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ORIGINAL RESEARCH ARTICLE

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Diabetic macular edema outcomes in eyes treated with fluocinolone acetonide 0.2 µg/d intravitreal implant: real-world UK experience

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ABSTRACT

Purpose: To conduct an observational, multicenter study to evaluate real-world clinical efficacy and safety of the 0.2 µg/day fluocinolone acetonide (FAc) implant in the treatment of patients with chronic diabetic macular edema (DME) in 3 large hospital ophthalmology departments in the United Kingdom.

Methods: Fluocinolone acetonide implants were inserted into the study eyes following a suitable washout period; phakic eyes received FAc implant following cataract surgery. Follow-up visits took place 2-4 weeks postinjection and then at 3, 6, and 12 months; change in central macular thickness (CMT) from baseline was measured by optical coherence tomography and best-corrected visual acuity (BCVA) was also assessed. Adverse events and changes in intraocular pressure (IOP) were recorded in order to evaluate the safety profile for the FAc implant.

Results: Improvements in BCVA and CMT were observed from 3 months and sustained for the duration of observation. At 12 months, the overall mean change from baseline CMT was -126 µm and mean increase in BCVA from baseline was 5.1 letters. Increases in IOP following FAc implant were easily managed with IOP-lowering medication. Implant migration into the anterior chamber occurred in 2 eyes where prior vitrectomy had resulted in a posterior capsule defect; this was rectified and resolved.

Conclusions: The results of this study provide further efficacy and safety profile data for FAc implant treatment of chronic DME in a real-world clinical setting; the FAc implant appears to be a valuable therapeutic approach for patients with chronic DME who have suboptimal response to other treatment options.

Keywords: Diabetic macular edema, Fluocinolone acetonide, Iluvien®

Introduction

Diabetic macular edema (DME) is the leading cause of vision impairment in patients with diabetes. The global prevalence of DME in patients with diabetes is 6.8% (1) and 14%-25% of patients with diabetes develop DME within 10 years of initial diagnosis (2). These estimates are expected to rise due to aging populations, the increasing prevalence of diabetes, and the longer life expectancy of patients with diabetes. Given the association between DME and vision loss, early and effective treatment is critical. Without treatment, nearly half of all patients who develop DME will lose 2 or more lines of visual acuity (VA) within 2 years (3).

Improved understanding of the pathophysiologic mechanisms leading to DME has led to the development of a range of treatments, including laser therapy, intravitreal anti-vascular endothelial growth factor (VEGF) injections, and corticosteroid treatments. Laser macular treatments reduce the risk of DME-related progressive visual loss by 50% (4) but provide limited improvement in mean VA; patients may also require repeat treatment, and may experience sequelae such as peripheral and night vision loss as a result of panretinal photocoagulation, reduced contrast sensitivity, and paracentral scotomas (5-9).

Unlike laser treatment, intravitreal anti-VEGF treatments have demonstrated significant best-corrected VA (BCVA) increases in patients with DME in randomized controlled trials (7, 8, 10-13); however, patients with longer-term DME appear less likely to respond to anti-VEGF therapy (7, 11). Another therapeutic strategy, using intravitreal corticosteroid implants, has also been shown to be effective for the treatment of DME, with reduced frequency of injections required compared with anti-VEGFs (14-17).

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The fluocinolone acetonide (FAc) intravitreal implant (Iluvien®, Alimera Sciences Limited, Aldershot, UK) is a non-biodegradable polyimide cylinder, inserted into the vitreous cavity through a 25-G needle in an outpatient setting (18). The FAc implant releases a sustained, low dose (0.2 µg/day) of this corticosteroid into the vitreous for up to 36 months and has been shown effective in patients with DME (≥250 µm) who had at least one prior focal/grid macular laser photocoagulation treatment (14, 15). At 36 months postinjection, improvement in BCVA was most marked in the subset of patients with a longer duration of DME. Based on these data, the FAc implant has been approved by the UK National Institute for Health and Care Excellence for pseudophakic eyes with chronic DME if the DME has not responded sufficiently to other treatments (19).

It is valuable to examine whether trial results translate into clinical practice and this observational study was undertaken to evaluate the real-world clinical efficacy and safety of the FAc implant in the treatment of patients with chronic DME by analysis of electronic medical records (EMR) collected in 3 large hospital ophthalmology departments in the United Kingdom.

Methods

Study design

This was an observational, multicenter study of consecutive patients at 3 large hospital ophthalmology departments in the United Kingdom (James Cook University Hospital, Middlesbrough; Sunderland Eye Infirmary, Sunderland; Royal Victoria Infirmary, Newcastle), using information from EMRs collected between February 2014 and September 2015.

