TITLE:

Evaluation of Fluocinolone Acetonide 0.19 mg Intravitreal Implant in the management of Birdshot Retinochoroiditis

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SYNOPSIS

Retrospective study to examine therapeutic action of Iluvien® in retinal and choroidal inflammation in patients with birdshot retinochoroiditis. Our findings suggest retinal improvement but choroidal inflammation seems to persist.

ABSTRACT

Purpose: To report treatment outcomes and efficacy of the fluocinolone acetonide 0.19mg intravitreal implant (Iluvien®) in controlling retinal and choroidal inflammation in 11 patients with birdshot retinochoroiditis.

Methods: A single-centre, retrospective, interventional cases series. The primary efficacy end point was improvement in vascular leakage on fluorescein angiography (FA), effect on cystoid macular oedema (CMO) and resolution of hypofluorescent lesions on indocyanine green angiography (ICGA); secondary measures were improvements on pattern and full-field electroretinogram (PERG; ERG) parameters. Safety outcome measures were intraocular elevation, and cataractogenesis.

Results: Fifteen eyes received Iluvien® implant with an average follow-up of 31 months (range 12–36 months). Prior to the implant, 5 (33.3%) eyes had received dexamethasone intravitreal implant 0.7mg (Ozurdex®). FA showed evidence of vascular leakage in all eyes at baseline. Between month 6 and 12, FA showed that 73.4% of eyes had no leakage, this increased to 84.6% by month 24. Three eyes in our study had CMO at baseline. 6 months after Iluvien® implant, all eyes achieved complete CMO resolution. One year after insertion of the implant, the characteristic hypofluorescent lesions on ICGA were unchanged in all cases. There was baseline ERG evidence indicating a high incidence of peripheral cone system dysfunction and most showed PERG evidence of macular dysfunction. Retinal function improved and macular function improved or was stable in the majority following treatment.

Conclusions: The results show the possible therapeutic effect of Iluvien® in the management of Birdshot related-vascular leakage, CMO, and retinal dysfunction. However, choroidal lesions seem to persist with no detectable response to treatment.

Keywords Fluocinolone acetonide, intravitreal implant, Birdshot retinochoroiditis, choroidal lesions, hypofluorescent dots, indocyanine green angiography.

INTRODUCTION

Birdshot retinochoroiditis (BRC) is rare posterior non-infectious uveitis, usually of white patients, more commonly female. Patients often present in their sixth decade of life, and are otherwise well. Clinical signs include multiple creamy-white choroidal lesions ("birdshot lesions") [1-2]. BRC has a strong HLA-A29 association. The pathophysiology of BRC remains unknown, but may involve an autoimmune reaction to retinal and choroidal antigens [3-4] leading to retinal inflammation and stromal choroiditis [5]. BRC is a chronic, progressive disease, typically associated with retinal vascular leakage in the early stages, while birdshot lesions may only become visible in the later phases. Remission may occur spontaneously, but most untreated cases have a relentlessly progressive course [6,7]. Disease behaviour is monitored by structural and functional assessments. Active retinal vascular leakage is typically assessed with fluorescein angiography (FA). Choroidal inflammation is assessed using indocyanine green angiography (ICGA) to identify birdshot lesions, or optical coherence tomography (OCT) to measure choroidal thickness [8]. Functional assessment is performed using automated perimetry and electrophysiology (pattern and full-field electroretinogram (PERG; ERG) testing [9-12]. Patients usually require oral steroids and/or immunosuppressive drug therapy (IMT). As a consequence, intraocular drug delivery provides a potentially useful treatment option. Fluocinolone acetonide (FAc) 0.19 mg is a non-biodegradable, intravitreal implant (Iluvien®; Alimera Sciences Limited, Aldershot, UK), that releases fluocinolone acetonide over 36 months at a rate of 0.2 µg/day [13]. Limited reports exist, to date, detailing its use in uveitis. The objective of this report is to analyse efficacy of Iluvien® in controlling retinal and choroidal inflammation in BRC.

