Evaluation of the clinical effectiveness of fluocinolone acetonide 190 µg intravitreal implant in diabetic macular oedema: a comparison between study and fellow eyes

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Abstract

Objectives

To compare visual and anatomical outcomes between eyes treated with fluocinolone acetonide (FAc) 190 µg intravitreal implant for clinically significant chronic diabetic macular oedema (DMO) and fellow eyes not treated with FAc implant using data from the Iluvien Clinical Evidence study in the UK (ICE-UK) study.

Methods

In this retrospective cohort study, data on people attending hospital eye services and treated with FAc implant between 1 April 2013 and 15 April 2015 were collected. Changes in visual acuity (VA), central foveal thickness (CFT) and intraocular pressure (IOP) were compared between study eyes (intervention) and fellow eyes.

Results

208 people were selected. Mean age was 68.1 years and 62% were male. Mean change in VA was -0.09 LogMAR units for study eyes and 0.04 LogMAR units for fellow eyes at 12 months post implant ($p<0.001$). Over the same period, ≥5 letter, ≥10 letter and ≥15 letter improvements in ETDRS score were achieved by more FAc treated eyes than by fellow eyes (41% versus 23%, $p<0.001$; 28% versus 11%, $p<0.001$; and 18% versus 4%, $p<0.001$ at 12 months, respectively). Differences in the mean change in CFT (-113 µm versus -13 µm, $p<0.001$) and IOP (3.2 mmHg versus -0.2 mmHg, $p<0.001$) were also observed between study and fellow eyes at 12 months.

Conclusion

Visual acuity improved in study eyes and worsened in fellow eyes over the 12 months following FAc implant. Over the same period, study eyes showed a larger improvement in central foveal thickness. Intraocular pressure worsened in study eyes only. Change in visual acuity, central foveal thickness and intraocular pressure between FAc implant and the end of the 12 months follow-up period differed significantly between study and fellow eyes.

Introduction

Diabetic retinopathy is amongst the most feared of the microvascular complications of type 1 and type 2 diabetes mellitus and was until very recently the most common cause of visual loss and blindness in working-aged people.[1,2] Up to 2010, it was estimated that 35% of people with diabetes worldwide had diabetic retinopathy.[3] As diabetic retinopathy progresses, microvascular changes in the retina can lead to increased permeability, with leakage causing the accumulation of fluid in the macular. The global prevalence of diabetic macular oedema (DMO) in people with diabetes has been estimated as 7%[3] and the condition is the major cause of vision loss in the diabetic population.[4]

Several types of therapy are licensed for use in DMO. The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that focal photocoagulation can lead to a reduced loss of vision in people with clinically significant DMO.[5] Subsequently, data from several landmark trials have shown that anti-VEGF therapies can improve vision in people with DMO,[6–9] and anti-VEGF therapy has become the treatment of choice for the management of DMO. Nevertheless, anti-VEGF therapies are not effective in all people.[10] Dong and colleagues suggest that several cytokines associated with inflammation and angiogenesis contribute to the pathogenesis of diabetic retinopathy.[11] Therefore, a multifactorial approach to the management of diabetic retinopathy could be beneficial.[11] Intravitreal corticosteroids have been shown to be effective in improving visual acuity in DMO[12–14] and reduce not only the expression of the VEGF gene but also suppress other inflammatory mediators. Intravitreal steroids are therefore potentially useful second-line agents in the management of DMO.

Fluocinolone acetonide (FAc) 190 µg intravitreal implant is licensed in 17 European countries for the treatment of visual impairment associated with chronic DMO considered insufficiently responsive to available therapies. Two separate randomised clinical trials, Fluocinolone Acetonide in Diabetic Macular Oedema (FAME) A and FAME B, have been conducted to study the clinical effectiveness of FAc intravitreal implant in DMO.[13,15,16] These studies recruited people with DMO previously treated

with retinal laser therapy, and the combined results of the two trials indicated that the FAc intravitreal implant provided visual benefit for up to three years.[13,12] Due to its long duration of action, the FAc intravitreal implant needs to be administered less frequently compared with anti-VEGF and other steroid therapies for DMO.[17] However, intravitreal corticosteroids have been shown to be associated with side effects including steroid-induced cataracts and raised intraocular pressure (IOP).[12–14] The UK National Institute of Health and Care Excellence (NICE) currently recommends that FAc intravitreal implant be used only in eyes with pseudophakic lenses where the DMO has been insufficiently responsive to available therapies.[18]

The aim of the Iluvien Clinical Evidence study in the United Kingdom (ICE-UK) was to assess the real-world effectiveness of FAc intravitreal implant for chronic DMO in routine clinical practice. Changes in visual acuity, central foveal thickness (CFT) and IOP were compared between FAc treated and fellow eyes post implant. Whilst randomised trials of DMO-related treatments provide a direct comparison between FAc treated and untreated subjects, here we compared study eyes (first eyes treated with FAc implant) and fellow eyes (the patient's eye not treated with FAc implant, but which may have other standard care) in the same subject since this provides a natural experiment whereby the reference (control) eye is exposed to exactly the same physiological milieu. The low daily release of FAc from the intravitreal implant provides systemic FAc levels that are undetectable in the systemic circulation;[19] therefore the effect of the FAc implant in the study eye affecting the disease in the fellow eye is low. However, unlike randomised controlled trials, the decision as to which eye to treat is likely to be based on a clinical decision. Nevertheless the premise of the study was based on the assumption that there was homogeneity between study and fellow eyes.

Methods

Data Source

This study used a retrospective cohort design. The data source has been described previously.[20] Briefly, data were extracted from patient medical records for a representative cohort of patients registered at 13 participating UK hospitals. Data were pseudonymised and combined into a single dataset. Data included demographics, medical history, implant data, and data from multi-disciplinary and medication reviews at several time points within a designated period.

Ethical approval

The lead clinician and Caldicott Guardian at each centre gave written approval for extraction of anonymised data. The study protocol was approved by the head of research governance at the lead clinical centre. This study was conducted in accordance with the Declaration of Helsinki and the UK Data Protection Act.

Subjects

People with type 1 or type 2 diabetes treated with FAc intravitreal implant for DMO in at least one eye were included in the study. In order to allow for sufficient follow-up, it was required that the implant be inserted between 1 April 2013 and 15 April 2015 at a participating site as part of the patient's routine care. The period of observation ended on 15 April 2016. A minimum history of 12 months prior to implant was also required, providing information that is not available in randomised controlled trials. People with a history of participating in any interventional study for DMO or with insufficient follow-up were excluded. Reasons for insufficient follow-up included: non-attendance at the clinic and last appointment missing the last appointment post index. Study eyes were defined as the first eye to be treated with FAc implant. Fellow eyes were defined as the eye that received no FAc implant; these could receive other DMO treatments as deemed clinically necessary in routine practice. People whose fellow eye was treated with FAc intravitreal implant within

12 months of the study eye's first treatment were censored at the time of implant, with all remaining subjects followed for 12 months post implant. The index date was defined as the date of the first recorded FAc intravitreal implant into the study eye.