Patients with chronic DME, defined as patients who had an insufficient response to prior treatment, underwent a washout period of at least 2 months following last anti-VEGF treatment, or more than 6 months following last steroid treatment before FAc implant insertion. Patients with phakic eyes and who underwent cataract surgery were eligible to receive the FAc implant following surgery. Visits took place 2-4 weeks postinjection and then at 3, 6, and 12 months.

Standardized information on all patients was prospectively collected using a jointly agreed database. Data were collected on demographics, duration of DME, prior treatment, VA, optical coherence tomography (OCT) parameters, intraocular pressure (IOP), and IOP-lowering medication use.

Efficacy evaluation

The primary efficacy outcome measure was the change in central macular thickness (CMT) from baseline measured by OCT. The BCVA was primarily assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) letters. Where a Snellen chart was used to assess BCVA, a conversion table was used to convert into approximate ETDRS letters.

Safety evaluation

Safety was evaluated throughout the study period through collection of data on IOP and any other recorded complications. Under UK guidelines, the analysis was classified as a service evaluation and as such did not require ethical approval.

Results

Patient demographics

Data are available for 57 patients (31 male, 26 female) treated with the FAc implant (Tab. I). Mean age of patients was 69.8 years (range 44-86 years) and mean duration of DME was 30.9 months (range 4-120 months). All patients had unilateral FAc implants (31 right and 26 left eyes treated). Seventy-seven percent of treated eyes (44/57) were pseudophakic at baseline; 25% of treated eyes (14/57) received the FAc implant with phacoemulsification.

Treated eyes had mean (SD) baseline BCVA of 52.7 (16.5) letters and mean baseline CMT of 452 (120) µm. The majority of treated eyes had received previous laser therapy (49/57) and almost half (25/57) had been vitrectomized. Prior intravitreal therapy was very common (46/57): intravitreal anti-VEGF therapy was recorded for all 46 eyes, with a mean (SD) of 4.8 (2.3) previous anti-VEGF injections. In addition, 6 eyes had received prior intravitreal triamcinolone injection and 1 eye had received a prior intravitreal dexamethasone implant.

Of the 57 patients included, 46 completed 3 months of follow-up, 34 completed 6 months, and 22 completed 12 months of follow-up; all patients received only one FAc implant.

Efficacy results

Treatment of DME with FAc resulted in anatomical and BCVA improvements, which were observable from 3 months

TABLE I - Patient demographics and baseline characteristics

Characteristics	Values
Lens status, pseudophakic/phakic	44/13
Age, y, mean (SD)	69.8 (10.7)
BCVA, mean (SD)	52.7 (16.5)
CMT, µm, mean (SD)	452 (120)
IOP, mm Hg, mean (SD)	15.5 (3.2)
DME duration, mo, mean (SD)	30.9 (22.5)
Vitreoretinal adhesions[a]	10/57
Previous laser	
No	4
Yes	49
Not known	4
Previous vitrectomy	25/57
Previous anti-VEGF, mean (SD)	4.8 (2.3)

[a] Epiretinal membrane (n = 3), vitreomacular adhesions (n = 4), posterior vitreous detachment (n = 1), or unspecified (n = 2).
BCVA = best-corrected visual acuity; CMT = central macular thickness; DME = diabetic macular edema; IOP = intraocular pressure; VEGF = vascular endothelial growth factor.

TABLE II - Clinical outcomes

Measurement	Outcomes (SD)		
	3 mo (n = 46)	**6 mo (n = 34)**	**12 mo (n = 22)**
BCVA, mean (SD)	58.3 (15.8)	58.1 (15.8)	53.3 (16.8)
Mean letter gain	+5.8	+6.7	+5.1
CMT, µm, mean (SD)	339 (119)	329 (111)	351 (163)
ΔCMT, µm	-102	-117	-126
% Change CMT	-18	-24	-26
IOP, mm Hg, mean (SD)	17.7 (6.2)	17.5 (4.6)	18.9 (5.3)
ΔIOP	+2.4	+1.6	+3.7
Number of patients on IOP medication	6/46	5/34	7/22

BCVA = best-corrected visual acuity; CMT = central macular thickness; IOP = intraocular pressure.

