

CASE SERIES

Case Series Investigating the Efficacy and Safety of Bilateral Fluocinolone Acetonide (ILUVIEN®) in Patients with Diabetic Macular Edema

Ibrahim Elaraoud · Alaa Attawan · Fahd Quhill

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ABSTRACT

Introduction: Patients with diabetic macular edema (DME), a chronic, vision-limiting condition, may be insufficiently responsive to standard-of-care anti-vascular endothelial growth factor (VEGF) and/or laser therapies. One approved treatment for such patients is 0.2 µg/day fluocinolone acetonide (FAC) sustained-release implant; however, data are limited for treatment strategies in patients with bilateral chronic DME insufficiently responsive to standard-of-care therapies.

Methods: Six pseudophakic patients with bilateral, chronic DME previously treated with laser and anti-VEGF therapy (and intravitreal

triamcinolone acetonide in 10 eyes) were retrospectively investigated for visual and anatomical outcomes, 6 months post-0.2 µg/day FAC implant in both eyes.

Results: At baseline, the mean best corrected visual acuity (BCVA) was approximately 6/38 or 43 [standard deviation (SD) ±17.4] Early Treatment Diabetic Retinopathy Study (ETDRS) letters; mean central retinal thickness (CRT) was 648 µm (SD ±160). Mean change in BCVA was +10 letters (SD ±12.2 letters), with 4/12 eyes maintaining or achieving driving vision (≥70 letters) and 3/12 eyes having unchanged BCVA. CRT was reduced 6 months after 0.2 µg/day FAC implant in 11/12 eyes. The mean intraocular pressure (IOP) was 16.1 mmHg [mean change of 1.1 mmHg (SD ±3.6)].

Conclusion: In a real-world setting, 0.2 µg/day FAC implant in both eyes was a feasible, effective choice for patients with severe bilateral DME, without notable increases in IOP.

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I. Elaraoud
Wolverhampton Eye Infirmary, New Cross Hospital,
Wednesfield Road, Wolverhampton, UK

A. Attawan · F. Quhill (✉)
Royal Hallamshire Hospital, Glossop Road,
Sheffield, UK
e-mail: fahd.quhill@sth.nhs.uk

Keywords: Bilateral diabetic macular edema; Central retinal thickness; Fluocinolone acetonide; Optical coherence tomography; Visual acuity

INTRODUCTION

Diabetic retinopathy (DR) is a visual complication that presents in around 35% of patients with diabetes [1]. A further visual complication manifesting in 6.8% of patients with DR is diabetic macular edema (DME), a chronic condition that results in significant reduction in vision and blindness in the working-age population [1]. DME can be unilateral or bilateral, with bilateral DME presenting in approximately 33–46% of patients with DME [2, 3]. Due to its chronic nature and persistence, DME can be difficult to manage, and without treatment nearly half of all patients who develop DME will lose two or more lines of visual acuity (VA) within 2 years [4, 5].

Historically, the standard of care for DME was laser therapy; however, vision gain following such treatment was limited [6]. More recently, several prospective randomized clinical trials have shown significant gains in VA in patients with DME following treatment with anti-vascular endothelial growth factor (VEGF) agents, resulting in a shift toward anti-VEGF treatment as the preferred standard of care and first line of treatment [6–9]. Despite promising efficacy, however, results from the RIDE (ClinicalTrials.gov identifier, NCT00473382) and RISE (ClinicalTrials.gov identifier, NCT00473330) trials investigating the anti-VEGF agent, ranibizumab, found that patients who crossed over from sham to ranibizumab at 24 months were notably less responsive to treatment. These data are indicative of a subgroup of patients with

longer-term chronic DME who may be insufficiently responsive to intermittent therapies such as the injection of anti-VEGF [8, 9].

