant IOP response to prior corticosteroid therapy.²⁴

A recent assessment of the fundus photographs from the FAME trial data was conducted to determine whether FA-treated patients had any clinically significant glaucomatous changes in the optic nerve head.³⁰ It is noteworthy that the use of the FA implant is contraindicated in the presence of pre-existing glaucoma.²⁴ The post hoc analysis of the changes in the mean cup-to-disc ratio (CDR) by Parrish et al³⁰ showed that there was no significant increase in the proportion of patients experiencing a CDR increase of >0.2 with the FA implant versus the sham control. This finding suggested that although IOP increases occur in patients after treatment with the FA implant, glaucomatous optic nerve changes were similar between FA and non-FA-treated patients within the 3-year study period. Despite this reassuring report of the benefit of the post hoc analysis of CDRs, it is important to follow patients with established steroid induced glaucoma and disk damage carefully with regular visual field testing as perimetry is regarded as more useful than optic disk morphometry in monitoring established glaucoma.³¹

Approved indications of FA implant

In Europe, the 0.2 µg/day, FA implant (Iluvien) is approved for the treatment of vision impairment associated with chronic DME considered insufficiently responsive to available therapies. In the USA, it is approved for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP.²⁴ In the UK, National Institute for Health and Care Excellence (NICE) guidance, based on efficacy-to-cost, stipulates its use only in pseudophakic eyes with DME that has not responded sufficiently to available therapies.¹⁵

Real-world outcomes

In recent years, there have been numerous clinical studies on the use of the FA implant in those patients whose DME has been insufficiently responsive to laser therapy and intravitreal anti-VEGF agents. This emerging evidence has been vital for clinicians to justify the use of the FA implant in those patients who have not responded to the first-line therapy of laser and anti-VEGF agents. The study by Massin et al was the first real-world study to assess the effectiveness of the FA implant at the Lariboisière Hospital in Paris, France.³² This was a Phase IV, prospective study evaluating the efficacy and safety of the FA implant in chronic DME patients considered insufficiently responsive to laser only (Group 1) or laser and anti-VEGF treatment (Group 2). Although only 16 patients (17 eyes) were included in this study, they all had chronic and particularly recalcitrant DME. Baseline visual acuities and central retinal thicknesses (CRT) were 47.7 letters and 550.6 µm (Group 1) and 44.8 letters and 701 µm (Group 2), respectively. The median duration of DME was 7.6 years in Group 1 and 3.6 years in Group 2, respectively, and the majority of eyes were pseudophakic as >80% of patients in both groups had prior intravitreal corticosteroid. Despite the poor visual acuity and the chronicity of DME, by month 12, the treated eyes had reduction of edema and visual gains of 299 µm and 5.6 letters (Group 1) and 251 µm and 0.9 letters (Group 2), respectively. The evidence from this study provides some justification for using the FA implant in those patients with lower visual acuity and chronic and persistent DME, despite prior intravitreal anti-VEGF and prior intravitreal corticosteroid who are often encountered in the real-world setting.^{32–36}

A case series of 15 eyes in 10 patients with similar characteristics was published by Schmit-Eilenberger in 2015.³³ Prior to treatment with the FA implant, all had an insufficient response to either anti-VEGF and/or triamcinolone or dexamethasone implants. Ten eyes were pseudophakic before or shortly after receiving the FA implant and seven eyes

had prior vitrectomy. Follow-up was unfortunately variable between two and 36 weeks with a majority of patients with at least 20 weeks of follow-up, but nevertheless there was an improvement in BCVA in eleven (73.33%) eyes, unchanged in two (13.33%) eyes, and decreased in two (13.33%) eyes at the last follow-up visit in comparison to baseline. In other words, visual acuity improved or was maintained in 86.7% of eyes. This case series highlights the types of patients who were being selected for treatment with the FA implant. Patients were either phakic or pseudophakic, but all had chronic DME, which was unresponsive to intravitreal anti-VEGF and in many cases intravitreal triamcinolone and dexamethasone implants as well.