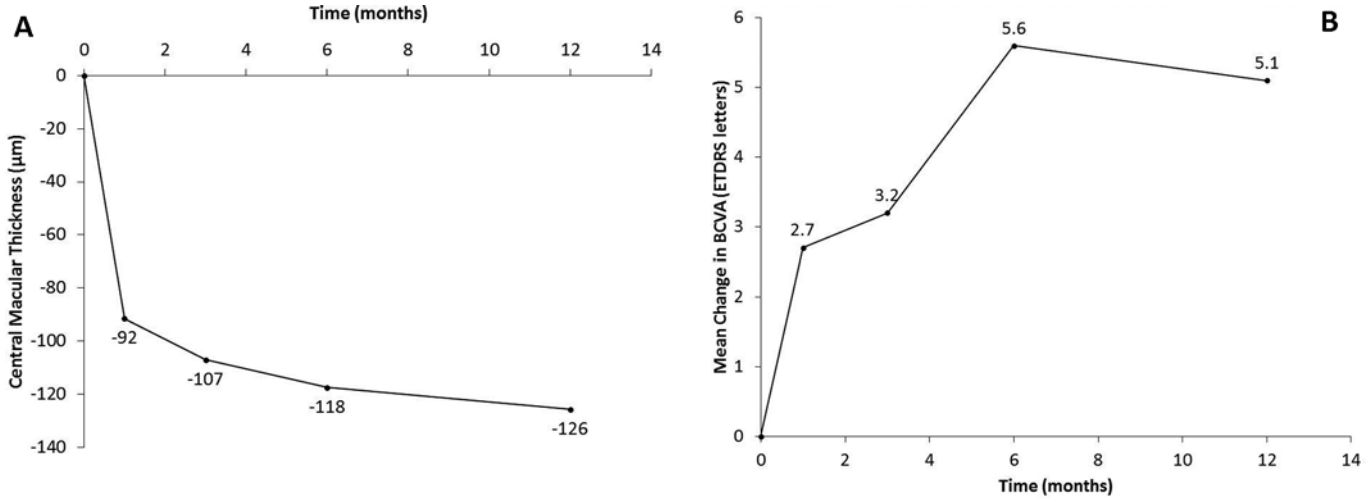

Fig. 1 - Mean change in (**A**) central macular thickness and (**B**) best-corrected visual acuity (BCVA) in treated eyes (n = 22) for patients who completed 12 months of follow-up. ETDRS = Early Treatment Diabetic Retinopathy Study.

and were sustained at 12 months (Tab. II). The mean change from baseline CMT (452 µm) was -102 µm at month 3, -117 µm at month 6, and -126 µm at month 12 (Fig. 1A shows the data from patients with 12 months of CMT data). The mean increase in BCVA from baseline (52.7 ETDRS letters) was 5.8 letters after 3 months, 6.7 letters at month 6, and 5.1 letters at month 12 (Fig. 1B shows the data from patients with 12 months of BCVA data); a similar pattern was seen in both vitrectomized and nonvitrectomized subgroups (Fig. 2). At month 12, an increase/maintenance from baseline BCVA (gain of =/>0 letters) was seen in 15/22 treated eyes. Gains of ≥5 letters were seen in 11/22 eyes, ≥10 letters in 7/22 eyes, and ≥15 letters in 5/22 eyes (Fig. 3). Of the 7/22 eyes that lost VA, 3 lost ≥10 EDTRS letters and 2 lost ≥15 letters (Fig. 3). Reasons for loss of VA were not provided in the EMR but could have included lack of response to therapy, progression of disease state, or poor diabetic control.

Month 12 data are available for 12 eyes that had undergone prior vitrectomy (reasons captured in the EMR were vitreous hemorrhage [n = 4], vitreomacular adhesion [n = 1], epiretinal membrane [1 possible case], DME [n = 2], proliferative diabetic retinopathy [n = 4], retinal detachment [n = 1], and aqueous misdirection [n = 1]; 3 records had more than one reason provided for the vitrectomy). In vitrectomised eyes, mean reduction in CMT from baseline was −156 µm CMT at month 12 and mean BCVA gain was 3.9 letters. In these eyes, mean baseline IOP was 14.4 Hg, with a mean change of +5.3 mm Hg at month 3, +2.9 mm Hg at month 6, and +5.5 at month 12. The IOP for all eyes (vitrectomised and non-vitrectomised) that completed 12 months are shown in Figure 4. In the 5/12 (42%) patients who had undergone prior vitrectomy and required IOP-lowering medications, mean increase in IOP from baseline was +10.2 mm Hg. Interestingly, 2 of these 5 eyes were treated bilaterally, suggesting the raised IOP was a disease related