METHODS

In this retrospective observational study at Moorfields Eye Hospital, we report 15 eyes of 11 BCR patients treated with FAc implant (Iluvien®; Alimera Sciences Limited, Aldershot, UK). The implant is injected through the pars plana into the vitreous cavity using a 25-gauge applicator in the same manner as in the intravitreal injection and can be done in the office setting. After the injection, there is a slow release of the drug from one end of the polyimide cylinder. All were HLA-A29 positive, and had had other non-infectious or infectious aetiologies excluded.

Study population

Fifteen eyes underwent FAc implantation between January 2014 and December 2018, by a single surgeon (C.P). Follow up occurred at 3, 6, 12, 24, and 36 months. Data were collected from electronic medical records and entered into an Excel 2016 database (Microsoft Corp, Redmond, Washington). Snellen visual acuities were converted to logarithm of the minimum angle of resolution (logMAR) scores to permit statistical analysis.

Angiographic and Electrophysiological testing Protocols, and data collection

The diagnosis of BRC was made by clinical evaluation supported by ultrawide-field fluorescein angiography (UWF-FA), ultrawide-field ICGA and Spectralis EDI-OCT. All UW-FA images were acquired with the Optos 200Tx ultra-widefield retinal imaging system (Optos PLC, Dunfermline, Scotland, UK), which can image up to 200-degree of the retina in a single view. FA was used for monitoring markers of disease activity, including vascular leakage. Baseline data from the FA prior to the FAc implantation was graded according to the following scale: 0=no retinal vascular leakage, 1=large vessel leakage, 2=small vessel leakage in the posterior pole, 3=CMO, 4= RPE atrophy in the posterior pole [11]. Similarly, hypofluorescent lesions on ICGA were recorded according to the angiography Scoring for Uveitis Working Group [14]. Large and small vessel leakage was gathered up in figure 4 as “vascular leakage”

but detailed in supplement 4. SA-R scored the angiographic signs seen on each angiogram (supplementary material 4)

Data on previous and concomitant local and systemic treatment, including the use of corticosteroids, conventional immunosuppressive medications and other biologic agents was recorded. Pattern and full-field Electroretinogram (PERG; ERG) testing protocols incorporated the published international standards [15,16] and were recorded using gold foil corneal recording electrodes. Pattern ERG testing included PERGs recorded to both a standard (15 x 12 degrees) and large (30 x 24 degrees) stimulus field. Baseline recordings immediately prior to FAc, and at all follow-up visits were obtained using the Espion visual electrophysiology system (Diagnosys LLC, Littleton, MA, USA). Pattern ERG P50 was used to assess macular function and dark-adapted (DA) and light-adapted (LA) full-field ERGs were used to assess generalised rod and cone system function; the LA 30Hz flicker ERG peak time was examined and plotted separately, as established in previous studies as a sensitive measure of retinal dysfunction in BRC [9, 10]. Pattern and full field ERGs obtained before and after treatment were compared and plotted as a percentage of the lower limit of normal, the latter defined as the lowest amplitude in a control group, minus 5% of the reference interval [17]. In all but one case PERG and ERG were performed prior to treatment with Ozurdex® and/or FAc implant with a mean follow-up of 26 months (median 24.5 months; range 10-54 months). Most had undergone repeated testing prior to FAc implant, enabling an assessment of ERG stability (mean pre-treatment period of electrophysiological monitoring 66.6 months; median 19.5 months; range -6 to 232 months). The majority had follow-up visits at intervals of approximately 3, 6, 12, 24 and 36 months with 4 undergoing additional testing at approximately 48 months after treatment. The study adhered to the tenets set forth in the Declaration of Helsinki.

