Real-World Cost Savings Demonstrated by Switching Patients with Refractory Diabetic Macular Edema to Intravitreal Fluocinolone Acetonide (Iluvien): A Retrospective Cost Analysis Study

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ABSTRACT

Introduction: It is hypothesized that using fluocinolone acetonide (FAC) implants such as Iluvien for the treatment of diabetic macular edema (DME) may reduce the total number of intravitreal injections and clinic visits, resulting in an overall treatment cost reduction. The primary aim of this study is to identify the real-world cost savings achievable in a tertiary National Health Service (NHS) hospital.

Methods: A retrospective cost analysis study was conducted. The inclusion criteria were patients with refractory DME who were switched to Iluvien. The average yearly costs were calculated both before and after the switch to Iluvien. All costs including medicines, investigations, clinics, and management of raised intraocular pressure (IOP) were calculated. The cost differences over the 3 years' worth of Iluvien treatment were calculated and analyzed. To ensure non-inferiority of this treatment intervention, the best corrected visual acuity (BCVA) and central retinal thickness (CRT) were

also analyzed. Statistical analysis was conducted with a Student *t* test where appropriate and statistical significance is identified where $p < 0.05$.

Results: Fourteen eyes of 13 patients met the inclusion criteria. Switching patients to Iluvien achieved on average a saving of £2606.17 per patient ($p = 0.33$) over the 3 years. However, seven cases (50%) had a rise in IOP after Iluvien that warranted medical treatment and two cases (14.3%) required glaucoma surgery. Incorporating the costs of glaucoma management reduced the overall savings over 3 years to £1064.66 per patient. The BCVA and CRT analysis showed a non-inferiority relationship between Iluvien and any previous treatment.

Conclusions: The use of Iluvien in refractory DME patients represents a cost- and time-saving procedure, while showing non-inferiority in terms of efficacy.

Keywords: Cost; Diabetic macular edema; DME; FAC; Financial; Fluocinolone acetonide; Iluvien

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INTRODUCTION

Diabetic macular edema (DME) is the most common cause of visual impairment in patients with diabetes and occurs in approximately 25% of cases [1]. In the UK, the estimated cost of treating diabetic retinopathy was £58 million in

2010 and this has been projected to increase to £97 million by 2035 [2]. In November 2013, the National Institute for Health and Care Excellence (NICE) released guidance for the use of a fluocinolone acetonide (FAC) intravitreal implant (Iluvien, Alimera Sciences Limited, Aldershot, UK) for DME [3]. This intravitreal implant contains 190 µg of FAC that releases 0.2 µg a day continuously into the vitreous body for up to 36 months [3]. The efficacy and safety of Iluvien were evaluated in the Fluocinolone Acetonide for Diabetic Macular Edema (FAME) study [4]. Other established options for the treatment of DME include macular laser photocoagulation, intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections, and intravitreal corticosteroid injections or implants. Use of Iluvien for DME represents a significant change in the longevity of any one single treatment modality.

Prior to the use of Iluvien, the standard practice for patients with refractory DME, where previous treatments had not completely resolved the DME, was to maintain them on regular established treatments indefinitely. This is based on experience that stopping all treatment can cause the central retinal thickness (CRT) and/or best correct visual acuity (BCVA) to deteriorate further. As this treatment will be indefinite and repeatable on a long-term basis, this will inevitably have serious financial cost implications. It has also been hypothesized that using a long-acting corticosteroid implant will reduce the frequency of clinic visits and other treatments, ultimately reducing the overall cost burden [5]. Therefore, the primary purpose of this study is to look at the real-world cost difference in patients treated with Iluvien in a tertiary hospital center.

METHODS

This is a retrospective cost analysis study and was registered as an internal hospital audit (audit no. 6918) at the University Hospitals of Leicester (UHL), UK. The research adhered to the tenets of the Declaration of Helsinki and all patient data were anonymized during extraction for analysis. In the UK, NICE has

recommended the use of Iluvien in patients with chronic DME who are pseudophakic and where the DME has been shown not to improve with other treatments [3]. The main inclusion criteria in this study are patients with refractory DME who had Iluvien treatment based on the NICE criteria. A local UHL policy meant that any patient with pre-existing glaucoma or ocular hypertension, whether on treatment or not, was precluded from treatment with Iluvien. The number, range, and duration of previous attempted treatments before switching to Iluvien has not been defined by NICE and therefore this is left to the discretion of the treating clinician. This data was recorded in order to compare it to the landmark studies.