Chronic DME is thought to be associated with a more inflammatory state following a shift in the expression of numerous inflammatory cytokines and VEGF-independent pathways responsible for its pathogenesis [10]. Consequently, chronic DME may require broader spectrum treatments such as corticosteroids, which have anti-inflammatory and angiostatic effects [11–13].

ILUVIEN® (Alimera Sciences Limited, Aldershot, UK) is an intraocular, nonbioerodible 0.2 µg/day fluocinolone acetonide (FAC) sustained-release implant that is approved in Europe for treatment of vision impairment associated with chronic DME considered insufficiently responsive to available therapies [14]. The Fluocinolone Acetonide in Diabetic Macular Edema (FAME; ClinicalTrials.gov identifier, NCT00344968) study compared 0.2 µg/day (the ultimately approved dosage) FAC with sham injections in patients with DME who were insufficiently responsive to the standard of care at that time, having received ≥ 1 focal laser treatment [15]. Three-year treatment with 0.2 µg/day FAC implant was associated with a significant improvement in vision outcomes, with the greatest benefit being reported in patients with chronic DME where 34.0% of patients treated with 0.2 µg/day FAC implant gained ≥ 15 in letter score at month 36 compared with only 13.4% of sham-treated patients [16]. However, the FAC implant was associated with increased intraocular pressure (IOP) compared with sham-treated patients and increased risk of cataract in patients who were phakic at baseline. As such, in the UK, National Institute

for Care and Health Excellence (NICE) technology appraisal TA 301 recommends 0.2 µg/day FAc implant for pseudophakic patients with chronic DME that are deemed by the clinician to be insufficiently responsive to laser or anti-VEGF.

Little published data exist for treatment strategies in patients with bilateral chronic DME who are deemed insufficiently responsive to other therapies. Based on the NICE TA301 guidance, the 0.2 µg/day FAc implant in both eyes could be a sensible consideration for these patients in the UK setting. The summary of product characteristics for 0.2 µg/day FAc implant states that ‘Administration in both eyes concurrently is not recommended’. Nevertheless, concurrent use, with both eyes injected at different time points, is not contraindicated [14]. Moreover, pharmacokinetic data over 36 months demonstrated negligible systemic exposure to FAc following treatment with 0.2 µg/day FAc implant, highlighting its localized nature [14], which would suggest concurrent treatment would not present an unexpected side effect profile. This retrospective study investigates visual function, anatomical outcomes and safety of 0.2 µg/day FAc implant in both eyes of six patients with bilateral chronic DME.

METHODS

This retrospective case series analysis assessed the visual function and anatomical measures at baseline and after a 6-month follow-up in six patients who received bilateral 0.2 µg/day FAc implants between April 2014 and October 2014. As a retrospective analysis, data were collected using case notes and optical coherence tomography (OCT) scans collected during treatment as part of the standard care

pathway. Consequently, institutional review board policies did not necessitate additional ethics committee approval for this analysis.

Baseline demographics were collected from patient records at the time of 0.2 µg/day FAc implant and included age, gender, general health, and disease and treatment history. In addition, Snellen VA (at 6 m) and anatomical measures using optical coherence tomography [e.g., central retinal thickness (CRT), central subfield foveal thickness (CSFT)] were noted at baseline. Snellen VA was converted into approximate Early Treatment Diabetic Retinopathy Study (ETDRS) letters to facilitate interpretation using the following equation: $85 + 50 \times \log(\text{Snellen fraction})$, as described by Gregori et al [17].

Efficacy assessments at 6-month follow-up included changes in VA, anatomical measures (including CRT and CSFT), and in the number of fields out of 9 over 300 µm thickness. In addition, safety was evaluated through collection of data on changes in IOP and any other recorded complications.