Outcomes

Primary outcome measures were presence or absence of retinal vasculitis on FA, presence or absence of hypofluorescent choroidal lesions on ICGA, and resolution of central macular oedema. Secondary efficacy outcome measures were best-corrected visual acuity (BCVA) and improvement on PERG and ERG. The electroretinograms were performed at baseline and at approximately 12, 24 and 36 months follow up to monitor macular and generalised retinal function. The light-adapted (LA) 30Hz flicker ERG peak time was chosen as the primary ERG measure of retinal function based on observations made in previous studies in patients with BRC [9, 10]. A change in LA30Hz peak time of 3ms or more and a change in PERG P50 or ERG amplitude of 30% or more were considered significant [18]. Safety end points included rise in IOP requiring topical or surgical treatment and development of cataract.

RESULTS

11 patients received 0.19mg FAc implants, including 4 patients who underwent bilateral procedures; thus, a total of 15 treated eyes were analysed. All patients were female, white, HLA-A29 positive and otherwise healthy. Indications for implant were intolerance to, or ineffectiveness of systemic IMT, or as a patient's informed decision to decline systemic treatment. Mean age at time of injection was 56.6 ± 8.3 years. Mean follow-up was 31 months (range 12 – 36 months), with 15 eyes monitored for 12 months, 13 eyes for 24 months and 12 eyes followed for at least 36 months. Clinical characteristics of the study population are summarised in Table 1.

Prior to treatment with FAc implant, 5 (33.3%) eyes had received dexamethasone intravitreal implant 0.7mg (Ozurdex®), and 1 (6.7%) eye had received intravitreal triamcinolone acetonide. Those eyes had a period of washout before having the FAc injection (Table 1). The remaining eyes were treatment-naïve. At time of implant, 6 out of 11 patients were on oral prednisolone, and 2 on systemic immunosuppressive therapy (IMT)

(Supplement 2). The number of patients on IMT decreased to 0 at 6 months post FAc implant. Subsequently, IMT was restarted in 2, 3 and 1 patients at 1, 2 and 3 years post FAc implant respectively being five patients on IMT at month 36 (out of eight followed up for that time).

FA prior to FAc implant showed evidence of vascular leakage in 15 eyes (100%), a hyperfluorescent disc in 10 eyes (66.7%), Retinal Pigment Epithelium (RPE) atrophy in 6 eyes (40%) and cystoid macular oedema (CMO) in 3 eyes (20.0%). The proportion of eyes with retinal vascular leakage decreased during follow-up whereas RPE atrophy became more prevalent. Between month 6 and 12, all patients had repeat angiograms, which showed that 73.4% of eyes had no leakage increasing to 84.6% by month 24. At 6 months following implantation, all eyes achieved complete resolution of CMO. This remained unchanged throughout the observation period of 3 years. (Figure 4, graph). ICG pre-FAc implant showed classic birdshot hypofluorescent lesions. One year after FAc implant, the frequency of these lesions remained either unchanged (9/15 eyes) or had increased in number (6/15) on ICG grading (Supplement 5) (Fig. 1 & 2). Visual acuity remained stable throughout the follow up period (supplementary table 1, $p = 0.87$). At baseline, 13 (86.7%) eyes were phakic and only 2 had cataract surgery prior to the injection (13.3%). Visually significant cataract formation occurred in 12 of 13 (92.3%) eyes: these eyes underwent cataract surgery after a mean time from implant of 22.2 ± 10.2 months. In the eyes undergoing cataract surgery mean visual acuity improved from 0.23 ± 0.21 logMAR before surgery to 0.11 ± 0.11 logMAR at 3 months postoperatively ($p = 0.12$) (Supplement 1).

Mean intraocular pressures (IOP) remained normal throughout the follow-up, and did not differ significantly across follow-up time points ($p = 0.67$), 66.7% of eyes (10) did not require pressure lowering eye drops. None of the study eyes required surgical intervention to reduce IOP (Supplement 1).

Full-field ERG and PERG findings are summarised in figure 3 (cases 1 and 3) and in Supplement 3(all cases). Baseline full-field ERGs were available in 10 of 11 patients, and showed a high incidence of LA 30Hz flicker ERG delay (14 eyes of 10 patients; delay 3-8ms) or borderline delay (3 eyes of 3 subjects; delay 2ms). Other ERG abnormalities included a reduced scotopic strong

flash (DA10.0) ERG b:a ratio (5 eyes of 4 subjects) and DA10 ERG a-wave reduction (both eyes of 1 subject).