Outcomes

Change in visual acuity, CFT and IOP were investigated at 3, 6 and 12 months post index date in study and fellow eyes. Visual acuity was measured using one of: Early Treatment of Diabetic Retinopathy Study (ETDRS) scores, Snellen fractions or LogMAR scores. All Snellen fractions were converted to approximate ETDRS scores for analysis using the following formula derived by Gregori and colleagues: approximate ETDRS = 85 + 50 x log (Snellen fraction). All approximate ETDRS scores were rounded to the nearest letter.[21] Snellen fractions were converted to LogMAR scores using the following formula: -1 x log (Snellen fraction).[21] These formulae were rearranged to convert between LogMAR and ETDRS. People who could only detect movement, detect light or count fingers were allocated to 2.3 on the LogMAR scale, the value attributed to people who can count fingers. As this was an observational study, there was no restriction on the optical coherence tomography (OCT) machine type used to measure retinal thickness.

Statistical analysis

Results were compared between study eyes and fellow eyes. Baseline characteristics were displayed for study and fellow eyes overall and by subgroup based on the difference in the mean change in visual acuity between study and fellow eyes at 12 months post implant (> and ≤-0.12 LogMAR units). Baseline characteristics were compared using the paired t-test or Wilcoxon signed rank test for continuous variables, depending on their distribution. Changes in visual acuity, CFT and IOP were compared between study and fellow eyes using the Wilcoxon signed rank test. Categorical variables were compared using McNemar's test. Due to the observational nature of this study, people did not visit the clinic at set times prior to and following insertion of the FAc intravitreal implant. Therefore last observation

carried forward prior to and after implant was implemented in order to impute missing values.[22]

Mean change in the four study outcomes on each day following baseline and mean values on each day in the 12 months prior and post index date were calculated using a dataset where missing values had been imputed using linear interpolation.[22] As linear interpolation was not suitable following the last observed value or prior to the first observed value, nearest observation carried forward and backward was used to impute the remaining missing values.

Generalised linear mixed multinomial modelling with a random intercept at subject level and a generalised logit link function was conducted. The dependent variable was change in visual acuity categorised as ≥5 letter improvement, between -4 and +4 letter change (i.e. stable visual acuity) and ≥5 letter worsening. The following variables were added as fixed effects: age, baseline visual acuity (LogMAR units), insulin treatment, sex, FAc implant, lens status, number of prior anti-VEGF injections, prior IOP-lowering therapy, number of prior laser therapies, number of prior steroid injections (triamcinolone or dexamethasone) and prior vitrectomy. All statistical analyses were carried out using IBM SPSS statistics version 20.

Results

Data were collected on 311 people, of whom 208 people contributing 208 study eyes and 208 fellow eyes were eligible for inclusion in the study cohort. The number of study subjects excluded has been described previously.[20]

Patient characteristics

Of the 208 people treated with FAc intravitreal implant in the study eye, 128 (62%) were male. Mean age was 68.1 years (Table 1). 176 (85%) people had type 2 diabetes. Median (IQR) duration of diabetes was 18.0 (11.0–27.0) years. For 137 (70%) people, vision was worse in the study eye.

185 (89%) study eyes and 111 (53%) fellow eyes had a pseudophakic lens ($p<0.001$). At the time of implant, median visual acuity was worse in the study eye than in the fellow eye (median 0.69, IQR 0.49–1.00 LogMAR units versus 0.40, 0.19–0.80 LogMAR units, $p<0.001$). Mean (standard deviation, SD) CFT was 483 (189) µm for study eyes and 371 (176) µm for fellow eyes ($p<0.001$). Study eyes had a history of receiving more anti-VEGF ($p<0.001$), steroid ($p<0.001$) and macular laser treatments ($p=0.028$) when compared with fellow eyes. IOP at baseline was similar in study and fellow eyes (median 15 versus 15 mmHg, $p=0.236$) and there was no significant difference in the number of study and fellow eyes that had been previously treated with IOP-lowering therapy (20% versus 16%, $p=0.143$). The percentage of patients receiving the FAc implant in a pseudophakic eye who had a phakic lens in their fellow eye was 37% for those receiving the FAc implant in their worse-seeing eye and 31% in those receiving the FAc implant in the study eye with the same or better visual acuity. Baseline characteristics by subgroup defined by difference in mean change in visual acuity between study eye and fellow eye at 12 months are displayed in Supplementary Table 1.

Other intraocular interventions

The number of eyes treated with anti-VEGF post FAc implant in the study eye were: 5% of study eyes versus 18% of fellow eyes between 0 and 3 months, 9% of study eyes versus 20% of fellow eyes between 3 to 6 months and 18% of study eyes versus 24% of fellow eyes between 6 and 12 months (Table 2). The number of eyes treated with steroids (other than FAc) post FAc implant in the study eye were: 2% of study eyes versus 1% of fellow eyes between 0 and 3 months, 1% of study eyes versus 1% of fellow eyes between 3 and 6 months and 5% of study eyes versus 1% of fellow eyes between 6 to 12 months. The corresponding figures for macular laser therapy were 2% of study eyes versus 2% of fellow eyes, 3% of study eyes versus 2% of fellow eyes and 5% of study eyes versus 4% of fellow eyes at 0 to 3 months, 3 to 6 months and 6 to 12 months, respectively.

23 study eyes (11%) had a phakic (natural) lens at baseline. A pseudophakic lens status or a cataract operation was recorded in 15 eligible phakic eyes (68%) between 0 and 3 months post implant (including 11 cataract operations performed on day of FAc implant) and one eye (14%) between 3 and 6 months post implant. At the time of FAc implant in the study eye, 97 (47%) fellow eyes had a phakic lens. 10, 3 and 4 eligible phakic eyes received a cataract operation or a change in lens status to pseudophakic at 0 to 3 months, 3 to 6 months and 6 to 12 months post implant.

Change in visual acuity

For the study eye, mean visual acuity was better in the 12 months following FAc implant when compared with the 12 months preceding implant (0.73 LogMAR units at -12 months, 0.76 LogMAR units immediately prior to implant and 0.67 LogMAR units at +12 months, Figure 1). Visual acuity in study eyes improved over the first four months of study follow-up (mean change -0.10 LogMAR units). Improvements in visual acuity decreased slightly between 4 and 12 months and mean change in visual acuity was -0.09 LogMAR units at 12 months post FAc implantation (Figure 2). For the fellow eye, mean visual acuity improved prior to index date (0.54 LogMAR units four months prior to implant to 0.5 LogMAR units at FAc implant) but then gradually

worsened over the 12 month follow-up period post implant (0.54 LogMAR units at 12 months). Change in visual acuity was significantly different in study eyes and fellow eyes at 3 months (mean -0.08 versus -0.02 LogMAR units, respectively, p=0.008), 6 months (-0.11 versus 0.03 LogMAR units, respectively, p<0.001) and 12 months post implant (-0.09 versus 0.04, respectively, p<0.001, Supplementary Table 2).

