Comparison of data characterizing the clinical effectiveness of the fluocinolone intravitreal implant (ILUVIEN) in patients with diabetic macular edema from the real world, non-interventional ICE-UK study and the FAME randomized controlled trials

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ABSTRACT

Objective: To compare the effectiveness and safety of the fluocinolone acetonide (FAc) intravitreal implant between the observational Iluvien Clinical Evidence study in the United Kingdom (ICE-UK) and the Fluocinolone Acetonide in Diabetic Macular Edema (FAME) randomized controlled trials (RCTs) in people with diabetic macular edema (DME). Clinical Trials Registration: NCT00344968.

Methods: This study selected patients randomized to receive 0.2 mg/day FAc insert (FAc treated eyes) or sham injection (control eyes) from the FAME RCTs, and patients' first FAc treated eye and non-FAc treated fellow (control) eye from the ICE-UK study. Outcomes included change in visual acuity (VA), central foveal thickness (CFT), and intraocular pressure (IOP).

Results: After 12 months follow-up, mean change in VA was 5.0 letters improvement (p< .001) and 1.6 letters improvement (p¼ .003) in FAME FAc treated and control eyes, and 3.8 letters (p¼ .012) and –2.1 letters (p¼ .056) in ICE-UK FAc treated and control eyes, respectively. Mean change in CFT was –144 mm (p< .001) vs –72 mm (p< .001) in FAME FAc treated and control eyes and –113 mm (p< .001) vs –13 mm (p< .001) in ICE-UK FAc treated and control eyes. For eyes with a follow-up of 12 months, 77 (22.3%) and 15 (8.6%) FAME FAc treated and control eyes and 25 (18.7%) and six (4.3%) ICE-UK FAc treated and control eyes required emergent IOP-lowering therapy.

Conclusions: Statistically significant improvements in VA 12 months after FAc implantation were observed in both the real-world study and in the RCTs. The improvement in VA and CFT in the RCTs was marginally greater than in the real-world study; however, recruits in the real-world study had more severe visual morbidity at baseline. Whilst there were many changes in the care of people with DME over this time, these data all support the value of treatment with FAc intravitreal implant.

Introduction

The fluocinolone acetonide (FAc) 190 mg intravitreal implant is licensed in Europe for the treatment of vision impairment associated with chronic diabetic macular edema (DME) considered insufficiently responsive to available therapies. In the UK, the National Institute for Health and Care Excellence (NICE) has recommended that the FAc intravitreal implant should be used in eyes with a pseudophakic lens.

The Fluocinolone Acetonide in Diabetic Macular Edema (FAME) study programme comprised two separate, identically designed, randomized, sham-controlled trials (RCTs), FAME A and FAME B, and studied the clinical effectiveness of the FAc implant in treating DME. Following analysis of their combined data, the FAc intravitreal implant was found to provide visual benefit after 24 months (primary endpoint) and 36 months (end of study). However, these RCTs were conducted in an era in which laser photocoagulation was considered the standard of care for treatment-naïve patients with DME, and prior to the widespread use of intravitreal injections of anti-vascular endothelial growth factor (antiVEGF) therapy. Recently, anti-VEGF therapy has been shown in several RCTs to lead to an improvement in vision in people with DME; consequently, anti-VEGF therapy is now considered to be the first line treatment for DME, and NICE recommends anti-VEGF as a treatment option in eyes with a central retinal thickness of >400 mm. However, in routine clinical practice, second line treatment may become necessary: a suboptimal improvement (<5 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) in visual acuity (VA) has been estimated to occur in 40% of eyes treated with ranibizumab anti-VEGF therapy plus prompt or deferred laser treatment in a recent study. Therefore, further research is required to investigate the effectiveness of the FAc implant in patients insufficiently responsive to prior firstline anti-VEGF therapy.

The results of the observational ILUVIEN Clinical Evidence study in the UK (ICE-UK) have been published previously. The study was devised to investigate the effectiveness of the FAc implant in routine clinical practice in National Health Service (NHS) England eye units where patients were likely to have been previously exposed to anti-VEGF therapy. This was confirmed when the data were analyzed: a high proportion of FAc treated eyes had indeed been previously treated with anti-VEGF therapy. An improvement in median VA was observed at 12 months post-implant. When first FAc treated eyes were compared with their fellow eyes over the same period,

5 letter improvements in ETDRS score were achieved by more FAc treated eyes than by fellow eyes. Differences in the mean change in central foveal thickness (CFT) and intraocular pressure (IOP) were also observed between study and fellow eyes at 12 months. However, fellow eyes had better vision and thinner CFT at baseline. The role of real-world clinical evidence in supplementing RCT data has been recognized by regulatory authorities. RCTs are considered the gold standard study design to investigate the safety and efficacy of a therapy, due in part to the randomization of patients and masking of study treatments leading to a reduction in bias. However, unlike RCTs, which apply strict selection criteria, observational studies like the ICE-UK study include people that are likely to be more representative of patients receiving the FAc implant in the realworld setting. Results from the UK Medisoft Audit, a study using data from the electronic medical records of patients with DME treated with the FAc implant, have been descriptively compared with the results from the FAME study, and it was reported that IOP-related adverse events were experienced in similar frequencies. Here, we aim to compare descriptively the effectiveness and safety outcomes of the ICE-UK observational study with those of the FAME RCTs in order to determine whether the outcomes of observational studies using real-world data collected using a standardized method reflect outcomes observed from RCTs at 12 months.

Methods

Data source

In the FAME programme, patients were selected if they had a foveal thickness of 250 mm, despite at least one prior focal or grid macular laser photocoagulation treatment, and had a BCVA of between 19 and 68 ETDRS letters. Exclusion criteria included glaucoma, ocular hypertension, IOP 21 mmHg, or use of IOP-lowering therapy. A full list of inclusion and exclusion criteria for the FAME RCTs has been detailed by Campochiaro et al. Patients were randomized in a ratio of 2:2:1 to 0.2 mg/day or 0.5 mg/day FAc intravitreal insert or sham injection. Since the 0.2 mg/day FAc implant was the strength chosen for the license application, only those eyes that were randomized to the 0.2 mg/day intravitreal insert (the FAc treated eye) and sham injection (the control eye) were included in this comparison. From the ICEUK study, a patient's first eye treated with FAc (the FAc treated eye) and their fellow eye not treated with FAc (the control eye) were selected.

The index date was defined as the date of first FAc or sham injection in the FAME study and the date of first recorded FAc injection in the study eye in the ICE-UK study. In FAME, patients were censored at the earlier of 12 months following the index date or the date of discontinuation from the study, where applicable. In the ICE-UK dataset, patients were censored at the earlier of 12 months following the index date or on the date of FAc implantation in the fellow eye, where applicable.

Ethical approval statements for the FAME and ICE-UK studies have been described previously. Clinical Trials Registration: NCT00344968.

Outcomes

The outcomes of this study were changes in VA, CFT, and IOP over a 12-month follow-up period. Patients who were not censored prior to the follow-up time point were included in the analysis at 3, 6, and 12 months post-index date. For analyses studying trends in outcomes over time, patients with a follow-up of 12 months were included in the analysis. The occurrence of cataract operations and the administration of IOP-lowering therapy and anti-VEGF, steroid, and laser therapy were also investigated.

Data analysis and statistical methods

Previously, data from the FAME trials were analyzed using the visit number detailed on the data collection form in order to allocate the data to the correct follow-up time point (personal communication via email from Barry Kapik [barry.kapik@alimerasciences.com], Alimera Sciences, 5 October 2017). Here we used the visit date to identify the most relevant data to include at each follow-up time point. The methods devised to analyze the data collected in the ICE-UK study were applied here to the FAME data; these have been discussed previously. This may have led to some small differences between the FAME data presented here and the previously published findings. Here, aligning the methods used to analyze the data aided the comparison of the two studies. VA, CFT, and IOP were descriptively compared between index date and the follow-up time point using the Wilcoxon signed ranks test.