RESULTS

Patients

Overall, six patients with bilateral chronic DME received 0.2 µg/day FAc implant in both eyes (12 eyes). Baseline values and patient demographics are summarized in Table 1. The average patient age was 62.5 years (range 44–82); four patients had type-II diabetes and two patients type-I diabetes. All patients were pseudophakic at baseline, with one patient having received unilateral vitrectomy (eye 9). Five of six patients had bilateral subretinal fluid (SRF), and four of six had bilateral epiretinal membrane (ERM); the remaining patient(s) had

Table 1 Patient demographics and baseline values

Patient number	Gender	Age	Diabetes type	Eye number	Left or right eye	IOP-lowering drops	Prior medical treatment for DME			Date of 0.2 µ/g day FAc implant
							Laser	RBZ	IVTA	
1	Male	70	II	1	LE	N	1 × grid	9×	1×	July 29, 2014
				2	RE	N	1 × grid	9×	1×	September 9, 2014
2	Female	58	II	3	RE	Lumigan/Azarga	1 × Focal	19×	1×	June 10, 2014
				4	LE	Lumigan/Azarga	2 × Focal	19×	1×	September 23, 2014
3	Male	44	I	5	RE	Latanoprost/timolol	1 × grid	6×	3×	July 25, 2014
				6	LE	Latanoprost/timolol	1 × grid	6×	2×	October 30, 2014
4	Male	82	II	7	RE	N	1 × grid	3×	2×	April 10, 2014
				8	LE	N	1 × grid	3×	1×	July 11, 2014
5	Male	63	I	9	LE	N	1 × grid	6×	0	July 18, 2014
				10	RE	N	1 × grid	9×	0	October 21, 2014
6	Female	58	II	11	RE	N	1 × grid	19×	1×	June 10, 2014
				12	LE	N	1 × grid	19×	1×	September 23, 2014

DME diabetic macular edema, *FAc* fluocinolone acetonide, *IOP* intraocular pressure, *IVTA* intravitreal triamcinolone, *LE* left eye, *RE* right eye, *RBZ* ranibizumab

unilateral SRF/ERM. Neovascularization of the disc or of the retina outside of the disc was not reported for any patients. At baseline, two patients were receiving drops for bilateral IOP (patients 2 and 3, Table 1).

Baseline BCVA ranged from 20 to 70 letters (6/120–6/12), with a mean baseline BCVA in all eyes of 43 letters (SD ±17.4; 6/38). At baseline, only one eye (eye 10) had CRT ≤300 µm, indicative of a dry macular. Mean baseline CRT and CSFT values in all eyes were 648 µm

(SD ±160) and 637 µm (SD ±140), respectively, and all eyes had ≥6 of 9 fields over 300 µm. Baseline values were generally similar in fellow eyes for each patient (Figs. 1, 2, 3, 4). All 12 eyes had received both prior macular laser (≥1 laser therapy) and anti-VEGF (≥3 intravitreal injections of ranibizumab) treatment, with 10 eyes having also received prior intravitreal triamcinolone (IVTA; ≥1 intravitreal injection) for DME. In the patients studied, prior IVTA was manageable with aqueous suppressants. The