Other studies define refractory as persistent DME for at least 6 months' duration despite two prior treatments which include a combination of macular laser photocoagulation, intravitreal triamcinolone acetonide (IVTA), intravitreal anti-VEGF, or intravitreal dexamethasone implant [6]. In our study, this definition would exclude patients who are considered refractory but have only had one other treatment modality because they are not eligible for other treatments. This primarily refers to patients excluded from intravitreal anti-VEGF treatment on the basis of the NICE requirement of 400 µm of CRT. Therefore, the definition of refractory DME in this study was modified to DME that shows no improvement for at least 6 months' duration after at least one other treatment. Other exclusion criteria are patients who have not had the implant in for at least 12 months, those who had an implant for indications other than DME, and those who were not deemed refractory to other treatment.

To calculate the average yearly cost of treatment, the following data were recorded both before and after the use of Iluvien: the number of clinics attended, the type and number of treatments given, the number of investigations performed, and the need for any intervention due to treatment adverse effects. To calculate the average yearly cost before Iluvien, the total cost of management was divided by the number of years each patient had been treated for DME. This ranged from between 1 and 7 years with a mean of 2.6 years of previous DME treatment.

To calculate the costs of treatment after Iluvien use, the authors also incorporated any associated rescue treatment costs, such as the use of intravitreal anti-VEGF or laser. Any costs associated with the development and management of steroid-induced IOP rises were included. The total cost over the 3-year life-span of Iluvien was calculated, as well as a yearly average. The purpose of this is to demonstrate the reduction of cost over time after the initial high layout cost for Iluvien. Not all patients had reached the 3-year end point of Iluvien treatment and therefore some years were extrapolated to achieve this. This extent and implications of this are evaluated in the discussion section of this paper.

The costs of the facilities and medications used are based on the NHS national tariff list 2014/15 [7]. All statistical analyses were performed using Excel Professional Plus 2010 (Microsoft Corporation, Seattle, WA, USA). Statistical analysis was conducted with a Student *t* test where appropriate and statistical significance is identified where $p < 0.05$.

The primary aim of this study is to compare treatment costs before and after the use of Iluvien for refractory DME patients. However, in order to justify a switch of treatment, the authors felt it important to demonstrate non-inferiority in terms of treatment efficacy and side effect profile. Given this, the BCVA, CRT, IOP, and adverse effect data were collected both before and after Iluvien treatment. Data for efficacy and side effects are real data and have not been extrapolated but have been averaged with reference to the number of years of treatment they received.

RESULTS

Fourteen eyes of 13 patients met the inclusion criteria. The patient population included seven women and six men with a mean age of 68.2. None of the eyes in this study had previously undergone a vitrectomy. Table 1 demonstrates the percentage of patients who had tried other DME treatments prior to Iluvien and the average frequency of their

administration; 64.3% of patients had previously tried two or more DME treatments before being considered for Iluvien.

Table 2 demonstrates a yearly breakdown of treatment numbers and clinic visits together with the associated costs both before and after Iluvien. This data does not account for the costs of associated IOP rises and subsequent glaucoma. Post-Iluvien patients had an average of two fewer clinic visits, three fewer intravitreal injections, and three fewer laser treatments over 3 years than before Iluvien use. After Iluvien there is a higher total cumulative cost in years 1 and 2 but by year 3, there is a £2606.17 cost saving. This occurs because of the initial cost of the Iluvien implant that is incurred in the first year, which is not recouped until the third year post treatment.

Seven cases (50%) of IOP rise after Iluvien warranted treatment. Five of these seven patients were controlled adequately on long-term glaucoma drops. However, two of these cases (14.3%) were not adequately controlled on medical therapy and required glaucoma surgery. One patient had a subconjunctival filtration stent inserted (XEN gel stent, AqueSys, Inc., Aliso Viejo, CA, USA), while the other patient had a trabeculectomy with mitomycin C, followed by an injection of 5-fluorouracil/dexamethasone in clinic and subsequent bleb needling. Both patients who underwent glaucoma surgery had adequately controlled IOPs without the need for long-term glaucoma medications. The pricing for the glaucoma drops was based on the British National Formulary [8]. Table 3 demonstrates the total average number of treatments and clinic visits per patient over the 3-year period associated with the raised IOP as a consequence of Iluvien. Table 3 also demonstrates the average costs over 3 years applied only to those who developed raised IOP or glaucoma. Factoring the extra cost of management of glaucoma, the cost saving after Iluvien treatment reduces to £1064.66 per patient over 3 years.