The types of patients that clinicians are selecting for treatment with the FA implant in the real world can also be seen from the consecutive case series published by Elaraoud et al of 22 patients who received an FA implant over an 8-month period in three hospital sites.³⁴ In this series, due to the restriction of its use in the UK to pseudophakic patients only, none of the treated eyes were phakic but all eyes had received prior intravitreal anti-VEGF therapies including six eyes with prior intravitreal triamcinolone. At 3 months after treatment with an FA implant, the mean reduction in CRT was 148 µm and the mean gain in visual gain was 6.4 letters. The majority (68.2%) of patients had improved CRT and improved vision at 3 months, but 4 out of the 22 eyes did not have any reduction in CRT at this time point.³⁴ In another paper, Elaraoud et al also reported 6- and 12-month outcomes of a series of patients receiving bilateral FA implants for bilateral chronic DME. At 12 months, 9 out of 10 patients had sustained and improved VA with a mean improvement in visual of acuity of 10.5 letters and a mean reduction in CRT of -357.9 µ from baseline.^{35,36} Another case of a bilateral FA implant was reported by Bertelmann and Schulze in a 31-year-old man with type 1 diabetes who received an FA implant in the left eye followed by the right eye 6 months later.³⁷ In the left eye, central macular thickness decreased from 642 µ to 372 at month 13. BCVA also improved rapidly following the FA implant from 0.3 (a Snellen fraction of 20/60 or a 61 ETDRS letter score) at baseline to 0.5 (20/40 or a 70 ETDRS letter score) after 1 month, which was sustained through to month 9. Cataract formation resulted in a reduction of BCVA at month 13, although this improved following cataract surgery. The right eye also had resolution of DME at 6 months of follow-up. These small case series lend some support to the use of FA implants in bilateral cases.

It has been postulated that in vitrectomized eyes, DME may be less responsive to anti-VEGF and more responsive to slow release formulations such as a dexamethasone implant

or an FA implant due to the increased clearance of anti-VEGF delivered in a single bolus injection.^{38–40} Kumar et al reported two cases of the FA implant used in refractory DME in vitrectomized eyes, which completely resolved up to 1 year.⁴¹ The first was a 50-year-old female who received multiple intravitreal anti-VEGF and triamcinolone injections for chronic DME and subsequent vitrectomy for severe macular traction. After vitrectomy, DME was still present despite additional intravitreal therapies. The patient received an FA implant 7 months after vitrectomy, which then resulted in resolution of DME with no further adjunctive therapy up to 1 year. The second case was a 48-year-old male who underwent right eye vitrectomy 3 years prior to bilateral treatment with an FA implant. The right DME resolved gradually over 1 year without adjunctive therapy but in the left eye DME responded only briefly before recurring. A year later, vitrectomy, with the FA implant preserved, was performed which led to DME resolution.⁴¹ These cases demonstrate the effectiveness of the FA implant up to 1 year after initial treatment in vitrectomized eyes and was the first reported case of reduction of edema in a vitrectomized eye which had received an FA implant before vitrectomy which was done without removal of the implant. Efficacy was demonstrated up to 2 years in one case report which showed that a single injection of the 0.2 µg/day FA implant lead to improvements in VA and CFT within 7 days. This was maintained over 2 years of follow-up despite 11 previous injections of ranibizumab.⁴²

Real-world outcomes of intraocular pressure effects of the FA implant

As mentioned earlier, 38.4% of FA-treated patients required IOP-lowering medication as opposed to 14.1% in the sham group in the FAME trial.¹ As definite steroid responders were excluded from the FAME trial and the use of IOP-lowering drugs was strictly controlled by the study protocol, it is useful to review the experiences seen in the real-world studies on the IOP effects of the FA implant.

In the study by Elaraoud et al of 22 patients unilaterally treated with the FA implant and a 3-month follow-up period, there was no substantial increase in IOP. The mean baseline IOP was 16.9 mmHg (standard deviation [SD]: ± 3.1 ; range: 10–22 mmHg), with the mean change of 0.3 mmHg (SD: ± 3.1 ; range: -7 to $+5$ mmHg) at month 3.³⁴ Four eyes were receiving IOP-lowering drops (timolol and/or latanoprost) prior to the FA implant. Following treatment with the FA implant, one additional eye required IOP-lowering medication. The case series by Elaraoud et al of 5 bilateral FA implants (10 eyes treated) had a 12-month follow-up. The mean IOP was 13.7 ± 3.6 mmHg (mean $\pm$ SD) at

baseline; 15.5 ± 4.0 mmHg at 6 months; and 16.0 ± 3.3 mmHg at 12 months. In all cases, IOP remained < 22 mmHg.³⁵

Massin et al reported elevated IOP in 3 out of 17 eyes; one patient in the prior laser-only group (maximal IOP value was 32 mmHg at month 1) and two patients in prior laser and ≥ 3 monthly anti-VEGF therapy group (25 mmHg at month 3 and 28 mmHg at month 12). These three patients had their IOP well controlled by IOP-lowering eye drops.³² The mean IOP remained stable in both groups from baseline to month 12: from 15.3 ± 2.7 (mean $\pm$ SD) to 16.8 ± 3.5 mmHg in Group 1 and from 15.5 ± 2.5 to 18.2 ± 4.7 mmHg in Group 2.