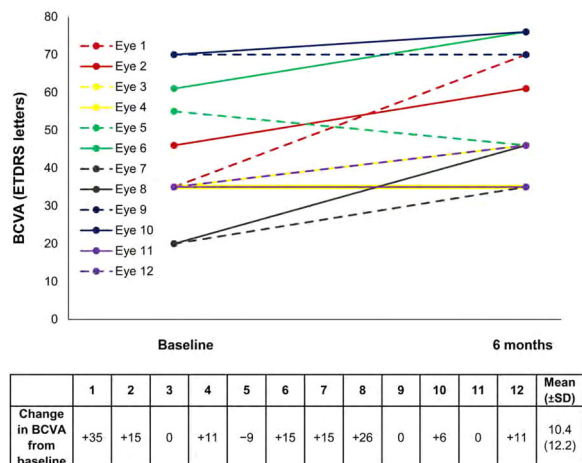


Fig. 1 Changes in BCVA before and 6 months after 0.2 µg/day FAc implant. Baseline BCVA and BCVA 6 months post-0.2 µg/day FAc implant is shown for each eye. Eyes from the same patient are shown in the *same color*, one with a *solid line* and the fellow eye with a *dotted line* (patient 1 red; patient 2 yellow; patient 3 green; patient 4 gray; patient 5 blue; patient 6 purple). The change from baseline is presented *numerically* for each eye and overall (mean ± SD) in *tabular format below the graph*. BCVA best corrected visual acuity, ETDRS Early Treatment Diabetic Retinopathy Study, FAc fluocinolone acetonide, SD standard deviation

history of prior treatment for DME is shown for each eye in Table 1. All patients received bilateral 0.2 µg/day FAc implant, with 2–3 months between injection of the implant into the first and second eyes.

Six months following 0.2 µg/day FAc implant, the mean change in BCVA for all patients was +10 letters (SD ±12.2; range -9 to +35 letters). A gain of >10 letters from baseline was reported in 7 of 12 (58.3%) eyes (Fig. 1), with 5 of 12 (41.7%) eyes gaining ≥15 letters from baseline and 4 (33.3%) eyes maintaining or achieving driving vision of 70 letters. BCVA remained unchanged 6 months post-0.2 µg/day FAc implant in three eyes (25.0%), with only one eye (8.3%) showing a worsening from baseline (by -9 letters); however, the latter eye showed the greatest reported reduction in CRT

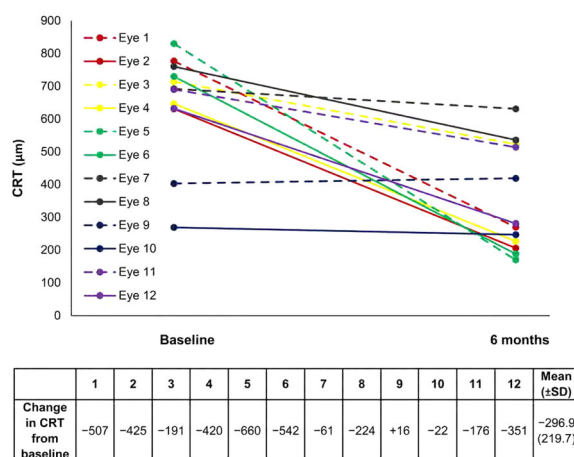
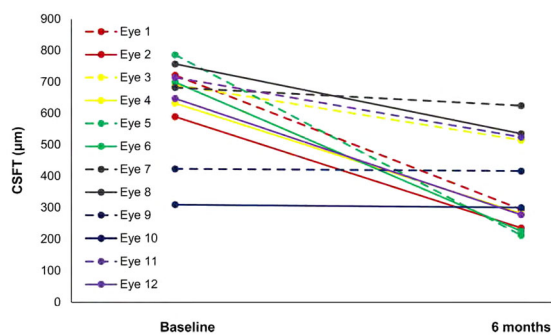


Fig. 2 Changes in CRT before and 6 months after 0.2 µg/day FAc implant. Baseline CRT (µm) and CRT 6 months post-0.2 µg/day FAc implant are shown for each eye. Eyes from the same patient are shown in the *same color*, one with a *solid line* and the fellow eye with a *dotted line* (patient 1 red; patient 2 yellow; patient 3 green; patient 4 gray; patient 5 blue; patient 6 purple). The change from baseline is presented *numerically* for each eye, and overall (mean ± SD) in *tabular format below the graph*. CRT central retinal thickness, FAc fluocinolone acetonide, SD standard deviation

(-660 µm from 830 µm). Overall, the trend of VA response was not consistent, and an improvement in one eye did not appear to predict a corresponding improvement in the fellow eye for four of six patients (66.7%; patients 2, 3, 5, and 6). Patients 1 and 4 showed the best improvements of +35 (eye 1) and +26 (eye 6) letters, respectively, in one eye with a slightly smaller, but still notable, improvement of +15 letters in the fellow eye (eyes 2 and 7) of both patients.

