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RETINAL DISORDERS

Time to disease recurrence in noninfectious uveitis following long-acting injectable fluocinolone acetonide implant

Cindy X. Cai[1] · Cindy Skalak[1] · Robert T. Keenan[2] · Dilraj S. Grewal[1] · Glenn J. Jaffe[1]

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Abstract

Purpose To determine the time to disease recurrence with long-acting injectable fluocinolone acetonide implant (FAi) for noninfectious intermediate, posterior, and panuveitis.

Methods This was a retrospective study of patients with at least 12 months of follow-up who had completed a 2-year prospective, investigational new drug study with 0.18-mg FAi. Time to uveitis recurrence or cystoid macular edema (CME) occurrence was recorded.

Results Twelve eyes from 12 participants (mean age 43 years, range 25–64 years) were included. Patients were followed for a mean of 34.2 months (range, 12.0–56.9 months) after completion of the prospective trial. Five eyes (42%) did not have a documented uveitis recurrence or CME occurrence. Five eyes (42%) had a uveitis recurrence with the mean time to recurrence 36.1 months (range, 22.8–61.1 months) after FAi implantation. Two eyes (16%) had CME alone, the mean time to occurrence 36.9 months (range 36.1–42.1 months). On Kaplan-Meier analysis, the estimated probability of remaining recurrence-free 36 months after FAi implantation was 0.67 (95% confidence interval, 0.34–0.86).

Conclusions Data of study participants after completing a clinical trial suggest that the injectable FAi for noninfectious uveitis can provide control for 3 years on average. These long-term data support the use of FAi to control noninfectious uveitis.

Keywords Noninfectious uveitis · Intraocular steroid · Injectable fluocinolone · Retina

Introduction

Corticosteroids are effective to treat uveitis, and there are multiple available routes of delivery that include systemic, oral, or intravenous administration or locally as topical drops, periocular injection, intravitreal injection, or intravitreal sustained-release drug delivery system. [1–5] Compared to other treatment modalities, sustained-release intravitreal corticosteroid treatment offers the advantage of decreased treatment burden and fewer systemic side effects. Currently, there are three FDA-approved sustained corticosteroid delivery systems to treat noninfectious uveitis: a surgically implanted fluocinolone acetonide system, an injectable dexamethasone implant, and an injectable fluocinolone acetonide insert (FAi) [2, 6, 7].

The newest of these sustained-release corticosteroid options, the FAi, can be safely administered through a custom-designed 25-gauge needle injector in an office-based procedure. This insert provides a low dose (0.18 mg) of medication with initial sustained-release rate of 0.25 mcg/day [8]. The FAi is designed to deliver a low, daily corticosteroid dose for 36 months after implantation [9].

In eyes with chronic noninfectious uveitis, the FAi reduces intraocular inflammation recurrences when compared to sham [7, 9, 10]. However, detailed published data so far only describe the incidence of uveitis recurrences during the initial 12-month or 24-month period after FAi insertion [7, 9]. Data on uveitis recurrence after the second year post-implantation, as the FAi starts to become drug-depleted, are critically lacking. This longitudinal follow-up study seeks to characterize the real-world duration of effect for the FAi beyond 24 months post-implantation.

✉ Glenn J. Jaffe
glenn.jaffe@duke.edu

[1] Department of Ophthalmology, Duke University Medical Center, Durham, NC, USA

[2] Department of Rheumatology and Immunology, Duke University Medical Center, Durham, NC, USA

Methods

This was a retrospective, longitudinal follow-up study of participants who had completed a 2-year prospective, interventional, investigator-sponsored, investigational new drug (IND) study with the injectable FAi (ClinicalTrial.gov Identifier: NCT01694186). Approval to conduct the study was granted by the FDA and the Duke Institutional Review Board. The study adhered to the Declaration of Helsinki and the United States Code 21 of Federal Regulations. Written informed consent was obtained from all the participants. Participants were recruited nonconsecutively to the Duke University Eye Center between June 27, 2012, and August 4, 2016, and a single physician (GJJ) placed all FAis.

Study participants

Participants were included in the longitudinal follow-up study if they had more than 12 months of follow-up after completion of the 2-year prospective trial. Each participant contributed only one eye to the study. In eyes that received a second, sequential FAi, only data from the first implant were analyzed.

Inclusion criteria for the prospective trial have been previously described. [9] In brief, participants had a history of recurrent, noninfectious intermediate uveitis, posterior uveitis, or panuveitis for at least 1 year that required either systemic corticosteroid or nonsteroidal immunosuppressive agent given for at least 3 months before enrollment or at least 2 sub-Tenon's corticosteroid injections during the 6 months before enrollment. Alternatively, they must have had at least 2 separate recurrences of uveitis within 6 months before enrollment requiring systemic, intravitreal, or sub-Tenon's injection of corticosteroid or recurrence of uveitis after having received an intravitreal steroid implant (Ozurdex [Allergan, Irvine, CA] or Retisert [Bausch & Lomb, Rochester, NY]), or they were unable to tolerate the side effects of therapy with systemic corticosteroids or other nonsteroidal immunosuppressive agents. Participants were excluded if they had elevated intraocular pressure (IOP, ≥ 21 mmHg) in the study eye with more than one anti-ocular hypertensive medication or had a history of glaucoma or elevated IOP (>22 mmHg) in the study eye while receiving corticosteroids, unless the participant previously had undergone filtration surgery (tube shunt or trabeculectomy) for glaucoma. Patients were also excluded if they were receiving systemic immunosuppressive therapy to manage non-ocular disease.

Fluocinolone acetonide implants

The implants used in the study were provided by pSivida (now EyePoint Pharmaceuticals, Inc., Watertown, MA) and comprised a 0.18-mg FA drug core in a polyimide polymer tube. The FAi is designed to release drug for up to 36 months. One end of the implant is capped with a permeable polymer (polyvinyl alcohol), through which the drug is released and the other with either a permeable polymer (polyvinyl alcohol) or with an impermeable polymer (silicone). The implants were packaged in an injector attached to a 25-gauge needle used to deliver the FAi. The FAi was injected in the inferotemporal quadrant through the pars plana in a sterile fashion as previously described. [9]

Office visit assessments

After the 24 (± 2)-month follow-up for the prospective study, patients were seen and examined in the Duke Uveitis clinic at follow-up intervals per the discretion of the principal investigator (GJJ), sub-investigator of the study (DSG), or a directly supervised vitreoretinal fellow (WZ, MJ, SS, SW).

Assessments at each visit included best-corrected visual acuity (BCVA) measured with the Early Treatment Diabetic Retinopathy Study chart, IOP measured with Tonopen, slit lamp biomicroscopy, indirect ophthalmoscopy, and optical coherence tomography (OCT) using a Spectralis system (Heidelberg Engineering, Heidelberg, Germany) with a 61-line volume scan and 7-line raster scan protocol. Anterior chamber cells and vitreous haze were graded as previously described. [11, 12]

Changes in anti-inflammatory therapy, including increasing frequency of topical corticosteroids, administration of sub-Tenon's corticosteroid injection (i.e., Kenalog-40, Bristol Meyers Squibb Co., Princeton, NJ), administration of intravitreal corticosteroid injection (i.e., Triesence, Alcon, Fort Worth, TX), administration of intravitreal steroid implant (Ozurdex, