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BRIEF REPORT

Clinical Effectiveness of Intravitreal Fluocinolone Acetonide (FAc) (ILUVIEN^{TM}) in Patients with Diabetic Macular Oedema (DMO) Refractory to Prior Therapy: The Manchester Experience

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ABSTRACT

Introduction: Diabetic macular oedema (DMO) remains a significant cause of sight loss in the UK. Despite macular laser and anti-VEGF agents, a large proportion of patients remain with persistent DMO. We present our results of using 0.19 mg fluocinolone acetonide (FAc) intravitreal implant in this cohort with up to 3 years of follow-up.

Methods: This is a single-centre retrospective review of patients treated with FAc implant for refractory DMO. The primary efficacy end point was visual acuity and secondary efficacy end point was central retinal thickness (CRT) on OCT. A primary safety end point was a rise in IOP requiring treatment.

Results: Twenty-one eyes were identified with an average follow-up of 27 months (6–36 months). Visual acuity change from baseline was − 0.1 ETDRS letters at year 1 (n = 13), 8.1 letters at year 2 (n = 13) and 10.7 letters at year 3 (n = 10). CRT improved by − 132.1 μm at year 1 (n = 15), − 172.8 μm at year 2 (n = 13) and − 157.8 μm at year 3 (n = 10). Five eyes (24%) required further anti-VEGF during follow-up and two (9.5%) required further focal laser. IOP rise requiring treatment was noted in eight eyes (38%). Seven were steroid induced. One was caused by rubeotic glaucoma. Six (75%) were managed medically and the remaining two also required surgery.

Conclusion: This data add to the limited real-world data on FAc in DMO with 3 years of follow-up. Vision and macular architectures both improved at varying rates over 3 years in patients with refractory DMO. IOP rise is a risk but, in the majority, it can be managed medically.

Keywords: Diabetic macular oedema; Diabetic retinopathy; Fluocinolone acetonide implant; Iluvien

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INTRODUCTION

Diabetic macular oedema (DMO) is a common cause of sight loss in patients with diabetic retinopathy. Up to 25% of patients with diabetes will develop DMO 10 years after diagnosis [1]. Breakdown of the blood-retinal barrier leads to the leakage of plasma into the outer

plexiform layer [2]. Over time fluid builds up throughout the retinal layers and this leads to dysfunction of the macular architecture resulting in decreased visual acuity. Without treatment, 50% of those with DMO will lose two or more lines of vision 2 years post diagnosis [3].

The pathological process of hyperglycaemic damage to the blood-retinal barrier is not fully understood. It occurs through complex biochemical pathways leading to a process of inflammation and angiogenesis. This creates a cycle of further oxidative stress and inflammation [2, 4]. The main molecules, currently identified, are vascular endothelial growth factor (VEGF), platelet-derived growth factor and insulin-like growth factor-1 [5].

The goal of treatment is to reduce macular oedema and stabilise or improve vision. The Early Treatment of Diabetic Retinopathy Study (ETDRS) [6] found that grid laser improved DMO and has been the mainstay of treatment for many years. There have now been multiple large trials establishing anti-VEGF as the new first-line treatment [7, 8]. However, anti-VEGF only targets one arm of this complex process. Despite optimal anti-VEGF administration, it has been shown up to 55% of eyes have chronic persistent DMO after 2 years of treatment [9]. Despite a variety of treatment protocols, anti-VEGF agents often demand frequent injections and hospital appointments presenting challenges to patients and hospitals.

Corticosteroids are well known to control inflammation but also reduce VEGF levels by cell and gene inhibition [10]. They downregulate multiple pathways involved in the pathogenesis of DMO making them a suit able treatment for refractory DMO.

Fluocinolone acetonide (FAc) is a steroid with mainly glucocorticoid effect. It can be administered via an intravitreal cavity via a 0.19-mg implant (Iluvien^{TM}). This slowly releases FAc into the vitreous cavity, lasting up to 36 months [11]. The long-acting nature of this implant potentially reduces the number of injections needed for patients and the frequency of follow-up. However, intravitreal steroids come at an increased risk of cataract formation and raised intraocular pressure (IOP). The landmark study looking at FAc in DMO, Fluocinolone Acetonide in Diabetic Macular Edema (FAME), found it to be effective [12]. However, this trial was performed on patients with DMO who had already had macular laser, pre-dating the anti-VEGF era. Current United Kingdom National Institute for Health and Care Excellence (NICE) 2013 guidance allows the use of FAc in DMO but only in those cases insufficiently unresponsive to available therapies, i.e. anti-VEGF, with an additional requirement that the implant may only be used in pseudophakic eyes [13]. The FAME study outcomes, therefore, cannot be extrapolated directly to those cases unresponsive to such newer agents.