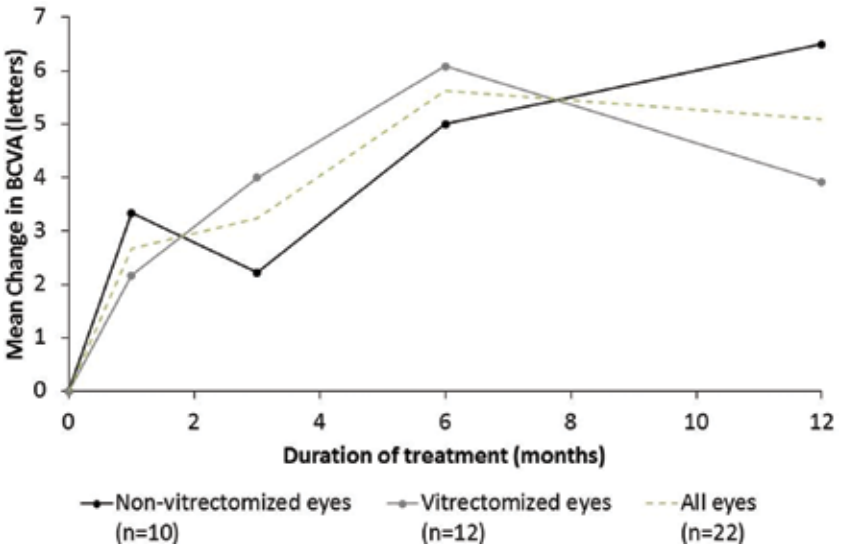

Fig. 2 - Mean change in best-corrected visual acuity (BCVA) in treated eyes for vitrectomized (n = 12) and nonvitrectomized (n = 10) subgroups who completed 12 months of follow-up.

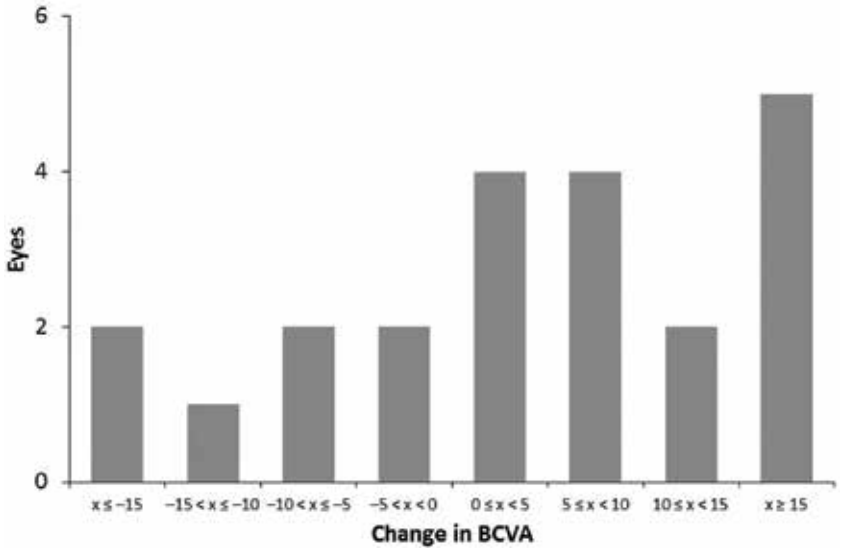

Fig. 3 - Change in letter score for eyes (n = 22) of patients who completed 12 months of follow-up. BCVA = best-corrected visual acuity.

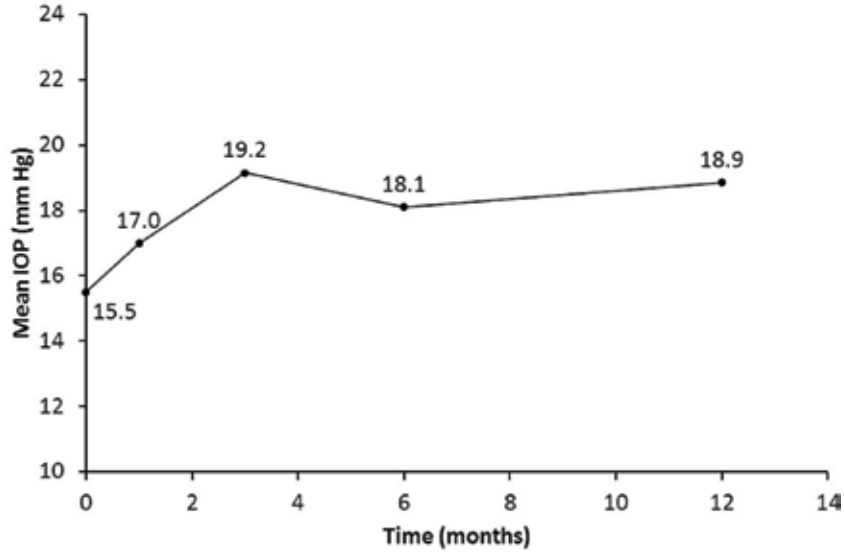

Fig. 4 - Mean in intraocular pressure (IOP) in treated eyes of patients who completed 12 months of follow-up (n = 22).

effect. Moreover, in these 5/12 patients IOP was =/<25 mmHg in all but one case.