A ≥5 letter improvement in ETDRS score was achieved by more study eyes than fellow eyes at each follow-up time point (44% versus 22%, p<0.001, at 3 months; 44% versus 30%, p=0.002, at 6 months; 41% versus 23%, p<0.001, at 12 months post implant, Figure 3). More study eyes also achieved a ≥10 letter improvement at 3 months (26% versus 12%, p<0.001), 6 months (30% versus 10%, p<0.001) and 12 months (28% versus 11%, p<0.001) post index date. For a ≥15 letter improvement in ETDRS the corresponding figures for study eyes and fellow eyes were 14% versus 7%, p=0.012 at 3 months; 16% versus 4%, p<0.001 at 6 months; and 18% versus 4%, p<0.001 at 12 months, respectively. At 6 and 12 months post FAc implant, fewer study eyes exhibited a worsening in visual acuity of ≥5, ≥10 and ≥15 letters compared with fellow eyes. However, this only achieved statistical significance for a ≥10 letter worsening in ETDRS letter score at 6 months (10% of study eyes versus 19% of fellow eyes, p=0.014).

Results from the generalised linear mixed multinomial modelling showed that the study eyes were more likely to achieve a ≥5 letter gain in visual acuity and this result was significant at three months (exponential of the coefficient 2.09, 95% CI 1.13–3.88, p=0.019) post implant (Table 3). Study eyes were not significantly more or less likely to have a worsening of ≥5 letters in visual acuity at 3, 6 and 12 months post implant.

Change in central foveal thickness

In the study eye, CFT fluctuated from 468 µm at -12 months to 445 µm at -4 months before increasing to 471 µm immediately prior to implant (Figure 1). Mean CFT then decreased gradually post implant from 407 µm immediately following implant to 358

µm at the end of the 12 months follow-up. For the fellow eye, there was little change in mean CFT in the 12 months before and after implant (CFT 345 µm, 343 µm and 330 µm at -12 months, index date and +12 months, respectively). A difference in the change in CFT was observed between study and fellow eyes between index date and 3 months follow-up (mean -87 µm versus -3 µm, respectively, p<0.001), 6 months follow-up (-90 µm versus -3 µm, respectively, p<0.001) and 12 months follow-up (-113 µm versus -13 µm, respectively, p<0.001, Supplementary Table 2).

Change in intraocular pressure

Mean IOP was similar and remained relatively stable in both the study and fellow eyes prior to implant (15.7 mmHg and 16.0 mmHg at -12 months and 15.6 mmHg and 16.1 mmHg at implant, respectively, Figure 1). Post FAc implant in the study eye, mean IOP increased to 18.8mmHg at the end of the 12 month follow-up period. Conversely, mean IOP remained stable in the fellow eye (15.9 mmHg at +12 months, Figure 2). Change in IOP differed between the study eye and fellow eye at 3 months (mean 1.9 mmHg versus 0.55 mmHg, p=0.004), 6 months (2.4 mmHg versus 0.4 mmHg, p<0.001) and 12 months (3.2 mmHg versus -0.2 mmHg, p<0.001) post index date (Supplementary Table 2).

The number of study versus fellow eyes with an IOP of ≤21 mmHg was 12 (8%) versus 11 (7%) at baseline (N=156 pairs of eye, p=1.000), 26 (18%) versus 19 (13%) at 3 months (N=147, p=0.167), 31 (20%) versus 12 (8%) at 6 months (N=154, p=0.001) and 39 (25%) versus 11 (7%) at 12 months post FAc implant (N=157, p<0.001).

IOP-lowering medicine was initiated in more study eyes than fellow eyes between 0 and 3 months (3% versus 1%), 3 and 6 months (7% versus 1%) and 6 and 12 months (11% versus 4%) post index date.

Discussion

In the study cohort, visual acuity and CFT improved in the 12 months following the insertion of the FAc intravitreal implant when compared with the 12 months prior to implant. Conversely, there was a small but significant increase in IOP in the study eye in the 12 months post FAc implant. For the fellow eye, CFT and IOP remained relatively stable across the 12 month periods prior to and following FAc implant in the study eye. However, there was a small deterioration in visual acuity in the fellow eye post FAc implant. At the end of the 12 month follow-up period, statistically significant improvements in visual acuity and CFT were observed in study eyes treated with FAc intravitreal implant when compared with the fellow eye. However, during the same period, a small statistically significant increase in IOP was observed in study eyes only. More fellow eyes were treated with anti-VEGF therapies in the 12 months post FAc implant when compared with study eyes. However, more study eyes than fellow eyes were treated with steroid therapy between 6 and 12 months post implant. The number of fellow eyes and study eyes receiving macular laser therapy post implant were similar. An important limitation of this study was the difference in visual acuity and CFT between study and fellow eyes prior to FAc implant. However, prior to implant, IOP was similar in study and fellow eyes, suggesting that the comparison between study and fellow eyes is reasonable for this outcome.

To date, the largest randomised controlled trials investigating the effectiveness of FAc have been the FAME studies, where people with DMO previously treated with macular laser therapy were randomised to receive sham injection (n=185), low-dose FAc implant (n=375) and high dose FAc implant (n=393).[12,13] Campochiaro and colleagues reported that 28.7% of people randomised to 0.2 µg/day FAc implant achieved a ≥15 letter improvement in ETDRS score after three years compared with 18.9% of people randomised to sham injection (p=0.018).[13] The 0.2 µg/day FAc group also received fewer off-protocol treatments for DMO (15.2% compared with 33% for the sham group).[13] In this study, where the fellow eye acted as a control, we found that a ≥15 letter improvement was observed in 18% of study eyes and 4% of

fellow eyes after 12 months follow-up (p<0.001). Here, some of the study eyes and fellow eyes also received other DMO treatments as part of their routine care. However, a higher number of fellow eyes received other treatments for DMO post FAc implant. However, unlike the people included in the FAME studies, whose DMO had previously only been managed with macular laser therapy, 82% of study eyes and 47% of fellow eyes in this study had previously been treated with anti-VEGF injections, and 43% of study eyes and 19% of fellow eyes had been previously treated with steroids (triamcinolone or dexamethasone). Compared with the FAME study, a higher proportion of study eyes and fellow eyes had a pseudophakic lens at baseline (89% of study eyes and 53% of fellow eyes in this study versus 34.6% of those randomised to sham and 37.3% of those eyes randomised to the 0.2 μg/day FAc implant in the FAME study). In addition, people in this study were generally older and there was a higher proportion of people with type 1 diabetes. In a pre-specified subgroup analysis, Cunha-Vaz and colleagues reported that a higher percentage of people with chronic DMO gained a 15 letter improvement in visual acuity when compared with those with non-chronic DMO.[23] Although the chronicity of DMO was not collected as part of the ICE-UK study, we undertook a subgroup analysis to determine the baseline characteristics of those people who went on to respond better to FAc implant (difference in mean change in visual acuity between study eye and fellow eye at 12 months ≤-0.12 LogMAR units). We found that people who responded better were in general younger, had worse vision in their study and fellow eye at baseline and were more likely to have been previously treated with at least one steroid injection in the study eye.