In Schmit-Eilenberger's case series of 15 eyes, 3 eyes had a rise of IOP of > 7 mmHg.³³ The rise in IOP was controlled either by a sectorial cyclocryotherapy and/or a medical treatment with fixed combinations.

Bertelman and Schulze's case study showed an increase in IOP in the left eye from 20 mmHg at month 3 to 32 mmHg at month 7.³⁷ This particular patient's IOP was successfully managed with combination topical IOP-lowering medication. At 13 months, left and right eye IOP, 6 months after FA implantation, was 21 and 18 mmHg, respectively.

With regards to the value of a corticosteroid provocation test, Breusegem et al looked at the predictive value of topical dexamethasone for IOP elevation before intravitreal triamcinolone and reported a positive predictive value of 100% and a negative predictive value of 62%.⁴³ Additionally, a family history of glaucoma is a significant risk factor for the development of steroid-induced IOP elevation and other risk factors include high myopia, diabetes mellitus, and connective tissue diseases.^{44,45} Although it has been quite reassuring from real-world case series of patients treated with the FA implant that an elevated IOP can often be managed successfully, the results of their corticosteroid provocation tests, their baseline optic disc and visual field status, and other risk factors should all be taken into account when deciding on whether to use an FA implant for their DME. A recent publication by an expert panel suggested a risk stratification algorithm for managing patients treated with the FA implant based on the presence of ocular hypertension and glaucoma at baseline and also the level of IOP reached during the follow-up.²⁸

Other adverse events

Moisseiev et al described a case of an FA implant causing a visually disturbing "floater" in the visual axis of previously vitrectomized eye.⁴⁶ This required neodymium:yttriumaluminum garnet laser vitreolysis of a vitreous attachment to remove the implant from the visual axis, which led to a resolution of the patient's symptoms. Migration of FA implants into the anterior chamber has been

reported in two eyes of patients with previous complicated cataract surgery and vitrectomy.⁴⁷ However, the successful repositioning from the anterior chamber into the vitreous cavity, without damage or complications to the eye or the implant, has been reported using a 23-gauge flute needle.⁴⁸ A theoretical risk of retinal detachment following intravitreal injection of the FA implant has not been demonstrated in the peer-reviewed literature.

Current on-going real-world studies on the Iluvien implant

The Iluvien Registry Safety Study is a European, multicenter, open label, registry study assessing the real-life tolerability of Iluvien.⁴⁹ Interim data analysis was presented in May 2016 with further analysis due to take place in 2017. The study involves 26 sites in the UK, 10 sites in Germany, and 1 in Portugal. Data were presented for 328 eyes (292 patients). The average period of follow-up in the interim analysis was 281.9 days (range: 3–763 days). 81.6% of patients did not require initiation of IOP treatment post-FA implantation. However, 2 of the 328 eyes required IOP-lowering surgery. In this group of patients with an extended duration of DME and 98.8% of whom had received prior therapy including intravitreal anti-VEGF and laser, visual acuity reportedly improved in 58% of patients at 6 months and 61% at 12 months. The Medisoft® electronic auditing tool has been used in the UK to retrospectively review real-world IOP events in 290 eyes of 258 patients following the FA implant.⁵⁰ 14.8% of patients required the initiation of IOP-lowering medication. In the overall group, 69.4% of eyes maintained or had an improvement in visual acuity from month 3 through to month 24.

The RESPOND study is a prospective, nonrandomized, multicenter, open-label Phase IV pilot study that has been conducted across four sites in Portugal.⁵¹ In this study, 12 patients received Iluvien 190 µg intravitreal implant at the inclusion visit and were followed up for eight visits over 12 months. Changes in BCVA, CRT, and adverse events, namely cataract and elevated IOP, were studied from baseline to month 12. The results of this study are due to be published in the near future.