Eight of the 15 treated eyes showed improvement in LA30Hz ERG peak times (peak time shortened by 3-7ms), with the maximum change occurring in an eye treated with Ozurdex and then FAc implant (case 4). There was borderline improvement (2ms) in 1 treated eye; peak times were stable in 5 treated eyes of 4 subjects and in the treated case without baseline recordings there was progressive delay during the monitoring period (case 8). Improvement in LA 30Hz timing was accompanied by an increase in the initially abnormal DA10 ERG b:a ratio in 4 of 4 treated eyes of 4 subjects. Untreated eyes showed significant worsening of the LA30Hz ERG peak time and worsening of the DA 10 ERG a- and b-waves (case 3; Fig 3e); other untreated eyes were stable (cases 7 and 8), showed an improved DA10 ERG b:a ratio (case 9) or showed only borderline ERG changes (cases 4 and 10). In summary, generalised (peripheral) cone system function improved in 8 of 15 treated eyes and there was concomitant improvement of inner retinal rod system function in 4 eyes of 4 subjects.

Thirteen eyes of 9 subjects showed PERG P50 reduction prior to treatment with FAc implant. Nine eyes showed P50 amplitude enlargement following FAc, although in 4 eyes of 4 subjects improvement was not immediate and occurred 15, 18, 27 or 38 months post-treatment. Five treated eyes showed stability (undetectable in 3 eyes of 2 cases).

Case 1

Patient 1 was naïve to systemic or local therapy. FA highlighted disc hyperfluorescence and retinal vascular leakage. ICGA showed hypofluorescent spots around the optic discs and the arcades (Fig. 1D, M). Spectralis OCT showed no CMO. Both eyes received FAc implants and subsequent to that the patient remained off IMT for 18 months. During this time, fundus autofluorescence (Fig.1A,B,J,K) showed progression of retinal pigment epithelium atrophy (RPE-defects) with progression of areas of hypo-AF around the optic disc and vessels 18 months after the implant. Those hypo-AF lesions seem to fade after starting treatment with adalimumab 8months after the FAc implant (Fig. 1C, L). Baseline EDI-Spectralis OCT

measurements showed thickened choroid (fig. 1G, P) that worsened over the 18 months of whilst on FAc implant monotherapy (Fig. 1H, Q). ICGA findings revealed persistence of choroidal lesions (Fig. 1E, N) remaining unchanged during this period. Hence, adalimumab treatment was commenced. After starting Adalimumab, choroidal thickness markedly improved (Fig. 1I, R), and this correlated with near complete disappearance of choroidal ICG hypofluorescent lesions (Fig. 1F, O). The LA30Hz ERGs, reflecting generalised (peripheral) cone system function, were relatively stable for approximately 1 year after implantation, but the right eye showed significant but mild (3ms) worsening after 19 months, with only borderline (2ms) recovery after adalimumab (Fig. 3a). Mild progressive attenuation of left eye PERG P50 occurred in spite of initial treatment with Ozurdex (Fig. 3b). Pattern ERGs were mildly abnormal before FAc implantation and showed an increase in P50 amplitudes (normalisation) in the year that followed, consistent with improved macular function bilaterally (Fig. 3b). Reduction in PERG P50 was evident bilaterally 18 months after FAc. Further ERG and PERG changes after treatment with adalimumab indicated a lack of stability, but were mostly suggestive of borderline recovery of macular and retinal function (Fig. 3a-d).