The purpose of this article is to present our experience of FAc implantation in the clinical setting, using real-world data from those patients that have been insufficiently unresponsive to anti-VEGF agents. We report 3-year follow-up outcomes for a proportion of patients; at the time of writing available data with this duration of follow-up are limited.

METHODS

We performed a single-centre, retrospective case series review of all consecutive cases treated with 0.19 mg FAc implant (ILUVIEN) for DMO at our unit. Data were obtained from an electronic patient records system (Medisoft Ophthalmology, Medisoft Ltd, Leeds, UK) and the patient's paper record.

Patients were included if they had received FAc as part of their DMO treatment. No patients were excluded from our analysis.

Baseline data included age, sex, baseline visual acuity (VA) (ETDRS letters), duration of DMO, IOP (Goldman applanation tonometry), ocular co-morbidities, lens status, central macular thickness, macular volume scan and any previous DMO treatment.

Post-implantation of FAc patients were followed up to monitor response to treatment and identify any side effects. Follow-up data included VA (ETDRS letters), central macular thickness, IOP (Goldman applanation tonometry), glaucoma treatment and adjunctive DMO treatment. The decision to administer adjunctive DMO treatment was made by a consultant

Table 1 Prior intravitreal therapies for all treated

	Avastin	Lucentis	Eylea	Ozurdex	IVTA	Total
No. of 21	11	14	3	4	5	19
Mean prior IVI	4.7	11.7	7.7	1.3	1.4	13.2

IVTA intravitreal triamcinolone, *IVI* intravitreal injection

Medical Retina specialist if there was insufficient benefit from current therapy. This was in cases where clinically the DMO was felt to be still active with a persistent refractory foveal centre involving oedema, increasing CRT measurement or decreasing VA attributable to the DMO.

Optical Coherence tomography was performed on the Topcon 3D OCT 2000. Central retinal thickness was calculated by the OCT software. The central 1-mm circle on the ETDRS grid was used. DMO was defined as increased retinal thickness with or without hyporeflective cystic areas within the retina seen on OCT.

No ethical approval for this article was required as it was a locally registered retrospective audit.

RESULTS

Overall 21 treated eyes of 17 patients were identified who received FAc at our unit during the study period. Six were female and 11 were male, with mean age 67.6 years old. One patient was phakic with the rest being pseudophakic. The average duration of DMO was 44 months (range 13–72 months). All patients had had prior treatment for their DMO. Seventeen of the eyes had previous focal macular laser treatment. Nineteen of the eyes had prior intravitreal treatment (see Table 1). Ocular co-morbidities included ocular hypertention (OHT) in three patients, glaucoma in four patients and previous vitrectomy and ILM peel in one patient.

A subset of ten eyes that had completed a minimum of 3-year follow-up was identified. Five were female and two males. They were 63.5 years old on average. Duration of DMO was 32.8 months (range 13–36 months). All were pseudophakic. Eight patients had received prior intravitreal therapy (Table 2).

For all patients treated mean follow-up was 27 months (6–36 months) based on visual acuity measurements. The phakic eye was excluded from all VA analysis. At last clinical follow-up visual acuity had improved on average 3.8 letters; however, those that completed 36 months of follow-up gained on average 9.3 letters. For the effect on visual acuity with time, see Table 3. Two patients did not have baseline VA recorded so were not included in this analysis. Of those that completed 3 years of follow-up, five were able to comply with current UK DVLA driving standards [14]. Prior to FAc therapy, only two patients met DVLA standards.