Six months post-0.2 µg/day FAc implant, CRT was reduced in 11 (91.7%) eyes, and CSFT was reduced in all eyes, with mean reductions of -296.9 µm (SD ±219.7; range -660 to +61 µm) and -267.7 µm (SD ±186.4; range -574 to -7 µm), respectively (Figs. 2, 3). Both CRT and CSFT were reduced by ≥200 µm in seven (58.3%) eyes, and the fellow eyes of individual



	1	2	3	4	5	6	7	8	9	10	11	12	Mean (±SD)
Change in CSFT from baseline	-427	-354	-176	-351	-574	-474	-58	-222	-7	-9	-190	-370	-267.7 (186.4)

Fig. 3 Changes in CSFT before and 6 months after 0.2 µg/day FAc implant. Baseline CSFT (µm) and CSFT 6 months post-0.2 µg/day FAc implant are shown for each eye. Eyes from the same patient are shown in the *same color*, one with a *solid line* and the fellow eye with a *dotted line* (patient 1 *red*; patient 2 *yellow*; patient 3 *green*; patient 4 *gray*; patient 5 *blue*; patient 6 *purple*). The change from baseline is presented *numerically* for each eye, and overall (mean ± SD) in *tabular format below the graph*. CSFT central subfield foveal thickness, FAc fluocinolone acetate, SD standard deviation

patients appeared to be mostly comparable. The number of fields out of 9 over 300 µm was also reduced in 8 of 12 (66.7%) eyes.

Two eyes (eyes 1 and 6, patients 1 and 3) that achieved driving vision of 70 letters following 0.2 µg/day FAc implant showed correspondingly large reductions in CRT of -507 and -542 µm (from 777 and 730 µm), respectively. Patient 5 (eyes 9 and 10) showed no notable change in CRT from baseline in either eye; however, both eyes showed relatively low baseline CRT values in comparison to the other eyes included in this study (403 and 269 µm). In addition, baseline BCVA was 70 letters in both eyes, and driving vision was maintained following 0.2 µg/day FAc implant. Patient 5 was also the only one who had not received prior IVTA treatment; all other patients had received bilateral IVTA. Patient 5 received