For the ICE-UK data, only pairs of observations recorded on the same date in each eye were selected. The exception to this was the analysis of any IOP increase during the 12-month period post-index date, where all IOP measurements were included, regardless of whether a measurement was recorded in the other eye on the same date.

In the ICE-UK study, best-corrected VA was measured by ETDRS score or by converting the logarithm of the minimum angle of resolution (LogMAR) score or Snellen fraction to approximate ETDRS letters using the method adopted by Gregori et al. In FAME, however, best-corrected VA was measured using an ETDRS chart only, and no conversion was required[5]. CFT was recorded using time domain ocular coherence tomography (TD-OCT, Stratus 3 instrument) in the FAME RCTs. However, there was no restriction on the type of OCT machine that could be used in the ICE-UK study.

Sub-group analysis

In order to compare groups of eyes with similar characteristics, several sub-group analyses were carried out.

In the UK, the FAc implant is licensed for the treatment of visual impairment associated with chronic DME considered insufficiently responsive to available therapies. Although the duration of diagnosed DME was not recorded in the ICE-UK study, it is likely that a high percentage of its patients were treated according to the licensed indication. However, in the FAME studies, patients were not required to have chronic DME, but were eligible for inclusion if they had a centre point thickness on OCT > 250 mm, despite prior focal/grid macular photocoagulation treatment and best-corrected VA between 19 and 68 ETDRS letters. Therefore, a sub-group analysis was carried out that included only those FAME FAc and control eyes that had been categorized as having chronic DME. The definition of chronic DME was based on a duration of diagnosed DME greater than or equal to the observed median duration of 3 years.

Patients were excluded from the FAME study if the VA in their study eye was <19 or >68 letters at screening. In order to account for difference in baseline vision between studies, patients from the ICE-UK and FAME studies were stratified by baseline VA into the following sub-groups: <20, 20–29, 30–39, 40–49, 50–59, 60–69, and 70 ETDRS letters.

Patients were excluded from the FAME studies if they had any of the following at screening: glaucoma, ocular hypertension, an IOP > 21 mmHg or concurrent IOP-lowering therapy. Therefore, a sub-group analysis was conducted comprising all FAME patients, but only those ICE-UK FAc treated eyes that had no prior glaucoma surgery, no prior IOP-lowering therapy, and an IOP of 21 mmHg at baseline (the application of these criteria resulted in the exclusion of 48 patients from the sub-group analysis). In the ICE-UK study, a patient's FAc treated eye and control eye might not have the same IOP at baseline or the same history of IOP-lowering intervention. Therefore, in order to avoid selecting ICE-UK FAc treated eyes without their matched control eye and vice versa, ICE-UK control eyes were excluded from the sub-group.

Results

In the FAME study, 376 patients were randomized to FAc, and 185 patients were randomized to sham. Of the FAME FAc patients, 375 patients were included in this study because the FAc implant attempt failed in one patient. In the ICE-UK study, data were collected on 311 patients, of whom 208 patients contributing 208 FAc treated, and 208 control eyes were eligible for inclusion in the study cohort, as described previously.

Three hundred and sixty-nine FAME FAc treated eyes, 184 FAME control eyes, and 200 ICE-UK FAc treated and control eyes had a follow-up 3 months. Of these, 367, 179, 181, and 181 eyes had a follow-up 6 months, and 352, 176, 171, and 171 had a follow-up 12 months, respectively.

Baseline characteristics

In the ICE-UK study, more patients were male (62% vs 57% and 58% for FAME FAc treated and control eyes, respectively) and older (mean age 66.7 years vs 63.2 and 62.1 years, respectively, Table 1). A higher percentage of eyes in the ICE-UK study had a pseudophakic lens, particularly for FAc treated eyes (89% for ICE-UK FAc treated eyes, 53% for ICEUK control eyes, 37% for FAME FAc treated eyes, and 35% for FAME control eyes). Mean VA at baseline was better in the FAME FAc treated and control eyes than in the ICE-UK FAc treated eyes (mean 53.3 and 54.7 ETDRS letters vs 47.2 letters, respectively, Table 1). However, ICE-UK control eyes had the best vision (mean 58.1 letters). Mean CFT was similar for FAME FAc treated (461.4 mm) and control eyes (451.3 mm) and ICE-UK FAc treated eyes (482.8 mm), but lower for ICE-UK control eyes (370.7 mm). IOP was similar across the four cohorts.

Visual acuity

FAME FAc treated eyes experienced the largest change in VA at 12 months post-index date (mean 5.0 letters, $p < .001$, Table 2). For ICE-UK FAc treated eyes, the mean change in VA was 3.8 letters ($p ¼ .012$) at the same time point. ICE-UK control eyes experienced the smallest improvement in vision (mean –2.1 letters at 12 months following index date, $p ¼ .056$). For FAME control eyes, mean change in VA was 1.6 letters at 12 months ($p ¼ .003$) post-index date.

At 12 months post-index date, 192 (55%) FAME FAc treated eyes, 69 (39%) FAME control eyes, 65 (41%) ICE-UK FAc treated eyes, and 36 (23%) ICE-UK control eyes achieved an improvement in VA of 5 letters (Figure 1a). VA worsened by 5 letters in 64 (18%) FAME FAc treated, 40 (23%) FAME control eyes, 42 (27%) ICE-UK FAc treated eyes, and 50 (32%) ICE-UK control eyes over the same follow-up period (Figure 1b).

In ICE-UK FAc treated eyes, mean VA improved over the first 4 months of follow-up (from mean 47.8 to 52.5 letters) before stabilizing (mean was 51.6 letters 12 months postindex date, Figure 2a). For FAME FAc treated eyes, mean VA increased from 53.3 letters at implant to 60.0 letters at 6 months post-index date before decreasing gradually to 58.3 letters at 12 months post-index date. For FAME control eyes, mean VA increased from 55.0 letters at implant to 57.4 letters at 2 months post-index date, before decreasing to 56.6 letters at 12 months post-index date. ICE-UK control eyes had the highest VA at index (60.6 letters), which decreased to 58.5 letters at 12 months post-index date.

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Table1. CharacteristicsattimeofFAcimplant.

	FAME						ICE-UK		
	AlleyesEyeswithchronicDMEAlleyes								
	FAcControlFAcControlFAcControl								
N	375185209112208208								
Males,n %)215(57%)108(58%)120(57%)68(61%)128(62%)128(62%									
Age,years,mean(SD)63.2(9.39)62.1(9.71)63.9(8.94)63.1(9.43)66.7(10.69)66.7(10.69)									
Diabetestype									
Type1diabetes									
n %)29(8%)13(7%)18(8%)10(7%)32(15%)32(15%									
Timesincediagnosis,years									
Mean(SD)28.6(11.28)22.8(9.79)30.7(10.69)24.9(8.32)30.7(12.5)30.7(12.5)									
Median(IQR)27(22	−35)21(17	−30)30(23	−39)24(19	−30)31(22.5	−37.5)31(22.5	−37.5)			
Type2diabetes									
n %)340(91%)170(92%)186(91%)101(92%)176(85%)176(85%									
Timesincediagnosis,years									
Mean(SD)16.1(8.61)15.9(8.24)17.2(8.43)17.21(8.02)18(10.3)18(10.3)									
Median(IQR)16(10	−21)16(10	−21)17(11	−22)17(12	−21)17(10	−25)17(10	−25)			
Uncertain									
n %)6(2%)2(1%)5(2%)1(1%)0(0%)0(0%									
Timesincediagnosis,years									
Mean(SD)13.5(4.51)21(2.83)14.0(4.85)19									
Median(IQR)12(10	−18)21(19	−23)13(10	−18)19(19	−19)					
Lensstatus, n %)									
Phakic235(63%)121(65%)114(55%)66(59%)23(11%)97(47%)									
Pseudophakic140(37%)64(35%)95(45%)46(41%)185(89%)111(53%)									
VA,ETDRSletters,mean(SD)53.3(12.7)54.7(11.27)52.2(13.36)54.0(11.15)47.2(19.5)58.1(21.99)									
CST,µm,mean(SD)463.5(143.28)452.6(128.8)460.1(151.46)456.3(130.23)471.4(162.24)369.8(147.02)									
CFT,µm,mean(SD)461.4(160.17)451.3(151.97)456.2(165.89)461.8(153.5)482.8(188.52)370.7(176.49)									
IOP,mmHg,mean(SD)15.2(2.94)15(3.08)15.0(2.93)15.2(2.77)15.5(3.34)15.9(3.7)									