One cost that has been excluded from this study is cataract surgery. The reason for this is that the development of cataracts is not considered a manifestation of the DME and in the

Table 1 Attempted treatments prior to Iluvien

	Lucentis	Eyelea	Avastin	Intravitreal triamcinolone	Ozurdex	Macular laser
Percentage of patients who had therapy (%)	78.6	0	7.1	50.0	0	64.3
Mean number of treatments given per patient	5.1	0	0.2	0.6	0	1.2

Table 2 Comparison of yearly treatment numbers and costs before and after Iluvien

Types of clinic, treatment, investigation	Before Iluvien		After Iluvien					
	Mean annual treatment numbers and cost (<i>n</i> = 14)		Mean annual treatment numbers and cost					
			Year 1 (<i>n</i> = 14)		Year 2 (<i>n</i> = 7)		Year 3 (<i>n</i> = 4)	
	No.	Cost	No.	Cost	No.	Cost	No.	Cost
Clinic visits	5.2 (SD 1.9)	£445.48 (SD £165.43)	4.3 (SD 1.1)	£368.57 (SD £91.94)	3.7 (SD 1.5)	£319.43 (SD £128.66)	2.3 (SD 0.5)	£193.50 (SD £43.00)
Intravitreal Iluvien	0	0	1	£6976.00	0	0	0	0
Intravitreal ranibizumab	2.6 (SD 2.2)	£3240.82 (SD £2782.39)	0.1 (SD 0.3)	£90.55 (SD £338.50)	0.4 (SD 1.1)	£542.83 (SD \$1436.19)	0	0
Intravitreal aflibercept	0	0	0	0	0.4 (SD 1.1)	£580.80 (SD £663.77)	0.3 (SD 0.5)	£338.80 (SD £677.60)
Laser therapy	1.0 (SD 1.6)	£337.00 (SD £545.00)	0	0	0	0	0	0
OCT	3.8 (SD 2.2)	£244.00 (SD £141.00)	4.8 (SD 2.2)	£306.00 (SD £142.20)	2.6 (SD 1.9)	£164.57 (SD £121.75)	1.5 (SD 0.6)	£96.00 (SD £36.95)
FFA	0.3 (SD 0.4)	£37 (SD £41.75)	0	0	0	0	0	0
IVTA	0.2 (SD 0.3)	£84.21 (SD £113.39)	0	0	0	0	0	0
Total cost	£4387.94		£7618.86		£1333.34		£1605.45	
Total cumulative cost	Year 1: £4387.94 Year 2: £8775.88 Year 3: £13,163.82		£7618.86 (SD £229.52)		£8952.20 (SD £2950.58)		£10,557.65 (SD £4534.76)	
<i>p</i> value			<i>p</i> < 0.05		<i>p</i> = 0.90		<i>p</i> = 0.33	

OCT optical coherence tomography, *FFA* fundus fluorescein angiogram, *IVTA* intravitreal triamcinolone

Table 3 Cost of glaucoma treatment post-Iluvien over 3 years

Glaucoma treatment and clinic	Mean visits per patient	Mean cost per patient
Average cost per patient ^a (<i>n</i> = 14)		
Topical medications	N/A	£744.79 (SD £532.38)
Surgery	N/A	£538.71 (SD £933.88)
Clinic visits	2.4 (SD 4.2)	£208.86 (SD £357.55)
VFT	0.6 (SD 1.1)	£49.14 (SD £97.51)
Total mean cost per patient		£1541.51 (SD £1867.90)
Glaucoma treatment and clinics	Topical medications alone (<i>n</i> = 5)	Topical medications + glaucoma surgery (<i>n</i> = 2)
Average cost of glaucoma management in patients needing topical medications alone versus topical medications and glaucoma surgery ^b		
Topical medications	£457.34 (SD £252.92)	£1885.50 (SD £392.44)
Surgery	N/A	£1463.41 (SD 0)
Clinic visits	No additional clinics	£731.00 (SD £60.81)
VFT	No VFTs performed	£172.00 (SD £121.62)
Total mean cost per patient	£457.34 (SD £252.92)	£4251.91 (SD £331.63)

N/A not applicable, VFT visual field test

^a This is an average 3-yearly cost over all patients. It includes those who did and did not develop glaucoma

^b This is an average 3-yearly cost for only patients who developed glaucoma

Table 4 Average BCVA and CRT change before and after Iluvien over 3 years

	Pre-Iluvien (mean)	Post-Iluvien (mean)	Difference	<i>p</i> value
BCVA (logMAR)	0.75 (SD 0.2)	0.73 (SD 0.5)	0.02 (SD 0.41)	0.88
CRT reduction (µm)	415 (SD 150)	315 (SD 94)	100 (SD 174)	0.05

UK, if adhering to NICE guidance, all patients must be pseudophakic to be considered for Iluvien treatment. No patients intentionally underwent cataract surgery to meet the criteria of Iluvien use. Seven patients were pseudophakic before the pre-Iluvien DME treatment began and seven had cataract surgery during these pre-Iluvien years.