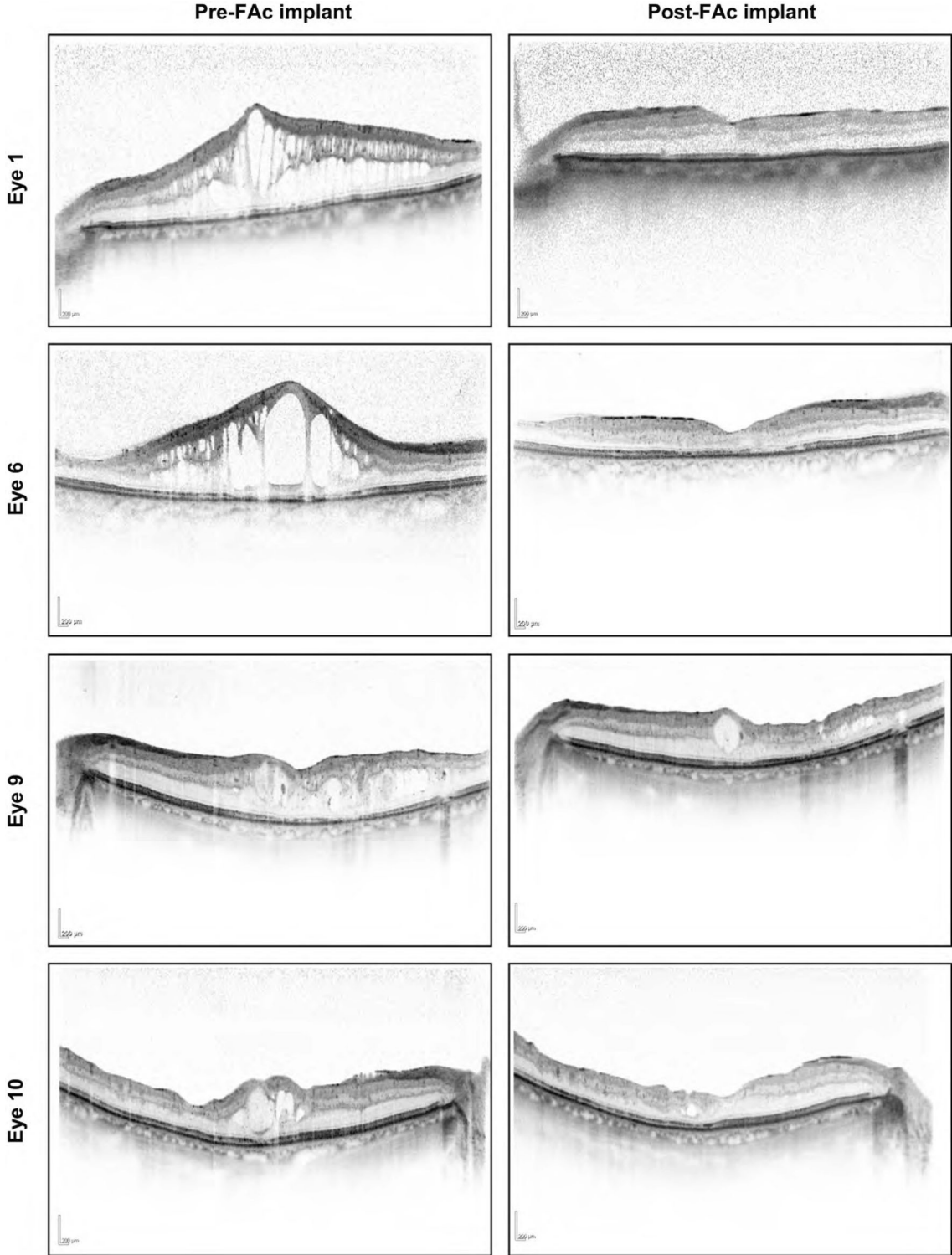
Fig. 4 OCT images pre- and post-0.2 µg/day FAc implant in eyes 1, 6, 9, and 10. The OCT images pre- and post-0.2 µg/day FAc implant are shown for eyes 1, 6, 9, and 10. Large reductions in CRT from following 0.2 µg/day FAc implant are shown for eyes 1 and 6; eyes 9 and 10 show less of a reduction. CRT central retinal thickness, FAc fluocinolone acetate, OCT optical coherence tomography, SD standard deviation

rescue ranibizumab treatment 5 months post-0.2 µm/day FAc implant.

Mean baseline IOP was 14.6 mmHg (SD ±3.8, range 10–20). Six months post-0.2 µg/day FAc implant, mean IOP was 16.1 mmHg (SD ±3.8, range 10–21), a mean change of 1.1 mmHg (SD ±3.6, range -4 to +9). Patients 3 and 4 continued on bilateral IOP-lowering eyedrops, with no other patients initiating IOP-lowering treatment following 0.2 µg/day FAc implant. No other treatment-related complications were reported.