The FAMOUS (Fluocinolone in Human Aqueous) RCT, where people were randomised to the 0.2 μg/day implant, reported a mean change in visual acuity of 5.7 letters at 12 months.[24] In a retrospective study carried out by Elaraoud and colleagues, an improvement in visual acuity and CFT was observed in 15 out of 22 eyes treated with FAc intravitreal implant.[25] The subjects included were similar to those included in the ICE-UK study in that all included eyes had a pseudophakic lens and the majority had been previously treated with multiple anti-VEGF and laser therapies.[25]

Unlike an RCT where people are randomised to FAc or sham injection, this study had a retrospective observational design whereby the untreated eye acted as a natural control that had been exposed to the same patient and disease factors. However, in 70% of people, the FAc intravitreal implant was inserted into the worse-seeing eye. At baseline, CFT was greater in the study eye when compared with the fellow eye. Baseline vision is likely to dictate the improvement or worsening of vision observed in an eye and the difference in visual acuity at baseline between study and fellow eyes. In addition, more fellow eyes received anti-VEGF treatments in the 12 months post FAc implant. These limitations need to be taken into account when interpreting the comparisons between study and fellow eye.

Five cataract operations were observed in study eyes over the follow-up period. However, the majority of people had a pseudophakic lens in the study eye at the time of implant (89%). In the FAME study, in those with no history of receiving a cataract operation, cataract surgery was reported in 75% of the 0.2 µg/day FAc group and 23% of the sham group after 24 months of follow-up and was the most commonly reported adverse event.[12] At 36 months, these figures were 82% and 51%, respectively.[13] The percentage of eyes with a phakic lens at baseline was higher in the FAME study when compared with ICE-UK (11% versus 65%).[12] More study eyes initiated IOP-lowering medication post index date. IOP-lowering surgery was carried out in one study eye and two fellow eyes within 12 months of implant. However, following insertion of the FAc intravitreal implant, there was a small but statistically significant increase in IOP in study eyes when compared with fellow eyes. Furthermore, a statistically significant higher percentage of study eyes had an IOP of ≥21 mmHg when compared with fellow eyes. In the FAME study, all included individuals had no prior history of glaucoma.[12] Laser trabeculoplasty and incisional IOP-lowering surgery were reported to have been carried out in 1.3% and 4.8% of the 0.2 µg/day FAc implant group and 0% and 0.5% of the sham group, respectively.[13]

Strengths and limitations

The general study limitations have largely been discussed previously.[20] The comparison of study and fellow eyes had statistical limitations. The decision to treat one eye with FAc instead of or before the fellow eye is based on clinical judgment and is not a random event. The study eye often had poorer visual acuity and CFT at baseline compared with the fellow eye. This could have led to confounding by severity. Conversely, worse characteristics at baseline could have potentially led to improved outcomes and therefore favoured the study eye. The FAc implant is licensed for the treatment of DMO considered insufficiently responsive to available therapies. Therefore, when the FAc implant was inserted into the worse-seeing eye, the better-seeing eye could still have been responsive to other DMO treatments. However, little improvement was observed in the fellow eye over the 12 months before and after index date, and only 18%, 20% and 24% of fellow eyes received anti-VEGF therapy at 0 to 3 months, 3 to 6 months and 6 to 12 months post index date. The UK NICE guidelines recommend that the FAc intravitreal implant be prescribed in eyes with a pseudophakic lens[18] and this may have also influenced the decision as to which eye to treat with FAc. For 37% of patients who received an FAc implant in their worse-seeing eye, the fellow eye was phakic at the time of implant. For those patients, whose visual acuity was the same or better in the study eye, 31% had a phakic lens in their fellow eye. Collection parameters included DMO type for each eye, but a status of no DMO could not be recorded. Unilateral cases of DMO were reported separately for three study subjects. The level of misclassification of the unilateral and bilateral DMO status is unknown, although 26% patients had no history of receiving any treatment for DMO (laser, intravitreal steroids or anti-VEGF therapy) prior to index date (compared with 3% of study eyes).

Several types of OCT machine were used to measure retinal thickness across the 13 participating ophthalmology centres, and this has been discussed in detail elsewhere.[26] Retinal thickness measurements have been shown to vary depending on machine type, possibly due to variation in the retinal segmentation algorithms used by different OCT machines.[27] However, the same OCT machine type was used to measure retinal thickness in the left and right eye during the same visit.

Due to the low level of systemic absorption, the effect of the FAc implant on the fellow eye is thought to be low. However, bevacizumab has been reported to significantly reduce the level of VEGF in the blood plasma for up to 28 days post injection in people with DMO and age-related macular degeneration.[28,29] Furthermore, studies have shown that anti-VEGF therapy administered unilaterally can have beneficial effects in the contralateral eye of people with bilateral DMO,[30] age-related diabetic macular degeneration,[31] proliferative diabetic retinopathy,[32] uveitis-related cystoid macular oedema.[33] The potential crossover effect of anti-VEGF therapy on the contralateral (study or fellow) eye is a limitation of the study design.

Conclusion

At the end of the 12 months follow-up period, a statistically significant improvement in visual acuity and CFT and a small but significant increase in intraocular pressure were observed in study eyes treated with FAc intravitreal implant when compared with the fellow eye. Differences in baseline visual acuity and CFT between study and fellow eyes were a limitation of this study. However, considering the study and fellow eyes independently, trends in visual acuity and CFT over the 12 month periods before and after FAc implant highlight the benefit of FAc intravitreal implant in the often poorer study eye. Over the same period, little or no improvement in these outcomes was observed in fellow eyes.

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Tables and figures

Table 1 | Baseline characteristics

Parameter	Study eye		Fellow
Patient characteristics			
Subjects, n	208		208
Age last clinic visit, mean (SD)[a]	68.1	(10.7)	68.1
Males, n (%)	128	(62%)	128
Type 1 diabetes, n (%)	32	(15%)	32
Oral hypoglycaemic agents	0	(0%)	0
Insulin	28	(88%)	28
Insulin plus oral antihyperglycaemic agents	4	(13%)	4
Type 2 diabetes, n (%)	176	(85%)	176
Oral antihyperglycaemic agents	76	(43%)	76
Insulin	43	(24%)	43
Insulin plus oral antihyperglycaemic	57	(32%)	57
Number of years with diabetes, median (IQR)[a]	18	(11-27)	18
Eye characteristics			
Pseudophakic lens status, n (%)[d]	185	(89%)	111
Visual acuity, LogMAR units[bc]			
n (%)	196	(94%)	196
Median (IQR)	0.69	(0.49-1)	0.4
Visual acuity, ETDRS letters[bc]			
n (%)	196	(94%)	196
Median (IQR)	50	(35–60.5)	65
Visual acuity compared with other eye, n (%)[bc]			
Same	20	(10%)	20
Better	39	(20%)	137
Worse	137	(70%)	39