All patients had baseline OCT measurements so could be included in therapeutic analysis. At final follow-up visits, mean CRT decreased by 151.5 ± 65.9 μm (mean ± SD) from a baseline of 410.3 ± 138.1 μm (mean ± SD). See Table 4 for analysis. Figures 1 and 2 show how the VA and central retinal thickness (CRT) changed over time respectively. For those with 3 years of follow-up the mean CRT decreased by 157.8 μm ± 70.3 μm from a baseline of 410.3 μm ± 138.1 μm.

During follow-up 5 out of 21 eyes required combination treatment with anti-VEGF agents. These five eyes received on average 12.2 further anti-VEGF intravitreal injections. Two patients required macular laser therapy post implant.

For the eyes that completed 3 years of follow-up, only three required further anti-VEGF injections. On average these three patients received 13.1 injections over the 3-year period.

Seven patients (33%) had controlled ocular hypertension (OHT) or glaucoma at baseline. During follow-up 8 of 21 eyes required new or altered intra-ocular pressure (IOP)-lowering therapies. Four patients (19%) had an IOP increase up to > 30 mmHg during treatment

Table 2 Prior intravitreal therapies for patients completing 3 years of follow-up

	Avastin	Lucentis	Eylea	Ozurdex	IVTA	Total
No. of 10	8	4	0	0	5	8
Mean prior IVI	4.8	8.5			1.4	9.9

Table 3 VA analysis at 6 monthly time points post injection

BCVA (letters)	Baseline	6 M	12 M	18 M	24 M	30 M	36 M	LOCF
N	18	19	13	13	13	11	10	20
Mean	53.4	53.7	55.3	58.6	61.5	66.5	62.7	58.6
Median	51.0	58.0	56.0	64.0	67.0	68.0	68.5	60.0
SD	19.8	21.5	17.5	19.0	17.1	12.1	21.2	19.5
Δ baseline		0.3	− 0.1	5.2	8.1	13.2	10.7	3.8 $n = 18$

Table 4 CRT analysis at 6 monthly time points post injection

CRT (µm)	Baseline	6 M	12 M	18 M	24 M	30 M	36 M	LOCF
N	21	19	15	13	13	11	10	21
Mean	410.3	274.5	278.1	277.2	237.5	261.0	252.5	258.8
Median	389.0	268.0	263.5	279.0	240.0	255.0	262.5	254.0
SD	138.1	91.8	94.9	71.1	66.3	73.1	70.3	65.9
Δ baseline		− 135.8	− 132.1	− 133.1	− 172.8	− 149.3	− 157.8	− 151.5