DISCUSSION

This study evaluated the bilateral injection of 0.2 µg/day FAc implant in six patients with DME in both eyes in the real-world setting. All eyes had received ≥1 macular laser treatment and ≥3 ranibizumab injections and were deemed insufficiently responsive to these treatments. Ten eyes had also received ≥1 IVTA injection prior to 0.2 µg/day FAc implant. The average CRT at baseline was high (648 µm) and most eyes (10/12) had baseline BCVA below 70 letters (6/12), the minimum requirement for maintaining a driving license in Europe [18]. Six months post-0.2 µg/day FAc implant, 58.3% of eyes had gained >10 letters and 41.7% ≥15 letters. Although the patient numbers are small, these values are consistent with outcomes reported in the FAME studies, where 51.7% of eyes treated with 0.2 µg/day FAc



implant gained >10 letters [19] and 34% gained ≥ 15 letters [16]. Four patients had achieved or maintained driving vision and there was a notable reduction in CRT in all eyes with a baseline CRT $>600 \mu\text{m}$. This is an important outcome in the management of DME progression, as prolonged edema results in irreversible damage and permanent vision loss, emphasizing the need for early intervention [20]. Further, minimal increases in IOP were observed and no patients needed to initiate IOP-lowering medication post-0.2 $\mu\text{g/day}$ FAc implant.

Of the six patients who received bilateral 0.2 $\mu\text{g/day}$ FAc implant in this study, five had severe edema with CRT $>600 \mu\text{m}$ in both eyes, in addition to low VA below driving vision after multiple prior treatments with macular laser, ranibizumab, and IVTA. Further, all eyes had foveal eversion on OCT. Taken together, these data suggest that, in a real-world setting, clinicians selected patients with severe bilateral DME for 0.2 $\mu\text{g/day}$ FAc implant in both eyes. It is accepted that early intervention and management of DME is important in minimizing vision loss and maintaining the quality of life in patients with DME; this is perhaps even more important when both eyes are affected, increasing the risk of legal blindness. Further sub-analyses of the RISE and RIDE trials with ranibizumab found that patients with chronic DME may become refractory to anti-VEGF therapy once DME disease progresses [9]. If, as some evidence suggests [10], this is associated with a more complex inflammatory cytokine state, treatment with corticosteroids may be appropriate at an earlier stage in patients with chronic DME. In the FAME trials, the sustained and localized release of 0.2 $\mu\text{g/day}$ FAc implant resulted in

improved visual and anatomical outcomes that were maintained for up to 36 months [16]. However, the proportion of patients with chronic DMO that achieved driving vision following 0.2 $\mu\text{g/day}$ FAc implant was reduced in patients with lower baseline VA, highlighting the importance of early treatment for optimal visual outcomes [21]. Consequently, in patients with bilateral DME, treatment of both eyes with 0.2 $\mu\text{g/day}$ FAc implant may be beneficial and, as it is not contraindicated, should be considered.

Limitations

The main study limitations relate to the retrospective nature of the study and the limited study size (6 patients/12 eyes); however, the current case series does provide a real-world clinical perspective following the bilateral administration of the 0.2 $\mu\text{g/day}$ FAc implant. Another limitation relates to the period of follow-up and highlights the need for further, larger prospective studies to assess the efficacy and safety of the 0.2 $\mu\text{g/day}$ FAc implant in real-life practice as well as the affecting of the outcomes of visual acuity. Although baseline data were captured for the patients included in this study, the full scope of their disease history, including the timescale of DME progression, which might impact on response to 0.2 $\mu\text{g/day}$ FAc implant, was not captured. In addition, VA scores in these patients were originally obtained using Snellen charts and converted to approximate ETDRS letter scores for the purposes of this analysis. The line assignment method used in Snellen charts (e.g., variable letter sizes and variable letters per line, arbitrary progression of letter size) can introduce a degree of variability in VA scores, particularly in patients with poor VA

[22]. As such, changes in VA should be interpreted with a degree of caution.

CONCLUSION

This study demonstrates the potential efficacy of 0.2 µg/day FAc implant in both eyes of patients with bilateral DME. CRT was consistently reduced in all but two eyes, which had relatively low CRT values and good VA at baseline, and four eyes maintained or achieved driving-level vision. There was no notable increase in IOP and no additional IOP-lowering treatment required following 0.2 µg/day FAc implant; no other treatment-related complications were reported. These data suggest that it is safe to carry out bilateral 0.2 µg/day FAc implant in patients with DME in both eyes, with potential improvements in DME and in the management of the long-term negative impact of DME-mediated vision loss. This is the first case series that the authors are aware of, to demonstrate the feasibility of bilateral 0.2 µg/day FAc implant in a real-world setting, and it suggests that, in patients with bilateral DME insufficiently responsive to alternative therapies, bilateral 0.2 µg/day FAc implant should be considered.