BCVA was similar before and after Iluvien treatment but CRT was significantly less after 3 years ($p < 0.05$) with the use of Iluvien (Table 4).

DISCUSSION

This study builds on our previous work to predict the savings possible from using Iluvien [9]. In our previous study, projected calculations were used and extrapolated from 1 year's worth of Iluvien treatment data and predicted a saving of £8800 per patient over 3 years. The methodology was different in our previous study because the Iluvien group was compared to a different cohort of patients treated with the standard therapies, rather than the same patient

cohort before and after treatment. With the new methodology in this study, the actual costs saving was found to be less than previously anticipated. One explanation for the difference is the cost of the glaucoma management, which was not apparent after the first year.

Research into the cost saving with Iluvien is limited. Quhill [10] used the current prescribing patterns to calculate an estimated cost of switching 30 phakic patients from the current standard DME treatment regimen to an Iluvien treatment regimen. Yearly costs were based on a theoretical treatment model for anti-VEGF therapy and a predicted prescribing pattern for Iluvien. The Iluvien group incorporated an additional cost for rescue treatment, which was predicted as one ranibizumab injection per year for 50% of patients. The author suggests a potential saving of £119,655 for 30 patients (or £3988.50 per patient) over the 3-yearly treatment cycle [10]. Our study uses real-world data and outcomes as opposed to theoretical treatment models and therefore offers a more accurate reflection of the savings that can be achieved. In our cohort of patients, there was a slightly lower cost saving per patient treatment cycle. This is likely due to the associated glaucoma surgery costs that were incurred.

The main limitation of this study is that some patients had not reached the 3-year end point of Iluvien treatment and the data has to be extrapolated accordingly. We attempted to limit the effects of data extrapolation by eliminating those patients who have not had at least 1 year of Iluvien. At the time of writing this paper, all of the patients had Iluvien for at least 12 months, seven patients for 24 months, and four patients for the full 36 months. As demonstrated by our previous work [9], extrapolation is most likely to artificially elevate the savings figures because of the omission of potential rescue intravitreal anti-VEGF treatments or glaucoma management that occurs in the later years.

Intraocular pressure rise is a well-documented side effect of corticosteroid use and our figure of 50% is slightly higher than that recorded by the FAME study (38.4%). Our rate of glaucoma surgery (14.3%) was also higher

than that recorded in the FAME study (4.8%). This study had an exclusion criterion, identical to that of the FAME study, whereby any patient with pre-existing glaucoma or ocular hypertension (with or without treatment) was excluded. Therefore the only explanation for these higher glaucoma figures is the small sample size. The costs of glaucoma management have significantly reduced the average cost saving per patient and therefore in units where the glaucoma rate is more akin to that of the FAME study the cost savings will be substantially better.

A cost variability is also present amongst different units because of the rate of rescue intravitreal anti-VEGF treatments and Iluvien re-treatments. In the FAME trial, clinicians gave additional Iluvien to 23.9% of patients before the 36 months had elapsed. In our study, we have not given further Iluvien to any of our patients to date. Furthermore, in the FAME study, 40.7% of patients had rescue laser treatment at some point during their treatment and 6.6% had more than three sessions [4]. No rescue laser was required in this study. The rate of rescue anti-VEGF treatment (14.3%) in our study was also comparable to that of the FAME study (15.2) [4]. Iluvien re-treatment within 36 months and a more aggressive use of rescue treatments could increase the cost of the Iluvien treatment in these cases and reduce the savings accordingly.

The BCVA and CRT changes demonstrated in our Iluvien group cannot be directly compared to the FAME study outcomes as our patient cohort only incorporated refractory DME cases. However, besides the cost analysis, we have also demonstrated the non-inferiority of Iluvien compared to the other standard treatments and the potential switch of treatment to Iluvien does not compromise patient care. In our study, we currently have 14 eyes of 13 patients to date who have had Iluvien for refractory DME, which could equate to a saving of £14,905.24 over 3 years. Furthermore, if a similar cost saving could be demonstrated in the non-refractory DME patient population, provided that non-inferiority could be demonstrated, then the overall cost savings could be substantial.

CONCLUSION

Switching patients with refractory DME to Iluvien saves on average £1064.66 per patient over the 3-year treatment cycle, while showing non-inferiority in terms of efficacy. It is therefore a credible alternative to the current management of refractory DME.

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Compliance with Ethics Guidelines. This is a retrospective cost analysis study and was registered as an internal hospital audit (audit no. 6918) at the University Hospitals of Leicester (UHL), UK. The research adhered to the tenets of the Declaration of Helsinki and all patient data were anonymized during extraction for analysis.

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

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