Finally, another vendor sponsored retrospective study called the Iluvien Clinical Evidence in the United Kingdom study has completed data collection on >300 patients from 12 hospitals in the UK (Yang, unpublished data, 2017). The profiles on prior therapies, baseline characteristics at the time of Iluvien therapy, and 12-month outcome in visual acuity and IOP are expected to be reported in 2017.

In the coming years, there are likely to be many publications on the real-world outcomes of the FA implant for DME. There is a real possibility that the same cohort of patients either in part or in whole may be the subjects of more than one publication. In contrast to subsequent publications on post hoc analyses from the same data set of a clinical trial where it is clear where the patient data came from, this is not the case in real-world studies where data can be collected multiple times from the same patient or patients for several publications. Due to the high potential for duplication of reporting of real-world data, data from multiple publications originating from the same institutions must be interpreted with caution.

Conclusion

Since the initial FAME trial reporting the efficacy of FA implant for DME, intravitreal anti-VEGF agents have become firmly established as the first-line therapeutic agents for DME. The FA implant has been approved by regulatory authorities in many countries for the treatment of chronic DME and the role of FA implant has been mainly reserved for those patients who have persistent or recurrent sight-threatening edema despite multiple and frequent administrations of anti-VEGF therapy. For this challenging category of patients, there is now a wealth of published evidence-based real-world studies to support the clinical utility of FA implant in achieving further resolution of edema and improving visual acuity outcomes, thereby potentially reducing the burden of frequent injections and hospital visits.

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References

1. Campochiaro PA, Brown DM, Pearson A, et al; FAME Study Group. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology*. 2012;119(10):2125–2132.
2. Campochiaro PA, Brown DM, Pearson A, et al; FAME Study Group. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology*. 2011;118(4):626–635.e2.