Centre subfield thickness, μm[bc]			
n (%)	172	(83%)	172
Median (IQR)	445	(353-575)	325
Central foveal thickness, μm[bcd]			
n (%)	160	(77%)	160
mean (SD)	483	(189)	371
IOP, mmHg[bc]			
n (%)	156	(75%)	156
Median (IQR), mmHg	15.0	(13-18)	15.0
Prior macular laser treatments			
n (%)	127	(61%)	115
Median (IQR)	1	(0-2.5)	1
Prior anti–VEGF injections			
n (%)	170	(82%)	98
Median (IQR)	4	(2-7)	0
Prior ranibizumab injections			
n (%)	144	(69%)	78
Median (IQR)	3	(0-6)	0
Prior aflibercept injections			
n (%)	1	(0%)	0
Median (IQR)	0	(0-0)	0
Prior bevacizumab injections			
n (%)	63	(30%)	37
Median (IQR)	0	(0-2)	0
Prior steroid injections,			
n (%)	89	(43%)	39
Median (IQR)	0	(0-1)	0
Prior dexamethasone injections			
n (%)	14	(7%)	5
Median (IQR)	0	(0-0)	0
Prior triamcinolone injections			
n (%)	79	(38%)	34
Median (IQR)	0	(0-1)	0

IOP-lowering medication, n (%)	41	(20%)	34
Prostaglandin analogues, n (%)	26	(13%)	15
Beta blockers, n (%)	14	(7%)	14
Alpha agonists, n (%)	5	(2%)	6
Carbonic anhydrase inhibitors, n (%)	11	(5%)	9
Other, n (%)	7	(3%)	8

SD = standard deviation, IQR = interquartile range, LogMAR = logarithm of the minimum angle of resolution, ETDRS = Early treatm
intraocular pressure, VEGF = vascular endothelial growth factor.

[a] These are approximate estimates as it was not possible to determine the exact date on which these parameters were recorded i

[b] Nearest value recorded ≤index date providing that it occurs no more than 365 days prior to the index date.

[c] Pairs of values included only. Individuals with a value missing for study and/or fellow eye are not included.

[d] Central foveal thickness was measured using Heidelberg SPECTRALIS in 103 patients, Topcon 3D OCT in 55 patients and Topcon

Supplementary Table 1 | Baseline characteristics by subgroup based on difference in change in m

between study eye and fellow eye (change in visual acuity for study eye minus change in visual ac

	Difference in change in visual acuity ≥-0.13				Differenc
	Study eye		Fellow eye		Study
Subjects, n	96		96		62
Age last clinic visit, mean (SD)[a]	70.1	(9.2)	70.1	(9.2)	67
Males, n (%)	64	(67%)	64	(67%)	39
Type 2 diabetes, n (%)	82	(85%)	82	(85%)	56
Tablets	28	(34%)	28	(34%)	32
Insulin	22	(27%)	22	(27%)	9
Insulin plus tablets	32	(39%)	32	(39%)	15
Type 1 diabetes, n (%)	14	(15%)	14	(15%)	6
Tablets	0	(0%)	0	(0%)	0
Insulin	13	(93%)	13	(93%)	6
Insulin plus tablets	1	(7%)	1	(7%)	0
Number of years with diabetes, median (IQR)[a]	18	(10.8–28)	18	(10.8–28)	16
Pseudophakic lens status, n (%)	84	(88%)	57	(59%)	56
Visual acuity, median (IQR), LogMAR scale[bc]	0.6	(0.41–0.8)	0.31	(0.19–0.71)	0.8
Central subfield thickness, μm[bc]					
n (%)	85	(89%)	85	(89%)	53
Median (IQR)	436	(336–532)	316	(268–372)	453
Central foveal thickness, μm[bc]					
n (%)	77	(80%)	77	(80%)	49
median (IQR)	457	(360–587)	332	(258–387)	473
IOP, mmHg[bc]					

n (%)	78	(81%)	78	(81%)	45
Median (IQR), mmHg	15	(13–17)	15	(13–17)	16
Prior macular laser treatments					
n (%)	54	(56%)	48	(50%)	39
Median (IQR)	1	(0–2)	0.5	(0–2)	1
Prior anti–VEGF injections					
n (%)	79	(82%)	39	(41%)	50
Median (IQR)	4	(2–7)	0	(0–3.5)	5
Prior ranibizumab injections					
n (%)	70	(73%)	32	(33%)	43
Median (IQR)	3	(0–6)	0	(0–3)	3
Prior aflibercept injections					
n (%)	1	(1%)	0	(0%)	0
Median (IQR)	0	(0–0)	0	(0–0)	0
Prior bevacizumab injections					
n (%)	19	(20%)	11	(11%)	19
Median (IQR)	0	(0–0)	0	(0–0)	0
Prior steroid injections					
n (%)	37	(39%)	14	(15%)	30
Median (IQR)	0	(0–1)	0	(0–0)	0
Prior dexamethasone injections					
n (%)	6	(6%)	1	(1%)	5
Median (IQR)	0	(0–0)	0	(0–0)	0
Prior triamcinolone injections					
n (%)	32	(33%)	13	(14%)	28
Median (IQR)	0	(0–1)	0	(0–0)	0
IOP-lowering medication, n (%)	19	(20%)	16	(17%)	15
Prostaglandin analogues, n (%)	13	(14%)	7	(7%)	9
Beta blockers, n (%)	4	(4%)	3	(3%)	6

Alpha agonists, n (%)	3	(3%)	4	(4%)	2
Carbonic anhydrase inhibitors, n (%)	3	(3%)	4	(4%)	5
Other, n (%)	5	(5%)	5	(5%)	1

SD = standard deviation, IQR = interquartile range, LogMAR = logarithm of the minimum angle of resolution, ETDRS = Early treatm
intraocular pressure, VEGF = vascular endothelial growth factor.

[a] These are approximate estimates as it was not possible to determine the exact date on which these parameters were recorded i

[b] Nearest value recorded ≤index date providing that it occurs no more than 365 days prior to the index date.

[c] Pairs of values included only. Individuals with a value missing for study and/or fellow eye are not included.

Table 2 | Number of eyes prescribed therapies before and after treatment with fluocinolone intravitreal implant

Parameter	Study eye		Fellow eye	
	N	(%)	N	(%)
Subjects, n	208		208	
Macular laser treatments				
Prior to FAc implant	127	(61%)	115	(55%)
0 to 3 months	3	(2%)	3	(2%)
3 to 6 months	5	(3%)	4	(2%)
6 to 12 months	9	(5%)	6	(4%)
Anti-VEGF injections				
Prior to FAc implant	170	(82%)	98	(47%)
0 to 3 months	9	(5%)	35	(18%)
3 to 6 months	16	(9%)	37	(20%)
6 to 12 months	31	(18%)	41	(24%)
Steroid injections				
Prior to FAc implant	89	(43%)	39	(19%)
0 to 3 months	3	(2%)	2	(1%)
3 to 6 months	2	(1%)	1	(0.6%)
6 to 12 months	8	(5%)	2	(1%)
IOP-lowering surgery				
Prior to FAc implant	0	(0%)	1	(0.5%)
0 to 3 months	0	(0%)	0	(0%)
3 to 6 months	0	(0%)	1	(0.6%)
6 to 12 months	1	(0.6%)	1	(0.6%)
Vitrectomy				
Prior to FAc implant	45	(22%)	16	(8%)
0 to 3 months	1	(0.5%)	0	(0%)
3 to 6 months	1	(0.6%)	1	(0.6%)
6 to 12 months	2	(1%)	1	(0.6%)
Incident cataract operation				
Prior to FAc implant	185	(89%)	111	(53%)
0 to 3 months	15[a]	(68%)	10	(11%)
3 to 6 months	1	(14%)	3	(4%)
6 to 12 months	0	(0%)	4	(5%)
Newly prescribed IOP-lowering therapies				
Prior to FAc implant	41	(20%)	34	(16%)
0 to 3 months	5	(3%)	1	(0.6%)
3 to 6 months	9	(7%)	1	(0.7%)
6 to 12 months	13	(11%)	5	(4%)

[a] Includes 11 cataract operations carried out on the day of FAc implant.[b] Percentages post implant are calculated based on the number of phakic eyes remaining.