LOCF Last outcome from clinical follow-up

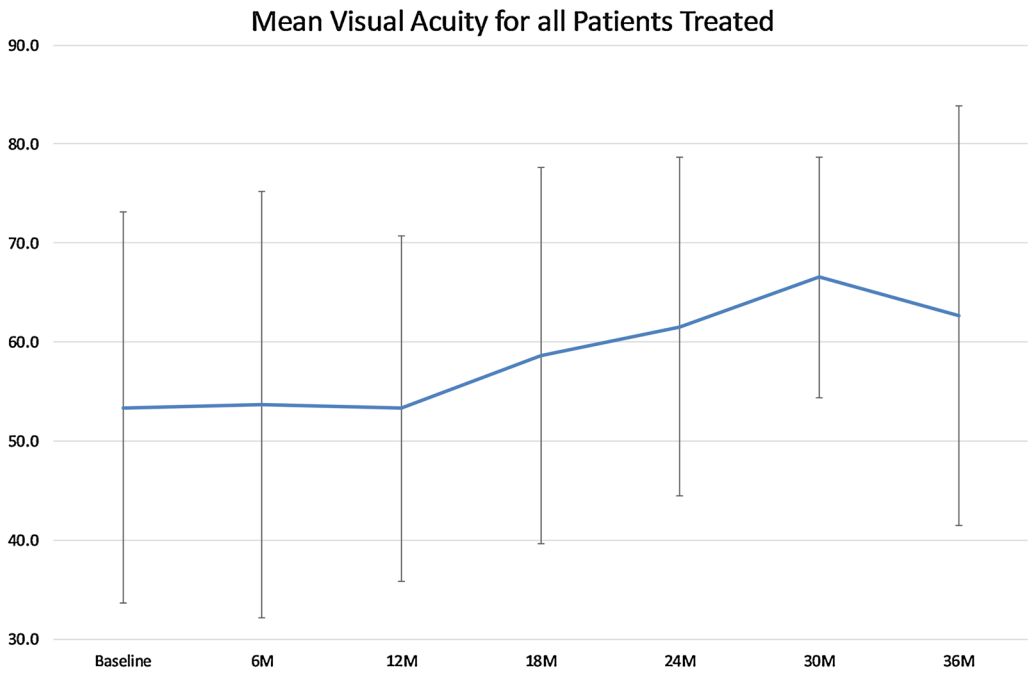

Fig. 1 This graph demonstrates the change in mean visual acuity (ETDRS letters) over time (± SD)

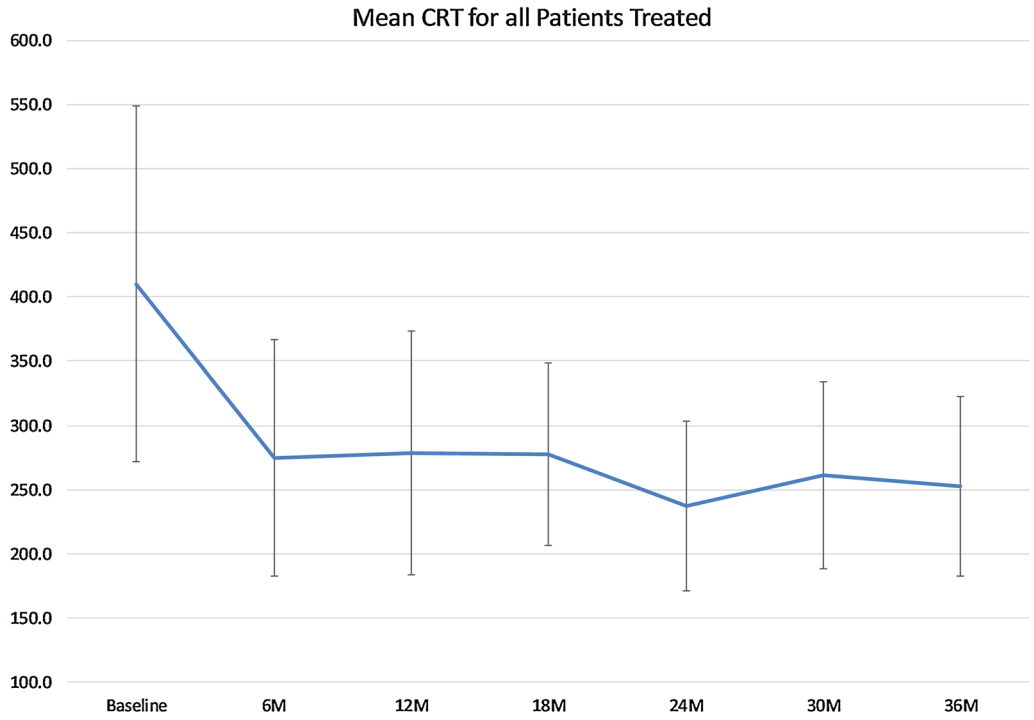

Fig. 2 This graph demonstrates central retinal thickness (micrometers) change over time (± SD)

with FAc. One patient required filtration surgery in the form of trabeculectomy + mitomycin C (MMC) and subsequently Baerveldt tube implantation. One patient developed raised IOP due to rubeotic glaucoma requiring a Baerveldt tube implantation and two cyclodiode lasers. The remaining raised IOPs were managed with topical therapies alone.

DISCUSSION

A paucity of 3-year outcome data exists on the current use of FAc in patients that have previously embarked on anti VEGF treatment. This retrospective review provides some of the first published 3-year outcomes of patients treated with FAc in the real-world setting. These patients had persistent DMO with an average duration of 4 years prior to FAc implantation. FAc was therefore used as a third-line therapy in most cases for refractory DMO. Our study adds to the real-world data that are becoming available supporting the benefits of FAc. Previously the only data available were from the original FAME study [12]. As previously discussed, the FAME study was in the pre-anti-VEGF era so a different cohort from those treated with FAc currently in the UK.