Case 2

Patient 2 FA demonstrated early vascular leakage with late hyperfluorescence and marked perivascular and disc leakage in the right eye (Fig. 2C). ICG highlighted choroidal hypofluorescent lesions consistent with choroidal BRC lesions (Fig. 2A). Macular oedema was absent. Electrophysiology revealed significantly subnormal PERG P50 component on the right, with only borderline DA and LA ERG abnormalities, left eye findings were normal with the exception of a borderline LA 30Hz ERG peak time. The patient declined oral prednisolone and IMT, and underwent right FAc implant. Visual symptoms in the right eye improved after the implant and left eye remained stable. At 1-year follow-up, FA findings revealed no vasculitis (Fig. 2D) but ICG showed persistent choroidal hypofluorescent lesions (Fig. 2B).

Case 3

Patient 3 was intolerant to IMT because of side effects. Left eye Intravitreal dexamethasone (Ozurdex®) was followed by FAc implant four months later. CMO resolved one month after the Ozurdex implant, and remained in abeyance after the FAc implant over a period of 36 months (Fig. 2G, H). Although CMO resolved, ICG showed that the hypofluorescent lesions remained unchanged from baseline (Fig. 2E) until follow-up (Fig. 2F). Baseline LA30Hz flicker ERGs showed mild delay, in keeping with generalised cone system dysfunction bilaterally (Fig. 3e). In the untreated right eye, LA 30Hz ERG timing worsened and the delay persisted for more than 2 years; peak times in the left eye remained normal and stable following treatment with Ozurdex and the FAc implant (peak time difference between eyes 6ms). There was PERG evidence of macular dysfunction bilaterally initially, with worsening of both eyes in the period immediately after treatment but with mild improvement on the right and marked increase in the P50 component amplitude (normalisation) on the left, 27.7 months after left eye treatment (Fig. 3f). Other full ERG components showed only minor fluctuation and were normal or of borderline amplitude (Fig. 3g and h).

DISCUSSION

The therapeutic role of local ocular corticosteroids in non-infectious posterior uveitis is well established [19-27]. Slow-release, sustained-delivery intravitreal corticosteroid implants are approved for non-infectious uveitis, including the FAc 0.19 mg intravitreal implant (Iluvien®; Alimera Sciences Limited, Aldershot, UK). Implants have demonstrated efficacy in controlling intraocular inflammation, and can reduce the need for systemic therapy. Local therapy is attractive in BRC as the disease is eye-limited [20-27]. This study evaluated the use of the FAc intravitreal implant in the management of BRC patients. Our patient cohort is similar to published series in terms of rates of retinal vascular leakage, CMO, abnormal ERG and relatively preserved visual acuity [28,29]. Rush et al. [28] reported outcomes of BRC patients treated with

intravitreal sustained release fluocinolone acetonide 0.59mg implant (Retisert®, Bridgewater, NJ, US). The implant was efficacious in preserving visual acuity, and electroretinographic parameters, and improved retinal vascular leakage. The Retisert® implant was able to effectively treat CMO in 100% of BRC patients at 24 months [28], with clinical outcomes similar to those of other non-infectious posterior uveitis treated with Retisert® [30]. The researchers reported a very high incidence of cataract progression and glaucoma [28]. In our study, the number needing IOP lowering drops was much lower and none required glaucoma surgery. This is because of the lower dose of fluocinolone steroid released by the Iluvien® implant compared to the Retisert®. Subsequently, different studies proved the therapeutic efficacy of FAc 0.59mg implants in the management of BRC, affirming the role of such devices in the successful discontinuation of systemic corticosteroids or conventional immunomodulatory therapy [29-31].

Our study differs from previously reported [28] in several ways. Firstly, all patients had at least 1 year of follow-up data. Secondly, all patients had both FA and ICG – with ICG we were able to assess choroidal involvement. Thirdly, all had complete electrophysiological assessment.