Supplementary Table 2 | Change in visual acuity, central subfield and central foveal thickness and

	N	Change in study eye				Change in f	
		Mean (SD)		Median (IQR)		Mean (SD)	
Change in visual acuity, LogMAR units							
At 3 months	168	-0.08	(0.35)	0.00	(-0.20–0.00)	-0.02	(0.3)
At 6 months	165	-0.11	(0.37)	-0.06	(-0.20–0.00)	0.03	(0.32)
At 12 months	158	-0.09	(0.38)	-0.02	(-0.20–0.10)	0.04	(0.29)
Change in central foveal thickness, µm							
At 3 months[a]	118	-87	(189)	-66	(-188–5.0)	-2.9	(122)
At 6 months[a]	118	-90	(218)	-75	(-208–9.0)	-2.9	(123)
At 12 months[b]	114	-113	(216)	-102	(-219–9.0)	-13.0	(121)
Change in IOP, mmHg							
At 3 months	116	1.9	(6.4)	1.0	(-1.5–4.0)	0.6	(5.3)
At 6 months	121	2.4	(6.8)	1.0	(-1–5.0)	0.4	(5.2)
At 12 months	120	3.2	(7.3)	2.0	(-1.4–6.0)	-0.2	(4.7)

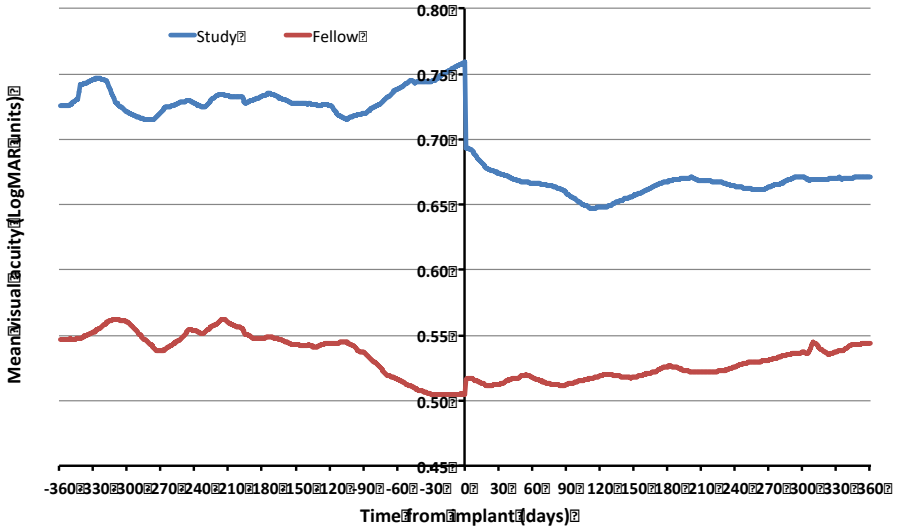
Pairs of eyes with complete data included only. Last observation carried forward was used to impute missing values in two stages and after index date. Eyes with missing visual acuity score (i.e. no visual acuity recorded between index date and the study time p

[a] Central foveal thickness was measured on different OCT machine types in 5% of eyes.

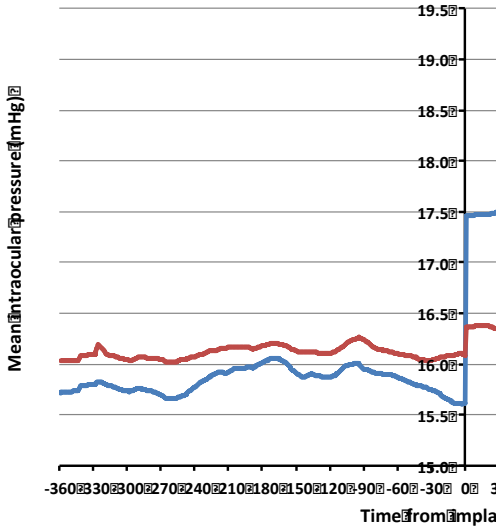
[b] Central foveal thickness was measured on different OCT machine types in 6% of eyes.

Figure 1 | Mean visual acuity, central subfield and central foveal thickness and IOP for study and fellow