We have shown how patients with reduced visual acuity as a result of DMO, despite current first-line therapy, can benefit in terms of visual acuity and regression of DMO over a 3-year treatment course. Our clinical data show slightly superior outcomes when compared with the FAME study, which showed a mean gain of 8.1 letters in visual acuity at 36 months, with a CRT reduction of 191 μm [12]. Our data for those patients with 3 years of follow-up were a mean letter gain of 9.3 letters and reduction in CRT by 157.8 μm ± 70.3 μm from a baseline of 410.3 μm ± 138.1 μm.

A recently published UK retrospective review by Fusi-Rubiano et al. of six patients treated with FAc in the 'real world' completing 3 years of follow-up showed an even better visual acuity gain at 3 years. They gained on average 11 letters and had a mean reduction in CRT of 141 μm [15]. A retrospective review from Germany by Augustin et al. [16] of 34 patients who completed 3 years of follow-up on average had on average a much lower visual acuity gain of

2.7 letters. This study had a high proportion of phakic patients at 26%, but the visual acuity gains at 3 years were similar in the pseudophakic and phakic groups. Both of these results and the FAME data are in keeping with our findings. This adds more evidence to advocate that FAc improves visual and anatomical outcomes in patients with chronic DMO inadequately responding to anti-VEGF alone. This is noteworthy, given that patients in the real world often have more 'severe DMO' and more complex treatment histories and may well have co-pathology that would exclude them from clinical trials.

In our cohort, 24% required ongoing anti-VEGF during follow-up. This increased to 30% of patients at 3 years of follow-up with an average of 13.1 injections over 3 years. This is much less than the 83.3% of these patients requiring supplementary anti-VEGF over the 3-year follow-up from Fusi-Rubiano et al. This suggests that some patients have an ongoing anti-VEGF drive despite FAc implantation; therefore, regular review of these patients is still required following FAc implantation.

Despite the long duration of persistent DMO in the patient cohort, CRT often improved within the first 6 months post treatment, with a mean reduction of 135 μm. The effect was maintained at a lower rate of improvement for the remainder of treatment. Visual acuity often took longer than 12 months to improve. This would indicate that once the macular has 'dried out' it can take a period of time for the macular cells to recover before we see an improvement in vision. This is helpful when advising patients, as visual acuity can continue to improve 3 years after implantation. This also helps clinicians in managing these patients. The effects of FAc take time to work and this should be born in mind before going straight back to anti-VEGF too soon.

The main complication with any intravitreal steroid use is a subsequent increase in IOP which puts the patient at risk of glaucomatous optic neuropathy. The original FAME study did not define what they felt to be a significant rise in IOP but stated it occurred in 37% of those patients treated with FAc compared with 12% in the sham control group. Incisional glaucoma surgery was reported as being required in 4.8% vs. 0.5% of the sham group [12]. In our study, in those patients that completed 3 years of follow-up, 70% had a rise in IOP requiring further glaucoma management. This may be because a large proportion of our patients already had OHT/glaucoma (33%) prior to FAc implantation making them at a higher risk of steroid response. Of all those treated, 38% had a rise in IOP requiring a change of treatment showing the risk of increased IOP rises with time from injection and hence the length of exposure to FAc. One patient (4.8%) required incisional glaucoma surgery to control raised IOP secondary to FAc.

The main limitation of our review is its retrospective nature and a small cohort of patients. Admittedly, longer term complications such as inadequate IOP control requiring surgical intervention may only become apparent with more longer follow-up data. However, the findings from this study are in keeping with published landmark trial data. It gives us valuable insight into the 'real-world' efficacy of FAc use within an NHS setting that uses anti-VEGF therapy as a first-line agent. We have shown how the implant can be used to gain clinical improvements in those patients that have had a poor response to anti-VEGF options, although all patients must be counselled regarding the risk of glaucoma. The vast majority of this however can be managed with topical medications. More collaborative, multicentred data are required to define the treatment and safety profile of FAc.

CONCLUSION

This review adds important results to the limited data on FAc use in the real world with 3 years of follow-up data. It potentially has effects on visual acuity 3 years post-implantation and reduces CRT. However, this may need supplemental anti-VEGF injections. A rise in IOP is a possible risk but if monitored regularly it can be detected early and managed medically in the majority of cases. We feel FAc can be effective in those cases of DMO resistant to other therapies.

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Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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