Our results show the efficacy of FAc implant in the management of vascular leakage, CMO and retinal dysfunction, as previously reported [25-28]. In our study, baseline full-field ERGs showed a high incidence of generalised cone system dysfunction, consistent with previous studies, [9,10,18] with additional inner retinal rod system dysfunction in a minority. Peripheral cone system function improved in most subjects following FAc, indicating the value of the LA 30Hz flicker ERG delay as a robust measure for monitoring inflammatory retinal dysfunction. The majority showed PERG P50 reduction prior to treatment that improved following FAc, but macular dysfunction could persist in spite of LA 30Hz ERG improvement, highlighting the value of comprehensive electrophysiological evaluation. [9,10,18]

However, the response was not complete since we observed with ICG that choroidal hypofluorescent lesions persisted in all of our patients after FAc implant. This suggests that choroidal birdshot lesions do not disappear after FAc implant. The clinical significance of choroidal lesions on ICG in birdshot patients is incompletely understood, but patients can experience visual

decline, even when typical intraretinal signs of inflammation, according to FA and OCT, are absent. It is postulated that the presence of persistent choroidal lesions indicates active choroidal inflammation. Few studies have studied the significance of evolution of these choroidal lesions over time with or without treatment [32,33,34]. In the long-term this likely results in RPE atrophy, and consequently outer retinal damage leading to worse visual prognosis [35]. Indirect evidence for this is provided by Rush et al [28], as they observed a very high incidence of RPE atrophy in the long term after Retisert® implant. Recently, Cheng et al. reported a case of one patient with Birdshot related-choroidal lesions unresponsive to Retisert® implant [35]. We analysed the choroidal response to Iluvien® implant of 15 eyes in 11 patients, and in all patients the choroid inflammatory involvement seemed to persist despite the steroid implant. Choroidal thickness has been mentioned in the literature as an indirect measure of choroidal activity, and can discriminate between active BRC patients and controls [19].

Case 1 in our series is illustrative, as choroidal thickening persisted after the Iluvien® implant and was associated with progressive peripapillary RPE changes. This suggests outer retinal damage secondary to active choroidal inflammation. The choroidal thickening, and the ICG "`birdshot" lesions only improved after systemic anti-TNF therapy.

Since choroidal inflammation does not seem to be responsive to monotherapy with intravitreal slow-release, sustained-delivery intravitreal steroids, we believe that patients with BRC require systemic corticosteroids or conventional immunomodulatory therapy to fully control their disease. Local intravitreal steroid therapy alone is insufficient to produce control of the choroidal inflammation, which could be due to poor penetration of drug into the choroid or a low dose in the vitreous. The report of the Retisert® case [35] seems to favour penetration, since the Retisert releases a much larger amount of the same steroid preparation in the vitreous. Although local steroid therapy alone cannot control the choroidal inflammation in BRC, this approach might be beneficial since it appears to control the retinal vascular leakage, retinal function and CMO leading to a reduction in the burden of exposure to large doses of systemic therapy. As Iluvien® alone seems not to guarantee complete remission of the disease, a strategy using combined local and

systemic therapy may very well prove to be the best alternative for these patients. However, our study has a number of limitations, and this includes the drawback that it is a retrospective study. We have reported a relatively small number of cases and we cannot exclude that possibility of erroneous findings of type 1 and type 2 bias. The retrospective nature of the study means that we cannot exclude bias, particularly as some patients received concomitant immunosuppressive therapy. We propose that further studies should be undertaken in order to confirm our findings. These studies should be prospective in design, and ideally multicenter.

TABLES.

Table 1. Patient Demographics and local treatment

Pat No.	Age Range *	Sex	Study Eye	Local treatment prior to Iluvien ("Nil", Ozurdex, or "IVTA"	Interval between any prior treatment and Iluvien (-Months)	Length of follow up from Iluvien (months)
1	50s	F	LE	Ozurdex	-7.5	36
			RE	Nil		36
2	40s	F	RE	Nil		12
3	40s	F	LE	Ozudex	-4.0	36
4	50s	F	LE	Ozurdex	-4.0	36
5	50s	F	RE	Nil		36
			LE	Nil		36
6	60s	F	RE	Nil		36
			LE	Nil		36
7	60s	F	RE	Nil		36
8	60s	F	LE	Ozurdex	-4.0	27.2
9	50s	F	LE	Ozurdex	-5.0	18
10	60s	F	RE	Nil		36
			LE	Nil		36
11	60s	F	RE	IVTA	-11. 0	36