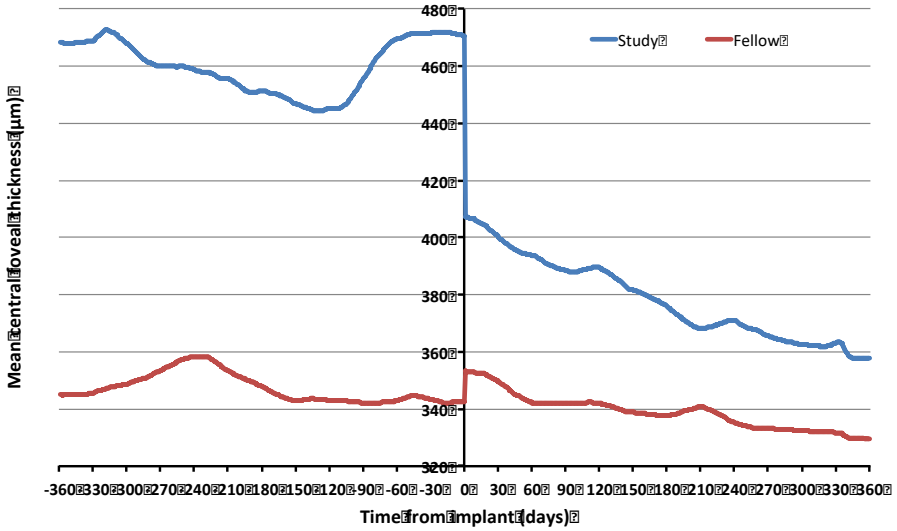
a) Visual acuity



b) IOP



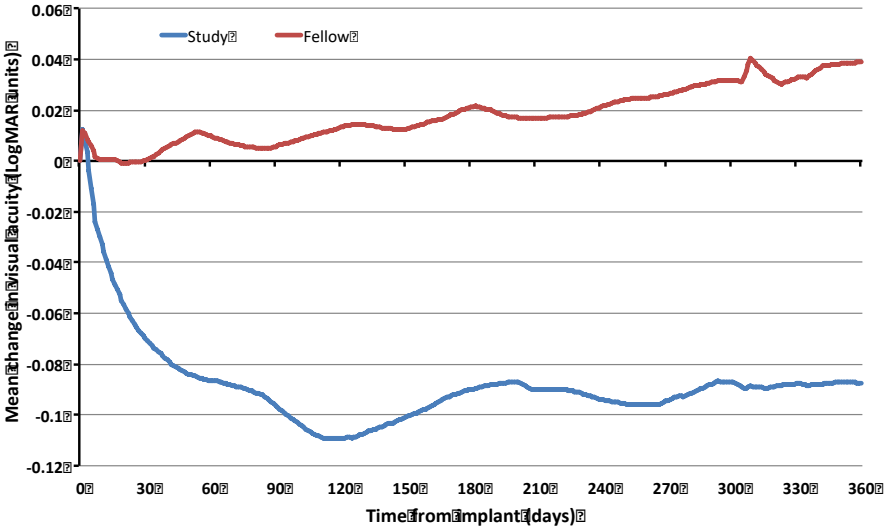
c) Central foveal thickness



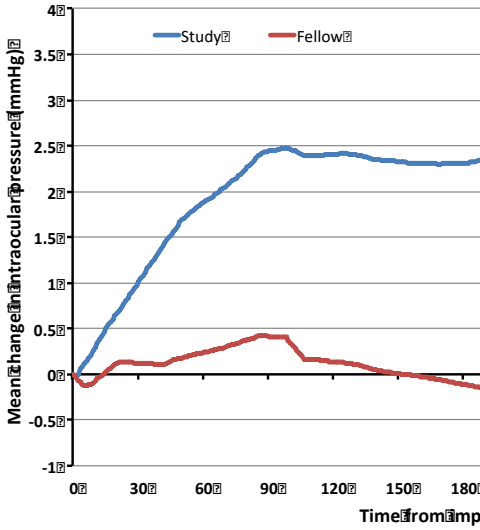
Missing values were imputed using linear interpolation. Last observation carried forward was then used following the last recorded valu
observation carried forward was used in the year prior to index date in order to impute missing values at the time of implant in the study

Figure 2 | Mean change in visual acuity, central subfield and central foveal thickness and IOP post inde

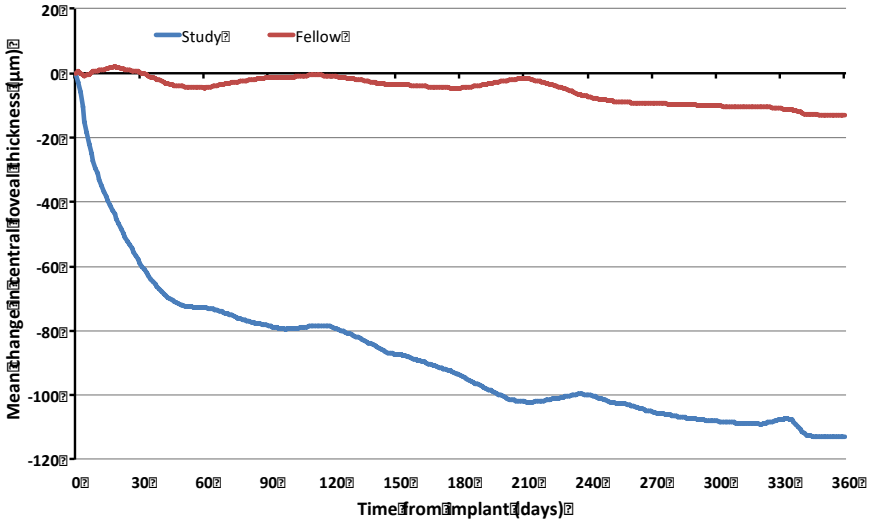
a) Change in visual acuity



b) Change in IOP

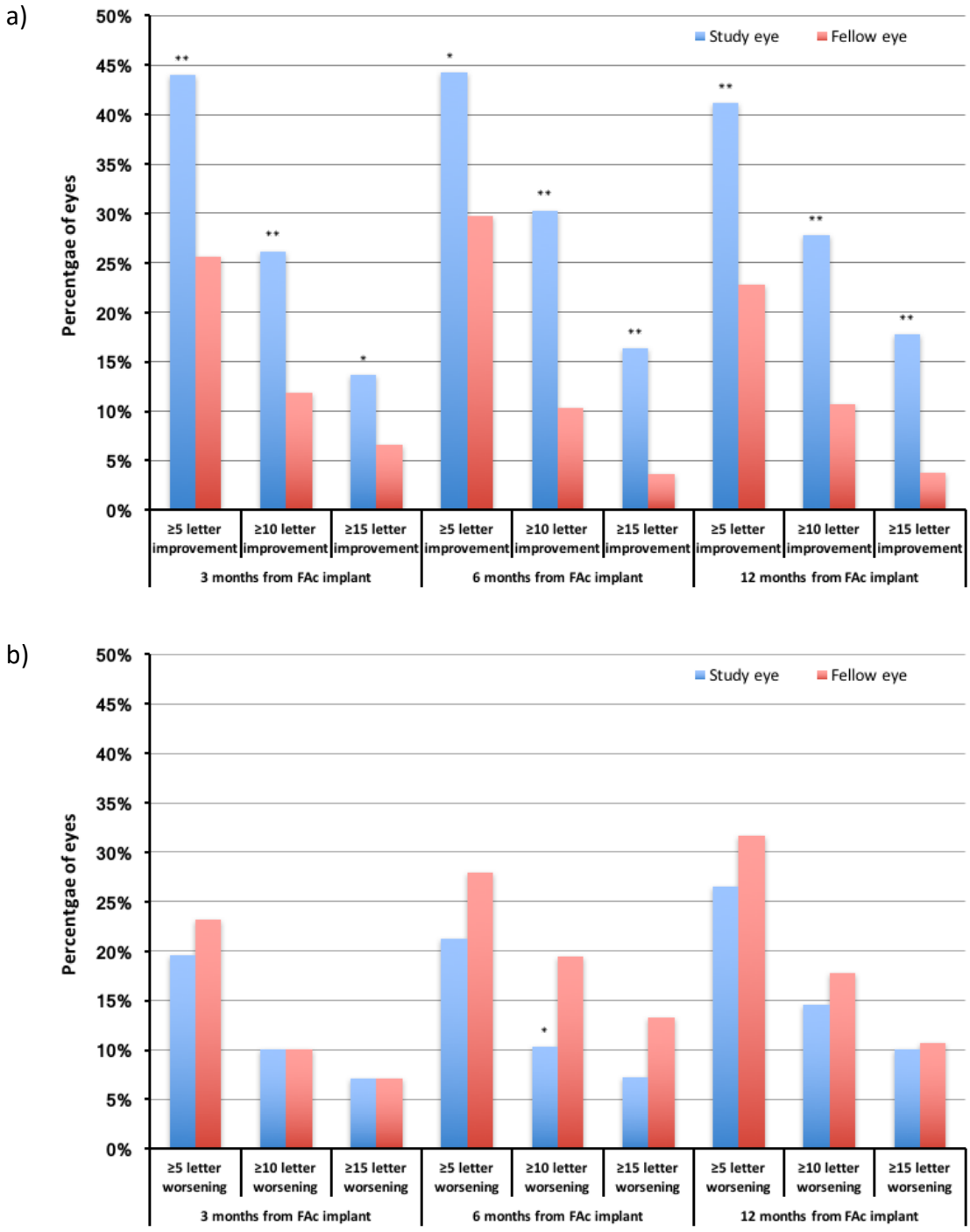


c) Change in central foveal thickness



Missing values were imputed using linear interpolation. Last observation carried forward was then used following the last recorded valu observation carried forward was used in the year before index date in order to impute missing values at the time of implant in the study

Figure 3 | Percentage of study and fellow eyes achieving a) ≥5, ≥10 and ≥15 letter improvement in ETDRS score and b) ≥5, ≥10 and ≥15 letter worsening in ETDRS score



* Indicates significance at the <0.05 level and **indicates significance at the <0.001 level.