Abbreviations.FAME,FluocinoloneAcetonideinDiabeticMacularEdema;ICE-UK,ILUVIENClinicalEvidenceStudyintheUK;SD,standarddeviation; IQR,interquartilerange; n,number;VA,visualacuity;CST,central subfieldthickness;CFT,centralfovealthickness;IOP,intraocularpressure;DME,diabeticmacularedema.

Table 2. Visual acuity, central foveal thickness, and intraocular pressure at index date and at 3, 6, and 12 months follow-up.

		Time from baseline (months)	Count	Baseline		Follow-up time point		Change between baseline and follow-up time point		*p*-value
				Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Visual acuity, ETDRS letters										
All FAME eyes	FAc	3	367	53.2 (12.7)	57 (46–63)	59.3 (14.4)	63 (52–69)	6.1 (10.1)	6 (1–11)	<.001
		6	366	53.3 (12.7)	57 (46–63)	59.7 (15.2)	62.5 (52–71)	6.4 (11.7)	6.5 (1–12)	<.001
		12	351	53.3 (12.7)	57 (46–63)	58.3 (16)	61 (50–70)	5.0 (14.8)	6 (−2–13)	<.001
	Control	3	184	54.7 (11.3)	58 (48–63)	57.4 (14.5)	59 (50–68)	2.6 (10)	3 (−2–8)	<.001
		6	179	54.7 (11.3)	58 (48–63)	57.1 (14.4)	59 (48–68)	2.4 (10.3)	3 (−3–8)	<.001
		12	176	55.0 (11)	58 (48.5–63)	56.6 (15.1)	58.5 (48.5–68)	1.6 (12.4)	2 (−3.5–8)	.003
FAME with chronic DME	FAc	3	207	52.1 (13.4)	55 (44–63)	59.3 (14.3)	62 (52–69)	7.1 (9.2)	6 (1–12)	<.001
		6	207	52.1 (13.4)	55 (44–63)	60.4 (14.6)	63 (54–71)	8.3 (10.2)	8 (2–13)	<.001
		12	200	52.3 (13.3)	55 (45–63)	58.6 (16.5)	63 (50–71)	6.3 (15.3)	7 (0–14.5)	<.001
	Control	3	112	54.0 (11.1)	57.5 (47.5–63)	56.5 (13.4)	58 (47.5–65.5)	2.5 (10.4)	2.5 (−2–8)	.001
		6	110	54.1 (11.1)	57.5 (48–63)	55.8 (12.4)	57 (48–65)	1.7 (9.7)	2 (−3–7)	.03
		12	110	54.1 (11.1)	57.5 (48–63)	55.7 (13.4)	58 (47–65)	1.7 (11.6)	2 (−3–7)	.028
All ICE-UK eyes	FAc	3	168	47.5 (20)	51 (35–61)	51.4 (20.2)	57 (40–65)	3.9 (15.5)	0 (0–10)	<.001
		6	165	47.6 (19.4)	50 (35–60)	52.2 (18.8)	55 (40–65)	4.6 (16.1)	3 (0–10)	<.001
		12	158	47.8 (19.3)	50 (35–60)	51.6 (18.4)	55 (40–65)	3.8 (17.1)	1 (−5–10)	.012
	Control	3	168	58.7 (21.8)	65 (45.5–75)	59.2 (22.5)	69.5 (45–75)	0.5 (12.6)	0 (−2–5)	.513
		6	165	60.5 (20.5)	68 (50–75)	58.9 (22.1)	65 (45–75)	−1.5 (13.3)	0 (−5–5)	.290
		12	158	60.6 (20.8)	67 (50–75)	58.5 (21.6)	65 (45–75)	−2.1 (11.8)	0 (−6–4)	.056
Central foveal thickness, μm										
All FAME eyes	FAc	3	357	463.6 (161.3)	455 (341–572)	333.8 (149.3)	308 (225–427)	−129.8 (151.2)	−104 (−214– −34)	<.001
		6	357	462.6 (161.4)	450 (334–572)	318.6 (147.8)	290 (208–404)	−144.0 (162.4)	−110 (−217– −34)	<.001
		12	342	463.6 (161.2)	450.5 (334–571)	313.3 (160.9)	280.5 (186–403)	−150.2 (169.3)	−117 (−252– −42)	<.001
	Control	3	180	451.0 (152.5)	458.5 (324.5–529)	436.7 (183.8)	418 (306.5–536.5)	−14.3 (141)	−12 (−88–58)	.127
		6	176	450.8 (152.4)	458.5 (324.5–529)	407.7 (185.1)	387 (274.5–527.5)	−43.1 (157.5)	−31 (−114.5–47)	<.001
		12	173	453.7 (152)	460 (329–529)	381.7 (195.7)	355 (223–520)	−72.0 (181.1)	−59 (−165–33)	<.001
FAME eyes with chronic DME	FAc	3	205	457.2 (165.6)	440 (319–555)	324.2 (146.3)	295 (216–405)	−133.0 (148.2)	−100 (−211– −35)	<.001
		6	205	457.2 (165.6)	440 (319–555)	315.2 (147.5)	282 (208–386)	−142.0 (158.5)	−106 (−215– −37)	<.001
		12	198	457.2 (166.7)	438 (319–555)	304.8 (157.8)	276 (172–399)	−152.4 (178.5)	−112.5 (−252– −36)	<.001
	Control	3	110	462.4 (154.1)	469.5 (350–549)	443.3 (180.8)	425.5 (320–558)	−19.1 (130.2)	−13 (−104–55)	.107
		6	110	459.3 (153.5)	462 (350–544)	403.4 (165.7)	383 (280–527)	−55.9 (134.2)	−38 (−121–40)	<.001
		12	109	459.3 (153.5)	462 (350–544)	378.6 (178.9)	365 (235–525)	−80.7 (167.2)	−64 (−165–17)	<.001
All ICE-UK eyes	FAc	3	118	482.1 (184.8)	470.5 (365–603)	395.6 (200.6)	367 (254–478)	−86.5 (189.3)	−66 (−188–5)	<.001
		6	118	475.6 (185.6)	461 (362–588)	385.4 (199.5)	358.5 (240–471)	−90.2 (218.3)	−74.5 (−208–9)	<.001
		12	114	470.7 (179.7)	458.5 (365–579)	357.7 (185.3)	324.5 (222–453)	−113.1 (215.8)	−102 (−219–9)	<.001
	Control	3	118	360.7 (180.9)	318.5 (247–399)	357.8 (201.7)	306.5 (244–377)	−2.9 (121.9)	−3.5 (−49–18)	.113
		6	118	346.6 (165.8)	317.5 (242–383)	343.7 (185.1)	293.5 (235–378)	−2.9 (123.2)	−5.5 (−55–26)	.130
		12	114	342.6 (167.5)	307 (239–377)	329.6 (176.8)	280 (222–357)	−13.0 (121)	−10 (−58–21)	.030
Intraocular pressure, mmHg										
All FAME eyes	FAc	3	367	15.19 (2.9)	15 (13–18)	17.49 (4.5)	17 (15–20)	2.31 (4.3)	2 (0–5)	<.001
		6	366	15.15 (2.9)	15 (13–17)	17.87 (5.5)	17 (14–20)	2.72 (5.4)	2 (0–5)	<.001
		12	351	15.18 (2.9)	15 (13–18)	17.58 (4.8)	18 (14–20)	2.4 (4.8)	2 (0–4)	<.001
	Control	3	184	15.05 (3.1)	15 (12–18)	14.89 (3.3)	15 (12–17)	−0.17 (3)	0 (−2–1.5)	.309
		6	179	15 (3.1)	15 (12–18)	15.11 (3.6)	14 (12–17)	0.11 (3.7)	0 (−2–2)	.876
		12	176	15.04 (3)	15 (12–18)	15.79 (4.8)	16 (13–18)	0.75 (4.7)	0 (−2–3)	.116
FAME eyes with chronic DME	FAc	3	207	15.02 (2.9)	15 (13–17)	17.07 (4.2)	17 (14–20)	2.05 (4)	2 (0–4)	<.001
		6	207	15.02 (2.9)	15 (13–17)	17.26 (5)	17 (14–20)	2.24 (4.9)	1 (0–4)	<.001
		12	200	15.01 (3)	15 (13–17)	17.37 (4.4)	17 (14–20)	2.36 (4.5)	2 (0–5)	<.001
	Control	3	112	15.17 (2.8)	15 (13–18)	15.13 (3.1)	15 (13–17)	−0.04 (2.9)	0 (−2–2)	.746
		6	110	15.13 (2.8)	15 (13–18)	15.24 (3.6)	14 (13–17)	0.11 (3.7)	0 (−2–2)	.750
		12	110	15.13 (2.8)	15 (13–18)	16.05 (5.4)	16 (13–18)	0.93 (5.4)	0 (−2–2)	.241
All ICE-UK eyes	FAc	3	116	15.77 (3.3)	15.3 (13.1–18)	17.64 (6.6)	17 (14–20)	1.87 (6.4)	1 (−1.5–4)	.001
		6	121	15.53 (3.3)	15 (13–18)	17.96 (6.7)	17 (14–20)	2.42 (6.8)	1 (−1–5)	<.001
		12	120	15.61 (3.2)	15 (13–18)	18.85 (6.7)	18 (14–21)	3.23 (7.3)	2 (−1.35–6)	<.001
	Control	3	116	16.19 (3.7)	16 (14–18)	16.74 (5.5)	16 (14–18)	0.55 (5.3)	0 (−2–3)	.313
		6	121	15.94 (3.7)	16 (14–18)	16.32 (4.6)	16 (14–18)	0.39 (5.2)	0 (−2–3)	.474
		12	120	16.09 (3.8)	16 (14–18)	15.88 (3.6)	15 (14–18)	−0.21 (4.7)	0 (−2.5–3)	.923