3. Aiello LP, Beck RW, Bressler NM, et al. Diabetic Retinopathy Clinical Research Network; Writing Committee. Rationale for the diabetic retinopathy clinical research network treatment protocol for center-involved diabetic macular edema. *Ophthalmology*. 2011;118(12):e5–e14.
4. Bandello F, Cunha-Vaz J, Chong NV, et al. New approaches for the treatment of diabetic macular oedema: recommendations by an expert panel. *Eye (Lond)*. 2012;26(4):485–493.
5. Mitchell P, Wong TY; Diabetic Macular Edema Treatment Guideline Working Group. Management paradigms for diabetic macular edema. *Am J Ophthalmol*. 2014;157(3):505–513.e1–e8.
6. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for DME. *Ophthalmology*. 2011;118(4):615–625.
7. Do DV, Nguyen QD, Boyer D, et al; da Vinci Study Group. One-year outcomes of the da Vinci Study of VEGF Trap-Eye in eyes with diabetic macular edema. *Ophthalmology*. 2012;119(8):1658–1665.
8. Kuppermann K. 'ILUVIEN: area Under the Curve (AUC) Pharmacokinetics – The CONSTANT Analysis: AUC comparisons to Protocol I Ranibizumab, Deferred Laser and OZURDEX' presented at: ISOPT Clinical; December 1; 2016; Rome. Available from: <http://www.isopt-clinical.com/Events/Display/ISOPT2016?Page=Program>. Accessed November 15, 2016.
9. Elmen MJ, Ayala A, Bressler NM, et al; Diabetic Retinopathy Clinical Research Network. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. *Ophthalmology*. 2012;119(11):2312–2318.
10. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. *Arch Ophthalmol*. 2012;130(8):972–979.
11. Diabetic Retinopathy Clinical Research Network; Elman MJ, Qin H, Aiello LP, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmology*. 2012;119(11):2312–2318.
12. Bressler SB, Ayala AR, Bressler NM, et al; Diabetic Retinopathy Clinical Research Network. Persistent macular thickening after ranibizumab treatment for diabetic macular edema with vision impairment. *JAMA Ophthalmol*. 2016;134(3):278–285.
13. Gonzalez VH, Campbell J, Holekamp NM, et al. Early and long-term responses to anti-vascular endothelial growth factor therapy in diabetic macular edema: analysis of protocol I data. *Am J Ophthalmol*. 2016;172:72–79.
14. Medicine and Healthcare products Regulatory Agency. *Iluvien® 190 micrograms intravitreal implant in applicator (fluocinolone acetonide)* [updated 2015]. Available from <http://www.mhra.gov.uk/home/groups/par/documents/websitesources/con171936.pdf>. Accessed October 23, 2016.
15. NICE guidelines [TA301]; 2013 [online]. Available from: <https://www.nice.org.uk/guidance/TA301/chapter/1-Guidance>. Accessed October 23, 2016.
16. Apte RS. What is chronic or persistent diabetic macular edema and how should it be treated? *JAMA Ophthalmol*. 2016;134(3):285–286.
17. Nauck M, Karakiulakis G, Perruchoud AP, Papakonstantinou E, Roth M. Corticosteroids inhibit the expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells. *Eur J Pharmacol*. 1998;341(2–3):309–315.
18. Kern TS. Contributions of inflammatory processes to the development of the early stages of diabetic retinopathy. *Exp Diabetes Res*. 2007;2007:95103.
19. Tamura H, Miyamoto K, Kiryu J, et al. Intravitreal injection of corticosteroid attenuates leukostasis and vascular leakage in experimental diabetic retina. *Invest Ophthalmol Vis Sci*. 2005;46(4):1440–1444.
20. Amoaku WM, Saker S, Stewart EA. A review of therapies for diabetic macular oedema and rationale for combination therapy. *Eye (Lond)*. 2015;29(9):1115–1130.
21. Felinski EA, Antonetti DA. Glucocorticoid regulation of endothelial cell tight junction gene expression: novel treatments for diabetic retinopathy. *Curr Eye Res*. 2005;30(11):949–957.
22. Antonetti DA, Wolpert EB, DeMaio L, Harhaj NS, Scaduto RC Jr. Hydrocortisone decreases retinal endothelial cell water and solute flux coincident with increased content and decreased phosphorylation of occluding. *J Neurochem*. 2002;80(4):667–677.
23. PubChem [database on the Internet]. Compound Summary for CID 6215. Bethesda, MD: National Center for Biotechnology Information, US Library of Medicine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/fluocinolone_acetonide#section=Top. Accessed December 2, 2016.
24. ILUVIEN. Summary of Product Characteristics. Available from: <https://www.medicines.org.uk/emc/medicine/27636>. Accessed October 30, 2016.
25. Kane FE, Green KE. Ocular pharmacokinetics of fluocinolone acetonide following Iluvien implantation in the vitreous humor of rabbits. *J Ocul Pharmacol Ther*. 2015;31(1):11–16.
26. Yang Y, Bailey C, Holz FG, et al; FAME study group. Long-term outcomes of phakic patients with diabetic macular oedema treated with intravitreal fluocinolone acetonide (FAC) implants. *Eye (Lond)*. 2015;29(9):1173–1180.
27. Cunha-Vaz J, Ashton P, Iezzi R, et al; FAME Study Group. Sustained delivery fluocinolone acetonide vitreous implants: long-term benefit in patients with chronic diabetic macular edema. *Ophthalmology*. 2014;121(10):1892–1903.
28. Goñi FJ, Stalmans I, Denis P, et al. Elevated intraocular pressure after intravitreal steroid injection in diabetic macular edema: monitoring and management. *Ophthalmol Ther*. 2016;5(1):47–61.
29. Parrish RK, Campochiaro PA, Pearson PA, Green K, Traverso CE; FAME Study Group. Characterization of intraocular pressure increases and management strategies following treatment with fluocinolone acetonide intravitreal implants in the FAME trials. *Ophthalmic Surg Lasers Imaging Retina*. 2016;47(5):426–435.
30. Parrish RK, Traverso CE, Green K, Dabis RP; FAME Study Group. Quantitative assessment of optic nerve changes in patients with diabetic macular edema treated with fluocinolone acetonide vitreous implants. *Ophthalmic Surg Lasers Imaging Retina*. 2016;47(5):418–425.
31. Jonas JB, Gründler AE. Correlation between mean visual field loss and morphometric optic disk variables in the open-angle glaucomas. *Am J Ophthalmol*. 1997;124(4):488–497.
32. Massin P, Erginay A, Dupas B, Couturier A, Tadayoni R. Efficacy and safety of sustained-delivery fluocinolone acetonide intravitreal implant in patients with chronic diabetic macular edema insufficiently responsive to available therapies: a real-life study. *Clin Ophthalmol*. 2016;10:1257–1264.
33. Schmit-Eilenberger VK. A novel intravitreal fluocinolone acetonide implant (ILUVIEN®) in the treatment of patients with chronic diabetic macular edema that is insufficiently responsive to other medical treatment options: a case series. *Clin Ophthalmol*. 2015;9:801–811.
34. Elaraoud I, Andreatta W, Kidess A, et al. Use of flucinolone acetonide for patients with diabetic macular oedema: patient selection criteria and early outcomes in real-world setting. *BMC Ophthalmol*. 2016;16:3.
35. Elaraoud I, Quhill H, Quhill F. Case series investigating the efficacy and safety of bilateral fluocinolone acetonide (ILUVIEN) in patients with diabetic macular edema: 10 eyes with 12 months follow-up. *Ophthalmol Ther*. 2016;5(1):105–109.
36. Elaraoud I, Attawan A, Quhill F. Case series investigating the efficacy and safety of bilateral fluocinolone acetonide (ILUVIEN) in patients with diabetic macular edema. *Ophthalmol Ther*. 2016;5(1):95–104.
37. Bertelmann T, Schulze S. Long-term follow-up of patient with diabetic macular edema receiving fluocinolone acetonide intravitreal implant. *Ophthalmol Ther*. 2015;4(1):51–58.
38. Chang-Lin JE, Burke JA, Peng Q, et al. Pharmacokinetics of a sustained-release dexamethasone intravitreal implant in vitrectomized and nonvitrectomized eyes. *Invest Ophthalmol Vis Sci*. 2011;52(7):4605–4609.
39. Lee SS, Ghosn C, Yu Z, et al. Vitreous VEGF clearance is increased after vitrectomy. *Invest Ophthalmol Vis Sci*. 2010;51(4):2135–2138.
40. Boyer DS, Faber D, Gupta S, et al; Ozurdex CHAMPLAIN Study Group. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. *Retina*. 2011;31(5):915–923.