Table 3 | Results from the generalised linear mixed model

Change in visual acuity (ETDRS letter score)	Parameter	Coefficient	Exponential of the c	
			Estimate	Lower CI
At 3 months				
≥5 letter improvement	Age	-0.008	0.992	0.964
	Baseline visual acuity	0.572	1.771	0.987
	Female	0.177	1.193	0.661
	Male (reference)	0		
	Insulin treatment	-0.037	0.963	0.501
	No insulin treatment (reference)	0		
	Intercept	-0.304	0.738	0.095
	Pseudophakic lens	0.07	1.073	0.504
	Phakic lens (reference)	0		
	Diabetes duration	-0.013	0.987	0.962
	Number of prior anti-VEGF injections	0.003	1.003	0.931
	Prior treatment for IOP	0.01	1.01	0.516
	No prior treatment for IOP (reference)	0		
	Number of prior laser therapies	-0.014	0.986	0.876
	Number of prior steroid injections[a]	-0.003	0.997	0.782
	Prior vitrectomy	0.142	1.153	0.537
	No prior vitrectomy (reference)	0		
	Study eye	0.737	2.09	1.127
	Fellow eye (reference)	0		
≤5 letter worsening	Age	0.022	1.023	0.987
	Baseline visual acuity	0.063	1.065	0.495
	Female	0.497	1.644	0.825
	Male (reference)	0		
	Insulin treatment	0.102	1.108	0.514
	No insulin treatment (reference)	0		
	Intercept	-2.872	0.057	0.004

	Pseudophakic lens	0.522	1.685	0.716
	Phakic lens (reference)	0		
	Diabetes duration	-0.008	0.992	0.963
	Number of prior anti-VEGF injections	0.066	1.069	0.978
	Prior treatment for IOP	-0.406	0.667	0.271
	No prior treatment for IOP (reference)	0		
	Number of prior laser therapies	0.041	1.041	0.899
	Number of prior steroid injections[a]	-0.378	0.685	0.439
	Prior vitrectomy	0.03	1.03	0.389
	No prior vitrectomy (reference)	0		
	Study eye	-0.08	0.923	0.451
	Fellow eye (reference)	0		
At 6 months				
≥5 letter improvement	Age	0.003	1.003	0.974
	Baseline visual acuity	0.725	2.064	1.107
	Female	0.51	1.665	0.917
	Male (reference)	0		
	Insulin treatment	-0.176	0.839	0.433
	No insulin treatment (reference)	0		
	Intercept	-1.203	0.3	0.035
	Pseudophakic lens	-0.139	0.871	0.411
	Phakic lens (reference)	0		
	Diabetes duration	0.005	1.005	0.978
	Number of prior anti-VEGF injections	0.025	1.025	0.951
	Prior treatment for IOP	0.059	1.061	0.547
	No prior treatment for IOP (reference)	0		
	Number of prior laser therapies	0.03	1.031	0.916
	Number of prior steroid injections[a]	-0.03	0.97	0.759
	Prior vitrectomy	0.184	1.202	0.554
	No prior vitrectomy (reference)	0		
	Study eye	0.516	1.676	0.882

	Fellow eye (reference)	0		
≤5 letter worsening	Age	0.008	1.008	0.974
	Baseline visual acuity	-0.075	0.928	0.428
	Female	0.906	2.475	1.276
	Male (reference)	0		
	Insulin treatment	-0.378	0.685	0.324
	No insulin treatment (reference)	0		
	Intercept	-1.115	0.328	0.028
	Pseudophakic lens	0.024	1.024	0.462
	Phakic lens (reference)	0		
	Diabetes duration	-0.004	0.996	0.967
	Number of prior anti-VEGF injections	0	1	0.916
	Prior treatment for IOP	-0.161	0.852	0.385
	No prior treatment for IOP (reference)	0		
	Number of prior laser therapies	0.04	1.041	0.905
	Number of prior steroid injections[a]	-0.148	0.863	0.612
	Prior vitrectomy	0.165	1.179	0.471
	No prior vitrectomy (reference)	0		
	Study eye	0.026	1.026	0.5
	Fellow eye (reference)	0		
At 12 months				
≥5 letter improvement	Age	-0.015	0.985	0.952
	Baseline visual acuity	0.426	1.531	0.808
	Female	0.507	1.661	0.847
	Male (reference)	0		
	Insulin treatment	-0.017	0.983	0.464
	No insulin treatment (reference)	0		
	Intercept	-0.476	0.622	0.05
	Pseudophakic lens	0.595	1.813	0.776
	Phakic lens (reference)	0		
	Diabetes duration	0	1	0.97
	Number of prior anti-VEGF injections	0.032	1.033	0.956

	Prior treatment for IOP	-0.141	0.869	0.436
	No prior treatment for IOP (reference)	0		
	Number of prior laser therapies	-0.038	0.962	0.845
	Number of prior steroid injections[a]	0.019	1.019	0.793
	Prior vitrectomy	0.07	1.073	0.438
	No prior vitrectomy (reference)	0		
	Study eye	0.606	1.832	0.921
	Fellow eye (reference)	0		
≤5 letter worsening	Age	-0.01	0.99	0.959
	Baseline visual acuity	-1.095	0.334	0.143
	Female	0.79	2.202	1.156
	Male (reference)	0		
	Insulin treatment	-0.76	0.468	0.222
	No insulin treatment (reference)	0		
	Intercept	0.561	1.752	0.169
	Pseudophakic lens	0.319	1.376	0.632
	Phakic lens (reference)	0		
	Diabetes duration	-0.005	0.995	0.967
	Number of prior anti-VEGF injections	0.058	1.06	0.982
	Prior treatment for IOP	-0.354	0.702	0.346
	No prior treatment for IOP (reference)	0		
	Number of prior laser therapies	-0.048	0.953	0.835
	Number of prior steroid injections[a]	-0.008	0.992	0.744
	Prior vitrectomy	0.927	2.527	1.069
	No prior vitrectomy (reference)	0		
	Study eye	0.114	1.12	0.546
	Fellow eye (reference)	0		