The statistical significance of the difference between baseline and follow-up was tested using a Wilcoxon signed rank test. Threshold statistical significance was selected at a *p*-value less than 0.05.

Abbreviations. SD, standard deviation; IQR, interquartile range; FAME, Fluocinolone Acetonide in Diabetic Macular Edema; ICE-UK, ILUVIEN Clinical Evidence Study in the UK; FAc, fluocinolone acetonide; DME, diabetic macular edema.

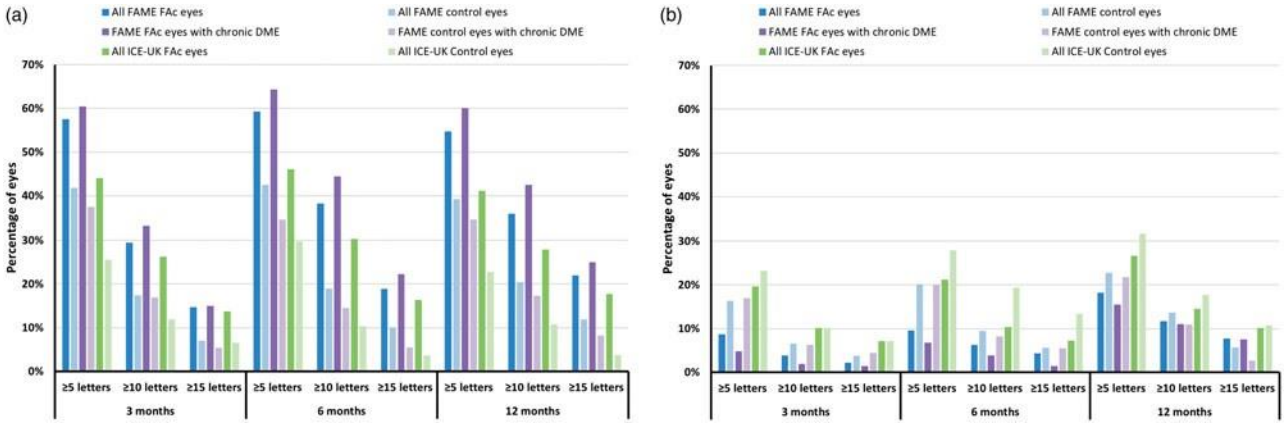

Figure 1. Percentage of FAc treated and control eyes achieving (a) 5, 10, and 15 letter improvement in ETDRS letter score and (b) 5, 10, and 15 letter worsening in ETDRS letter score. Abbreviations. FAME, Fluocinolone Acetonide in Diabetic Macular Edema; ICE-UK, ILUVIEN Clinical Evidence Study in the UK; FAc, fluocinolone acetonide; DME, diabetic macular edema.