Safety results

Overall, 6 patients were on IOP-lowering medictaions from month 3 onwards, but none required glaucoma surgery.

The FAc implant migrated into the anterior chamber in 2 patients who had undergone prior vitrectomy and had a defect in the posterior capsule. In both patients, the implants were retrieved using a 23-G flute needle cannula and reinserted back into the vitreous cavity; the intraocular lens was then repositioned to close the gap in the posterior capsule. There was no subsequent migration following the procedure. No other treatment-related complications were reported.

Discussion

This study evaluated the use of a 0.2 µg/day FAc implant for the treatment of chronic DME in a real-world setting. Improvements in CMT and BCVA were evident within 3 months of implant and were sustained at 12 months. The mean percentage reduction in CMT from baseline was 18% at 3 months and 26% at 12 months. The mean gain in BCVA was +5.8 letters at month 3 and +5.1 letters at month 12, with BCVA increased or maintained at month 12 versus baseline in 15/22 eyes (68.2%).

Our findings are in line with those of the FAME clinical trials (14, 15), which reported more than a quarter of FAc implant eyes having a ≥15 letter improvement in BCVA at 36 months postinjection; the results also corroborate other recent case reports and studies of the FAc implant for the treatment of DME in real-world settings (20-22).

Given that the majority of patients had received prior anti-VEGF injections, our findings highlight the potential additional value that can be gained in unresponsive cases by switching from anti-VEGF therapy to the FAc implant; indeed, in eyes that do not respond to anti-VEGF injections, it may be appropriate to consider treatment with the FAc implant sooner to avoid more damage and disruption of the retinal layers due to macular edema.

An additional consideration is the substantial treatment burden from the frequency of anti-VEGF injections, as demonstrated by the 9-10 injections required by patients on average to control DME over 12 months in a recent, large, comparative study of aflibercept, bevacizumab, or ranibizumab (13). A high frequency of intravitreal injections has been shown to affect quality of life and to increase anxiety and work absences in patients with DME (23); patients' most desired improvement to their treatment regimen was to have fewer injections and to require fewer appointments, to achieve the same visual results (23). The current evidence of long-term, real-world effectiveness from a single FAc implant, for the treatment of DME that was insufficiently responsive to anti-VEGF treatment, suggests this may be a viable approach to decrease treatment burden and potentially improve quality of life.

Results of this study support the effectiveness of the FAc implant for the treatment of DME in eyes that have undergone prior vitrectomy; however, caution is recommended before inserting the FAc implant into vitrectomized eyes with posterior capsule defects. If possible, gaps in the posterior capsule should be excluded prior to insertion of the implant. Should anterior migration occur, however, repositioning into the vitreous cavity can be achieved using a backflush/flute needle as previously described (24).

As in other studies, an increase in IOP was noted following insertion of the FAc implant. The mean overall change in IOP from baseline was +2.4 mm Hg at 3 months and +3.7 mm Hg at 12 months. The increase in IOP seen after FAc implant insertion appears to be easily manageable with IOP-lowering medication and does not appear to affect vision outcomes (25).

A key strength of this study was that it was undertaken at a combination of large district general and teaching hospitals enabling translation of these study findings to the majority of hospital ophthalmology departments; inclusion of all consecutively treated patients during the study period ensured that a representative cohort of patients was evaluated. A potential study limitation is the fact that, although baseline data were collected for all patients, the full scope of their disease history was not captured. This has particular importance for the time scale of DME progression, which might have an effect on response to the FAc implant.

Although this study illustrates the effectiveness of the FAc implant in the real-world setting, the study design introduces limitations. For example, information such as duration of diabetes, indicators of diabetes control (e.g., HbA1c), and reason for initiation of FAc treatment were not captured. In addition, the small number of subjects limits the opportunity for comparison between subgroups.

In conclusion, the results of this study provide further evidence of the efficacy and safety profile of the FAc implant for the treatment of chronic DME in a real-world clinical setting; the FAc implant appears to be a valuable therapeutic approach for patients with chronic DME refractory to other treatment options, and may reduce treatment burden.

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Disclosures

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Conflict of interest: None of the authors has conflict of interest with this submission.

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