41. Kumar A, Alfahad Q, Mitra A, Elsherbiny S, Lip PL. Intravitreal fluocinolone acetonide (ILUVIEN) for treatment of refractory diabetic macular oedema in vitrectomised eyes. *Eye (Lond)*. 2016;30(5):770.
42. Quhill H, Quhill F. Real-life ILUVIEN (Fluocinolone Acetonide) case study: rapid drying of the macula and improved vision within 2 years after therapy Initiation. *Case Rep Ophthalmol*. 2016;7(3):301–307.
43. Breusegem C, Vandewalle E, Van Calster J, Stalmans I, Zeyen T. Predictive value of a topical dexamethasone provocative test before intravitreal triamcinolone acetonide injection. *Invest Ophthalmol Vis Sci*. 2009;50(2):573–576.
44. Gaston H, Absolon MJ, Thurtle OA, Sattar MA. Steroid responsiveness in connective tissue diseases. *Br J Ophthalmol*. 1983;67(7):487–490.
45. Podos SM, Becker B, Morton WR. High myopia and primary open-angle glaucoma. *Am J Ophthalmol*. 1966;62(6):1038–1043.
46. Moisseiev E, Morse LS. Fluocinolone acetonide intravitreal implant in the visual axis. *JAMA Ophthalmol*. 2016;134(9):1067–1068.
47. Papastavrou VT, Zambarakji H, Dooley I, Eleftheriadis H, Jackson TL. Observation: fluocinolone acetonide (ILUVIEN) implant migration into the anterior chamber. *Retin Cases Brief Rep*. 2017;11(1):44–46.
48. El-Ghrably IA, Saad A, Dinah C. A novel technique for repositioning of a migrated ILUVIEN (Fluocinolone Acetonide) implant into the anterior chamber. *Ophthalmol Ther*. 2015;4(2):129–133.
49. Taylor S, Chakravarthy U, Bailey C: on behalf of the ILUVIEN Registry Safety Study (IRISS) Investigators Group. Changes in intraocular pressure after ILUVIEN (190 µg fluocinolone acetonide) – real-world experiences following usage in three European countries. Presented at the Royal College of Ophthalmologists Annual Congress. May 2016.
50. Bailey C, Chakravarthy U, Lotery A, Menon G, Johnston R, Talks J. UK multi-centre retrospective audit of electronic patient records to assess the real world intraocular pressure events following treatment with ILUVIEN 190 µg intravitreal implant for 24 months. Poster presentation at the Royal College of Ophthalmologists Annual Congress. May 2016.
51. Henriques J, Figueira J, Amaro M, Rosas V. Structural and functional outcomes of lens status in patients with chronic diabetic macular edema treated with the ILUVIEN implant (0.2 µg/day fluocinolone acetonide): results from the RESPOND trial. Presented at: EURETINA Congress. September 15; 2015; Nice, France.

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