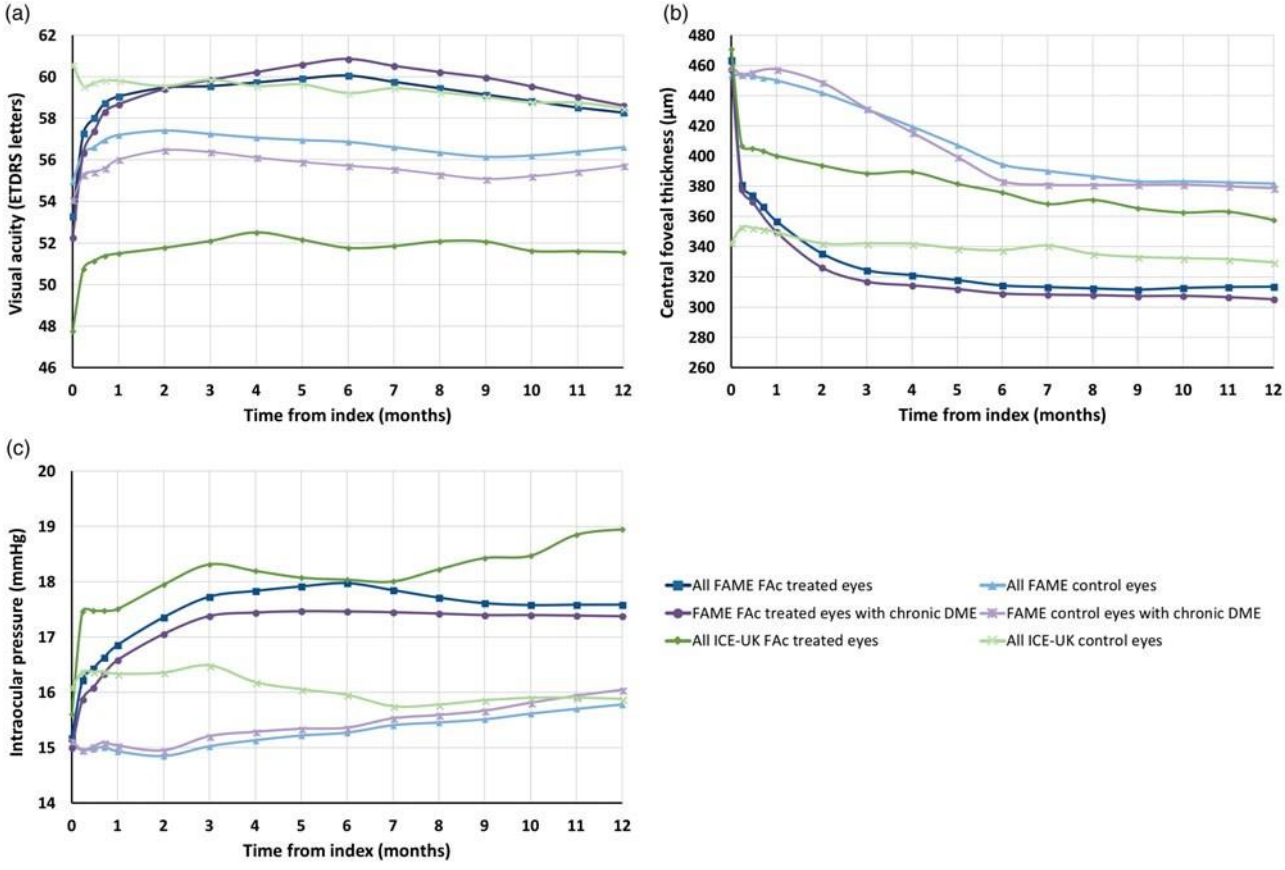

Figure 2. Mean change in (a) visual acuity, (b) central foveal thickness, and (c) intraocular pressure over 12 months follow-up. Patients who were not censored on or before 365 days following the index date were included. For visual acuity, all FAME FAc treated eyes ¼ 351 eyes, all FAME sham eyes ¼ 176 eyes, FAME FAc treated eyes with chronic DME ¼ 200, FAME control eyes with chronic DME ¼ 110, all ICE-UK study eye ¼ 158 eyes, all ICE-UK fellow eyes ¼ 158 eyes. For central foveal thickness, all FAME FAc treated eyes ¼ 342 eyes, all FAME control eyes ¼ 173 eyes, FAME FAc treated eyes with chronic DME ¼ 198, FAME control eyes with chronic DME ¼ 109, all ICE-UK FAc treated eyes ¼ 114 eyes, all ICE-UK control eyes ¼ 114 eyes. For intraocular pressure, all FAME FAc treated eyes ¼ 351 eyes, all FAME control eyes ¼ 176 eyes, FAME FAc treated eyes with chronic DME ¼ 200, FAME control eyes with chronic DME ¼ 110, all ICE-UK FAc treated eyes ¼ 120 eyes, all ICE-UK control eyes ¼ 120 eyes. Abbreviations. FAME, Fluocinolone Acetonide in Diabetic Macular Edema; ICE-UK, ILUVIEN Clinical Evidence Study in the UK; FAc, fluocinolone acetonide; ETDRS, Early Treatment Diabetic Retinopathy; DME, diabetic macular edema.

A similar trend in VA was observed in FAME FAc treated 84 days following implant and slightly better on and after 84 and control eyes with chronic DME and in all eligible FAME days following implant when compared with all eligible FAc FAc treated and control eyes. However, mean VA was slightly treated eyes. For FAME control eyes, mean VA was slightly worse in FAME FAc treated eyes with chronic DME in the first worse in those eyes with chronic DME when compared with all eligible eyes at each of the time intervals post-implant. Therefore, the difference in mean VA between FAME FAc treated eyes and FAME control eyes was greater in the chronic DME sub-group than was observed in all eligible FAME eyes.

Stratification by visual acuity at baseline

For FAME FAc treated eyes and baseline VA sub-groups between 20 and 69 letters, median change in VA at 12 months decreased with increasing baseline VA sub-group (median change was 18.0 letters in those eyes with a baseline VA of 20–29 letters and 4.0 letters in those eyes with a baseline VA of 60–69 letters, Supplementary Figure 1). For FAME control eyes, median change in VA at 12 months post-index date was relatively stable across the sub-groups (median change of 3.0, 2.5, 3.0, and 2.0 letters for baseline VA sub-groups between 30–39, 40–49, 50–59, and 60–69 letters, respectively). Similarly, for ICE-UK FAc treated eyes, the largest median change in VA at 12 months post-index date was observed in those eyes with a baseline VA of <20 letters (median change ¼ 13.0 letters). The second highest median change in VA in this cohort was observed in those with a baseline VA score of 30–39 letters (median change 5.0 letters). Median change in VA was 0.5 letters in ICE-UK FAc treated eyes with a VA score of 50–59 letters and 70 letters at baseline, and zero in those eyes with a VA of 20–29 letters, 40–49 letters, and 60–69 letters at baseline.

Central foveal thickness

FAME FAc treated eyes experienced the largest change in mean CFT at 12 months post-index date (–150.2 mm, $p < .001$, Table 2). Large mean changes in CFT were also observed in ICE-UK FAc treated eyes at 12 months post index date (–113.1 mm, $p < .001$). Mean change in CFT was lower for FAME control eyes than for FAME FAc treated eyes, but a statistically significant difference in CFT was observed at 12 months post index date (–72.0 mm, $p < .001$). Mean change in CFT was lowest for ICE-UK control eyes, but a statistically significant decrease in CFT was observed at 12 months postindex date (mean change –13.0 mm, p ¼ .030).

Mean CFT decreased to the greatest extent in FAME FAc treated eyes (mean CFT was 464 mm at index date, 359 mm at 1 month post-index and 314 mm at 7 months post-index date before stabilizing, Figure 2b). For ICE-UK FAc treated eyes, mean CFT decreased from 471 mm at index date to 401 mm at 1 month, 371 mm at 7 months, and 358 mm at 12 months post-index date. A similar but smaller decrease in mean CFT was observed in FAME control eyes (454 mm, 451 mm, 392 mm, and 382 mm, respectively, at the same follow-up time points). The trend observed in mean CFT in ICE-UK control eyes was different from that observed in the other three cohorts, with mean CFT remaining relatively stable over the 12 months of follow-up.

Intraocular pressure

A small, statistically significant increase in mean IOP was observed in FAME FAc treated eyes and ICE-UK FAc treated eyes at 12 months post-index date (2.4 mmHg [$p < .001$] and 3.23 mmHg [$p < .001$], respectively, Table 2). No statistically significant change in IOP was observed in FAME and ICE-UK control eyes.

In FAME FAc treated eyes, mean IOP was 15.2 mmHg at index date, increasing to 18.0 mmHg at 6 months, before decreasing to 17.6 mmHg at 12 months post-index date (Figure 2c). In ICE-UK treated eyes, mean IOP increased from 15.6 mmHg at baseline to 18.3 mmHg at 3 months, decreasing to 18.0 mmHg at 6 months before increasing to 18.9 mmHg at 11 months post-index date. Mean IOP in ICE-UK FAc treated eyes was 18.8 mmHg at 12 months post-index date. IOP remained relatively stable in ICE-UK control eyes and increased slightly in FAME control eyes (mean IOP was 15.0 mmHg at baseline and 15.8 mmHg at 12 months post-index date).