Age range*: at the time of the FAc injection

Abbreviations:

BE both eyes

F female

IVTA intravitreal triamcinolone

LE left eye RE right eye

SE side effects

Figure 1: Multimodal imaging of both eyes from patient 1.
(A) Right fundus Autofluorescence at baseline. (B) AF reveals progression of the hypo and hyperfluorescent lesions after 18months of Iluvien®. (C) Those changes remain similar or even seem to be regressed after 8 months of Adalimumab treatment. (D) Indocyanine green angiography at presentation demonstrating classic BRC hypofluorescent lesions which (E) are more prominent after 18 months into treatment with Iluvien® alone (off of all systemic immunomodulatory therapy) and (F) appears to resolve 8 months following Adalimumab treatment. EDI-Spectralis OCT of the right eye showing thickened choroid at baseline (G), which got worse over time (18 months after FAc implant) with a mean thickness 551µm in the right eye (H) compared to baseline. At that time, (I) patient was started on Adalimumab, which led to a significant reduction in choroidal thickness. Same findings for left eye. (J) Left fundus AF at baseline, (K) after 18months of Iluvien® and after Adalimumab treatment (L). (M) ICGA at presentation showing hypofluorescent lesions, which seems similar or even more prominent after treatment with implant alone (N) and seems to improve after Adalimumab treatment (O).
(P) Left EDI-Spectralis OCT at baseline, (Q) 18months after FAc and (R) after Adalimumab treatment.

Figure 2: Ocular findings of patient 2 and 3.
(A) Indocyanine green angiography at presentation demonstrating multiple hypofluorescent lesions that (B) remained the same 12 months after FAc implant. (C) Fluorescein angiogram at presentation showing retinal vascular leakage that (D) disappeared with the FAc implant. (E) Hypofluorescent lesions on ICGA at presentation. (F) Persistence of hypofluorescent lesions on ICGA over a period of 36 months. (G, H) Sequential SD-OCT images of the left eye from patient 3 showing cystoid macular oedema at baseline and complete resolution of CMO following Iluvien implant.

Figure 3

The LA 30Hz flicker ERG peak times (a), PERG P50 amplitudes (b) and main ERG component amplitudes in right (c) and left (d) eyes of case 1 are shown. The left eye (a, b and d) was treated with Ozurdex (vertical dotted line) 6 months prior to FAc implantation (solid vertical line for both eyes at time 0); the patient underwent additional treatment with systemic Adalimumab 18 months after implantation (vertical dashed line; a-d).
The LA 30Hz flicker ERG peak times (e), PERG P50 amplitudes (f) and main ERG component amplitudes in right (g) and left (h) eyes of case 3 are shown. The left eye (e, f and h) underwent treatment with Ozurdex (vertical dotted line) 4 months prior to left eye FAc implantation (0 months; vertical solid line); right eye was not treated with either.
In both individuals times in months are shown relative to implantation of Iluvien (FAc; 0 months; solid vertical line). The horizontal dashed grey line indicates the upper limit of normal timing (a, e) and the lower limit of normal amplitude (b-d and f-h). PERGs were recorded in both eyes to standard and large checkerboard fields, to better characterise macular function, and P50 amplitudes are plotted for both.

Figure 4: Results of fluorescein angiography of eyes with birdshot retinochoroiditis at baseline, 12,24 and 36 months after implantation of fluocinolone acetonide 0.19mg intravitreal device.

Vertical axis: percentage (%) of eyes
Horizontal axis: months after FAc implant
This graph demonstrates the change in fluorescein angiography findings over time in 15 eyes treated with FAc implant.

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d. **Contributorship statement**

S A-R performed data collection and wrote the manuscript with input from all authors. All authors contributed to literature review and preparation of the manuscript. MW, CP and AG R provided the concept and design, intellectual content and critical review of the manuscript. All authors read and approved the final manuscript.

e. **Competing interest**: there are no competing interests for any author

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