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Compliance with ethics guidelines. This article does not contain any new studies with human or animal subjects performed by any of the authors.

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REFERENCES

1. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35:556–64.
2. Minassian D, Owens D, Reidy A, et al. (2008) Diabetic macular oedema and related sight loss at first screening for eye disease. The Wales Diabetic Retinopathy Screening Service (WDRSS). UK Vision Strategy 2010.
3. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV.

- The long-term incidence of macular edema. *Ophthalmology*. 1995;102:7–16.
4. Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology*. 2011;118:626–35.
 5. Ferris FL III, Patz A. Macular edema. A complication of diabetic retinopathy. *Surv Ophthalmol*. 1984;28(Suppl):452–61.
 6. Boyer DS, Hopkins JJ, Sorof J, et al. Anti-vascular endothelial growth factor therapy for diabetic macular edema. *Ther Adv Endocrinol Metab*. 2013;4:151–69.
 7. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*. 2011;118:615–25.
 8. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012;119:789–801.
 9. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013;120:2013–22.
 10. Dong N, Xu B, Wang B, et al. Study of 27 aqueous humor cytokines in patients with type 2 diabetes with or without retinopathy. *Mol Vis*. 2013;19:1734–46.
 11. Sohn HJ, Han DH, Kim IT, et al. Changes in aqueous concentrations of various cytokines after intravitreal triamcinolone versus bevacizumab for diabetic macular edema. *Am J Ophthalmol*. 2011;152:686–94.
 12. Jonas JB. Intravitreal triamcinolone acetonide: a change in a paradigm. *Ophthalmic Res*. 2006;38:218–45.
 13. Tang J, Kern TS. Inflammation in diabetic retinopathy. *Prog Retin Eye Res*. 2011;30:343–58.
 14. European Medicines Agency. ILUVIEN 190 micrograms intravitreal implant in applicator: summary of products characteristics [online]. Available from: <https://www.medicines.org.uk/emc/medicine/27636>. Accessed June 26, 2015.
 15. Campochiaro PA, Hafiz G, Shah SM, et al. Sustained ocular delivery of fluocinolone acetonide by an intravitreal insert. *Ophthalmology*. 2010;117:1393–9.
 16. Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology*. 2012;119:2125–32.
 17. Gregori NZ, Feuer W, Rosenfeld PJ. Novel method for analyzing snellen visual acuity measurements. *Retina*. 2010;30:1046–50.
 18. Bron AM, Viswanathan AC, Thelen U, et al. International vision requirements for driver licensing and disability pensions: using a milestone approach in characterization of progressive eye disease. *Clin Ophthalmol*. 2010;4:1361–9.
 19. Data on File, 2015. Alimera Sciences Ltd.
 20. Virgili G, Parravano M, Menchini F, et al. Anti-vascular endothelial growth factor for diabetic macular oedema. *Cochrane Database Syst Rev*. 2014;10:CD007419.
 21. Downey L, Chakravarthy U. Exploratory analyses of long-term visual outcomes based on baseline vision in patients with chronic and nonchronic diabetic macular oedema (DMO) treated with fluocinolone acetonide (FAc) [abstract no.221]. Royal College of Ophthalmologists Annual Congress 19–21 May 2015.
 22. Kaiser PK. Prospective evaluation of visual acuity assessment: a comparison of Snellen versus ETDRS charts in clinical practice (An AOS thesis). *Trans Am Ophthalmol Soc*. 2009;107:311–24.