Between index date and the end of the 12-month follow up period, an IOP of 30 mmHg was recorded on at least one occasion in 11.1% of FAME FAc treated eyes, 12.1% of ICE-UK FAc treated eyes, 2.3% of FAME control eyes and 5.0% of ICE-UK control eyes (Figure 3a). In the sub-group analysis comprising only those ICE-UK FAc treated eyes with no history of raised IOP, 7.5% of ICE-UK FAc treated eyes had an IOP 30 mmHg on at least one occasion during the 12month follow-up period.

When compared with FAME FAc treated eyes, a higher percentage of ICE-UK FAc treated eyes experienced an IOP increase of 10 mmHg at any time between index date and 12 months follow-up (25.0% vs 21.1%, Figure 3b). The corresponding percentages for FAME and ICE-UK control eyes were 5.1% and 8.3%, respectively. In the sub-group analysis of ICE-UK FAc treated eyes having no history of raised IOP, 19.4% of ICE-UK FAc treated eyes experienced a change in IOP of 10 mmHg at any point between index date and 12 months follow-up.

Of those eyes with a minimum follow-up of 12 months, seven (2.0%) FAME FAc treated eyes, one (0.6%) FAME control eye, 37 (21.6%) ICE-UK FAc treated eyes, and 30 (17.5%) ICEUK control eyes had a history of receiving IOP-lowering therapy on or prior to the

index date. Of the remaining eyes, 77 (22.3%), 15 (8.6%), 25 (18.7%), and six (4.3%) required emergent IOP-lowering therapy over the 12-month follow-up period, respectively. The percentages of eyes requiring emergent IOP-lowering therapy between 0–3 months, 3–6 months, and 6–12 months post-index are described in Figure 3c.

Three FAME FAc treated eyes (0.9%; all conventional surgeries), one ICE-UK FAc treated eye (0.6%; selective laser trabeculoplasty), and two ICE-UK FAc treated eyes (1.2%; both conventional surgeries) required surgery for glaucoma over the 12-month follow-up period.

Cataract operations

Of those eyes with a minimum follow-up of 12 months, 221 (62.8%) FAME FAc treated eyes, 115 (65.3%) FAME control eyes, 18 (10.5%) ICE-UK FAc treated eyes, and 83 (48.5%) ICEUK control eyes had a natural lens at baseline. Of these, nine (50%) ICE-UK FAc treated eyes and one (1.2%) ICE-UK control eye had a cataract operation on the index date. Of the remaining phakic eyes, 38 (17.2%) FAME FAc treated eyes, 12 (10.4%) FAME control eyes, three (33.3%) ICE-UK FAc treated eyes and 10 (12.2%) ICE-UK control eyes had a cataract operation during the 12-month follow-up period.

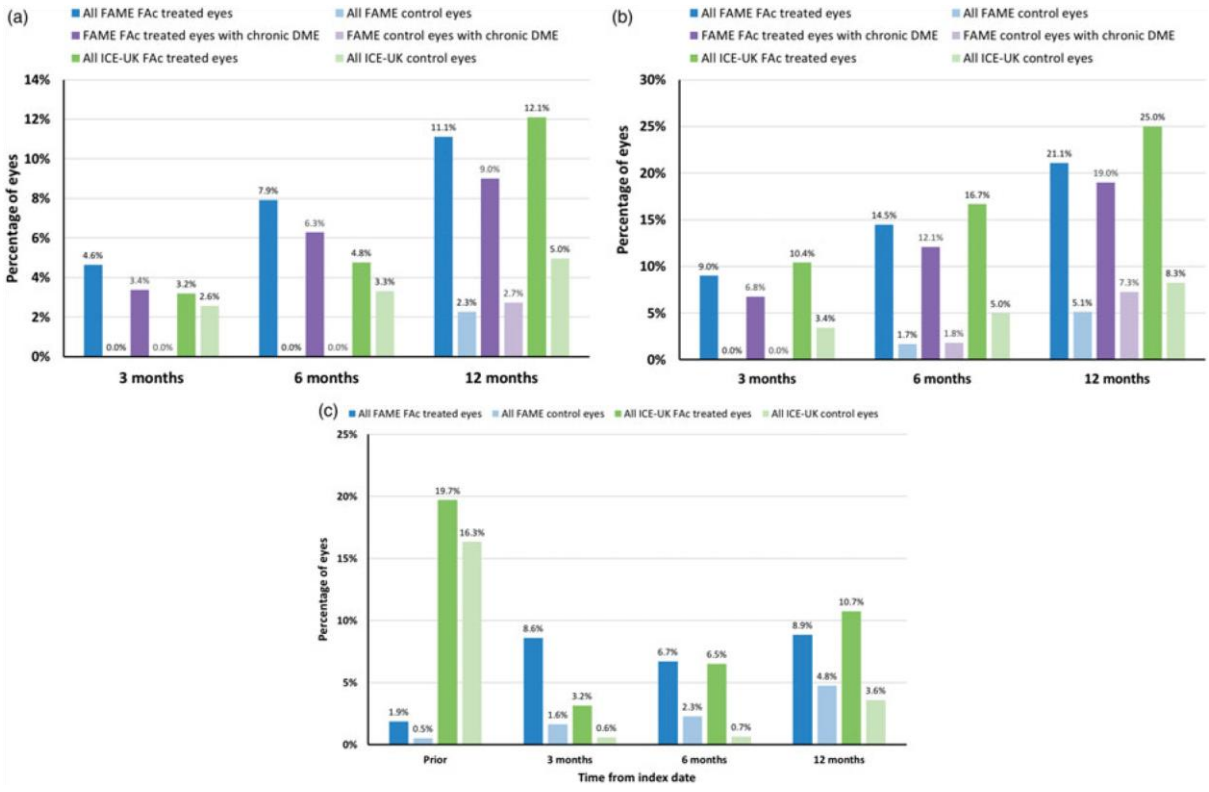

Figure 3. Percentage of eyes (a) with an intraocular pressure 30 mmHg, (b) with a change in intraocular pressure of 10 mmHg, and (c) requiring emergent intraocular pressure-lowering therapy at any time between index date and 3, 6, and 12 month follow-up time points. Abbreviations. FAME, Fluocinolone Acetonide in Diabetic Macular Edema; ICE-UK, ILUVIEN Clinical Evidence Study in the UK; FAc, fluocinolone acetonide; DME, diabetic macular edema.

Other interventions

No patients in the ICE-UK study received a second FAc implant in their FAc treated eye within the 12-month followup period; 2.8% of FAME FAc treated eyes and 5.1% of FAME control eyes received a second FAc implant within the 12 months follow-up period (all were administered more than 11 months from index date). After the index date, a higher proportion of FAc treated and control eyes in the ICE-UK study received anti-VEGF therapy compared with those in the FAME RCTs (Figure 4a). Compared with FAc treated eyes, a larger percentage of control eyes received anti-VEGF therapy between 6–12 months follow-up in the FAME RCT and between 0–3 months, 3–6 months, and 6–12 months in the ICE-UK study. In the FAME study, a larger percentage of control eyes than of FAc treated eyes received other steroid therapy (Figure 4b); in the ICE-UK study, the opposite was true. A higher percentage of FAME FAc treated and control eyes received laser photocoagulation compared with ICE-UK FAME FAc and control eyes (Figure 4c).

Discussion

In the FAME trial, statistically significant improvements in VA and CFT were observed over the 12-month follow-up period in FAc treated eyes, all of which had previously undergone laser therapy. The rapid and sustained improvements in VA and CFT observed in these treated eyes were greater than those observed in the FAME control eyes. In the sub-group of FAc treated patients with chronic DME who had worse vision and CFT compared with the entire cohort, even greater improvements in VA compared with the control arm were observed. In the ICE-UK study, statistically significant improvements in VA and CFT were observed in FAc treated eyes, a large proportion of which had previously been exposed to anti-VEGF therapy. However, the mean change in VA and CFT observed over the 12-month follow-up period was marginally greater in FAME FAc treated eyes than in their ICE-UK counterparts. A small deterioration in VA and CFT was observed in ICE-UK control eyes over the same period.

Patients treated with FAc in real-world clinical practice differed in several respects from those selected for inclusion in the FAME studies. In the UK, NICE restricts the use of first line anti-VEGF therapy to patients whose CFT is > 400 mm, and then these patients need to demonstrate a sub-optimal response to these first-line therapies prior to receiving the FAc intravitreal implant. Therefore, it could reasonably be assumed that many of the patients included in the ICE-UK study could be defined as having chronic DME. It is probable that the majority of patients in the ICE-UK study were treated in accordance with the licensed indication for the

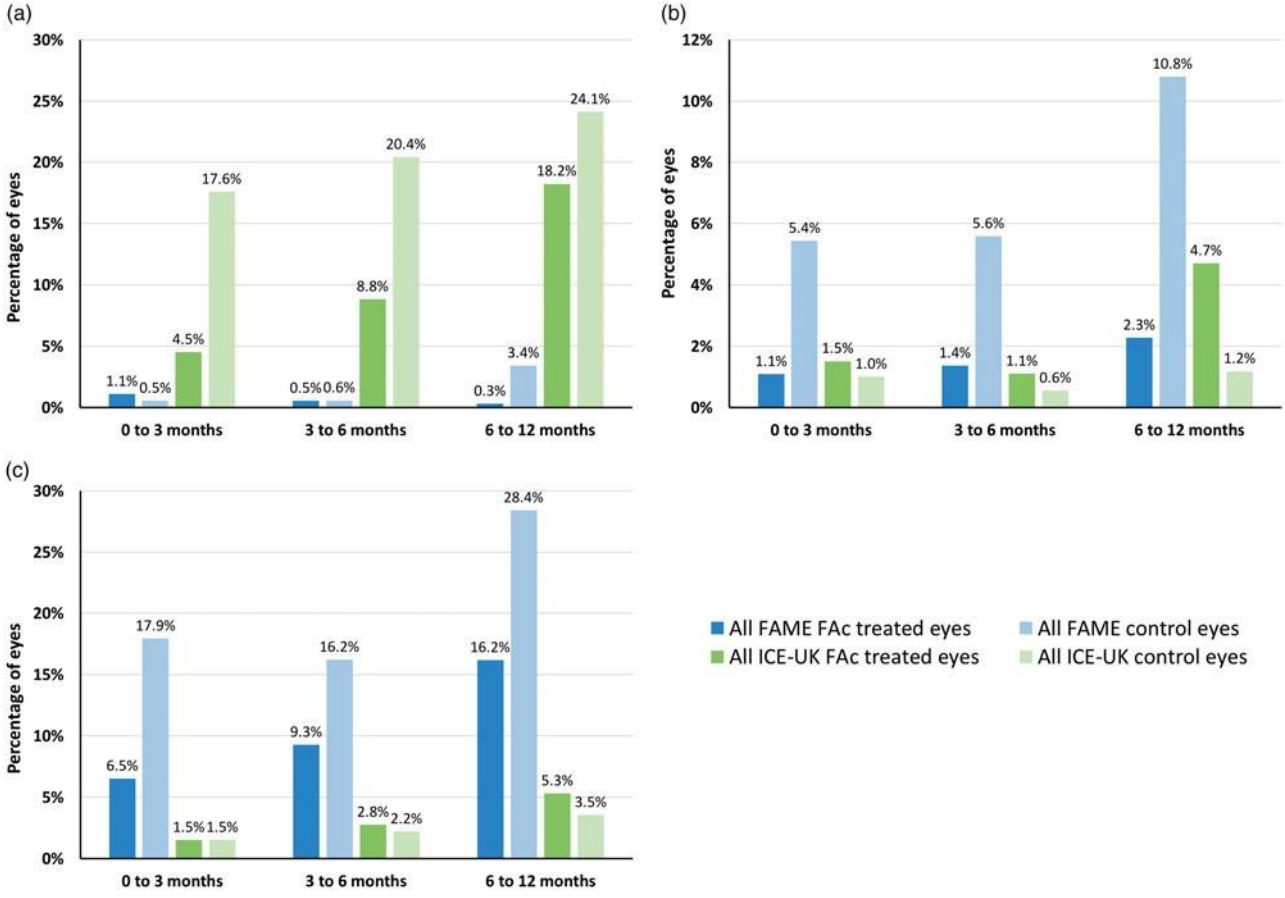

Figure 4. Percentage of eyes prescribed (a) anti-VEGF therapy, (b) steroid therapy, and (c) laser photocoagulation Abbreviations. FAc, fluocinolone acetonide; anti- VEGF, anti-vascular endothelial growth factor.

FAc implant. A high percentage of FAc treated eyes in that study were likely to have chronic DME. A high proportion of ICE-UK FAc treated eyes had been previously exposed to anti-VEGF therapy (82%), the current first line therapy for DME[14]. In addition, 41% had previously received steroid therapy and 61% had previously received laser therapy[14]. We have previously reported that, despite receiving routine clinical care, little change in mean VA occurred in the 12 month period prior to FAc implantation[14]. In comparison, patients enrolled in the FAME study were only required to have previously received laser photocoagulation therapy more than 12 weeks prior to screening[5]. Insufficient response to this therapy was not a requirement for patient selection. Although history of treatment with anti-VEGF therapy, intravitreal steroids and laser photocoagulation was not systematically collected at screening in the FAME RCTs, these trials were conducted prior to the widespread use of anti-VEGFs in DME.

A higher percentage of ICE-UK FAc treated eyes were pseudophakic at baseline compared with FAME FAc treated and control eyes. This is likely to be due to the recommendation by NICE that the FAc intravitreal implant be used only in eyes with pseudophakic lenses[1]. In real-world clinical practice, physicians may also be more reluctant to administer FAc in patients with a phakic lens due to the risk of progression to cataract. Conversely, study eyes in the FAME RCTs were not required to have a pseudophakic lens. In a post hoc analysis of the FAME data by Yang et al., comparable improvements in VA were observed in patients who underwent cataract extract before and after FAc insertion.

Patients treated with FAc in the ICE-UK study were also older and had a longer duration of diagnosed diabetes. NICE guidelines recommend that first-line anti-VEGF therapy should only be initiated in eyes with DME and a retinal thickness 400 mm , suggesting that most ICE-UK FAc treated eyes would have had a retinal thickness 400 mm at some point in their history.

The findings described above suggest that patients treated with FAc in the ICE-UK study may have had worse eye disease and an increased chronicity of DME compared with the patients enrolled in the FAME studies. In support of this thesis, the mean baseline VA and CFT were worse in ICE-UK FAc treated eyes than in their FAME counterparts. However, despite this difference in starting vision, mean VA improved in both FAME and ICE-UK FAc treated eyes. Nevertheless, the differences in the patients treated with FAc in FAME and in the real-world ICE-UK study could have had an impact on the magnitude of the improvements observed. The chronic DME subset of the FAc treated patients in the FAME trials showed greater improvement in VA over the follow-up period than did the entire FAc treated cohort, in spite of worse baseline vision and CFT. However, the ICE-UK treated eyes had still worse VA and CFT at baseline. It is, therefore, conceivable that the FAc treated eyes in the ICE-UK study had greater chronicity of DME than even the chronic DME subgroup of the FAME trials. Since the duration of diagnosed DME was not recorded in the ICE-UK study, it was not possible to determine if this was the case.

Differences in the populations of the FAME and ICE-UK studies at baseline and after 12 months follow-up could also be due in part to the application of strict inclusion and exclusion criteria in the FAME RCTs. For example, the exclusion in FAME of patients with a VA <19 or >68 ETDRS letters in the study eye led to differences in VA between FAME and ICE-UK eyes at baseline. Mean VA at baseline was highest in ICE-UK control eyes and worst in ICE-UK FAc treated eyes, and a wider range of VA was observed in the ICE-UK FAc treated cohort than in its FAME counterpart. To account for this difference in baseline vision we also report a sub-group analysis in which patients were stratified by their VA at baseline. Here, in the FAME FAc treated eyes, a clear trend towards a decreasing median change in VA with improving VA at baseline was evident. In the ICE-UK FAc treated eyes, the greatest median change in VA was observed in eyes with a baseline VA of <20 and between 30–39 letters at baseline.

In the FAME trials, for subjects with unilateral DME, the affected eye was selected. In patients with bilateral DME, the most severely affected eye was selected as the study eye and randomized to receive FAc or sham injection; therefore, the baseline characteristics between FAME FAc treated and control eyes were comparable. In the ICE-UK study, the FAc implant was inserted in the worst-seeing eye in 70% of cases. Differences in the baseline characteristics of the ICEUK FAc treated eyes and control eyes at baseline, therefore, make any comparison of the difference in the change in VA or CFT between FAME and ICE-UK study arms inappropriate. However, ICE-UK control eyes were exposed to the same physiological milieu as the corresponding FAc treated eye. Considering the ICE-UK FAc treated and control eyes independently, VA improved in the often poorer FAc treated eye following implantation, while VA decreased slightly in the control eye over the 12-month follow-up period. Therefore, the VA change observed in the ICE-UK FAc treated eyes is likely to be conservative. DME is a progressive chronic condition that we expect to lead to worsening vision over time (as was observed in the mean change in VA in ICE-UK control eyes). Therefore, we believe that the improvement observed in ICE-UK FAc treated eyes could have been larger had it been possible to take account of the expected deterioration in DME over the follow-up period. However, including patients with a follow-up greater than or equal to the follow-up time point may have led to the removal of more severe cases from the ICE-UK control eye cohort where ICEUK patients were censored on administration of the FAc implant in their fellow eye.

In the FAME RCTs, a statistically significant but clinically minor increase in mean and median IOP was observed in FAc treated eyes at 12 months post-FAc implantation (þ2.4 mmHg and þ2.0 mmHg, respectively). Eyes with a history of glaucoma or ocular hypertension at screening were excluded from the studies. In the ICE-UK study, 20% of FAc treated eyes and 16% of control eyes had a history of receiving IOP-lowering therapy prior to the index date. This could have an impact on the proportion of FAc treated eyes with an increase in IOP of 10 mmHg or an IOP elevation of 30 mmHg in the FAME and ICE-UK studies, but is less likely to affect the percentage of patients requiring emergent IOPlowering therapy during the 12-month follow-up period. Furthermore, when we analyzed only those ICE-UK FAc treated eyes with no history of IOP-lowering therapy or surgery for glaucoma and with a baseline IOP of 21 mmHg, the percentage of those eyes demonstrating an IOP increase 10 mmHg or an IOP 30 mmHg was lower than had been observed in FAME. The Medisoft Audit Group compared safety outcomes from their real-world data with those found in FAME and reported that 22% vs 26% of patients treated with the FAc intravitreal implant in the Medisoft and FAME studies, respectively, required IOP-lowering therapy after 18 months[16]. Furthermore, 13% vs 11%, respectively, experienced an IOP 30 mmHg at some point during the 18 month follow-up[16]. In this study, we reported that 12% of ICE-UK FAc treated eyes and 9% of FAME FAc treated eyes with chronic DME had an IOP 30 mmHg at some point during the 12 month follow-up.

The FAME study protocol allowed treatment with laser photocoagulation during the follow-up period. The use of other treatments for DME was prohibited by the protocol, but these were, nevertheless, administered in some instances during the course of follow-up[2]. In the ICE-UK study, FAc treated and control eyes received other treatments for DME as deemed clinically necessary and as part of their routine care. This may have had an impact on the percentage of patients prescribed alternative treatments for DME during the follow-up period. During the 12-month follow-up period, a much higher percentage of ICE-UK FAc treated and control eyes was exposed to anti-VEGF therapy compared with their FAME equivalents. Despite this, a smaller change in VA was observed in the observational study than in the RCTs. A higher proportion of FAc treated eyes in the FAME trials received laser treatment during the 12-month follow-up period compared with the ICE-UK study. A similar proportion of FAc treated eyes received additional steroid treatment (dexamethasone and triamcinolone) between 0–3 months, and 3–6 months post-index date. However, more ICE-UK FAc treated eyes were treated with additional intravitreal steroids between 6–12 months follow-up (2.3% vs 4.7%).

As was expected, when compared with FAME control eyes, a higher proportion of ICE-UK control eyes received anti-VEGF therapy during the follow-up period, whereas a lower percentage received intravitreal steroids and laser treatments. This is likely to be due to the lack of availability of anti-VEGF treatments at the time the FAME RCTs were conducted. Although mean CFT and VA improved over the 12-month follow-up period for FAME control eyes, little improvement was observed in mean CFT for ICE-UK control eyes, and mean VA decreased slightly. This could be due to the differences in VA and CFT at baseline (mean VA 58.1 vs 54.0 letters and mean CFT 371 mm vs 462 mm, for ICE-UK and FAME control eyes, respectively). Under NICE guidelines, aflibercept and ranibizumab anti-VEGF therapies are only recommended for the treatment of visual impairment associated with DME if the eye has a central retinal thickness 400 mm, and, therefore, some ICE-UK control eyes would not have qualified for anti-VEGF therapy during the followup period and, in addition, some centres may have had a restriction on the use of additional further therapies in addition to the fluocinolone intravitreal implant.

Limitations

The limitations of the FAME and ICE-UK studies have been discussed previously. Differences in the methods of assessing VA between studies need to be considered when interpreting these results. Furthermore, CFT was measured using TD-OCT (Stratus 3 OCT instrument) in the FAME studies and SD-OCT in the ICE-UK study. In the ICE-UK study, CFT was measured using one of the following OCT instruments: Heidelberg SPECTRALIS, Topcon 3D OCT-2000, and Topcon 3D OCT-1000. However, CFT was measured using the same OCT instrument at baseline and during follow-up in the majority of patients. No adjustment has been made for the type of OCT instrument used to measure CFT in this comparison. Retinal thickness measurements have been shown to vary depending on the type of machine, which is thought to be due to variation in the retinal segmentation algorithms. Bressler et al. reported a difference in mean CST of þ67 mm between SPECTRALIS and Status OCT instruments. From data produced using a Cirrus or SPECTRALIS instrument, the same authors recommend that a minimum change of 10% in central sub-field thickness is required between visits to indicate that a real change in retinal thickness has occurred when the same OCT instrument was used.

Conclusions

A statistically significant improvement in VA and CFT was reported in FAc treated eyes in both the randomized controlled FAME trials and the real-life ICE-UK study over an initial 12-month follow-up period. The median change in VA and CFT in the FAME RCTs was greater than in the real-life observations from the ICE-UK study. However, patients in the ICE-UK study appeared to have a heavier burden of disease. A similar, small increase in IOP following FAc implantation was observed in both FAME and ICE-UK over the same period. Baseline characteristics and outcomes differed between the eyes included in the FAME and ICE-UK studies, owing to different study selection criteria, changes in the management of DME in clinical practice, and NICE recommendations on the use of the product within the UK National Health Service.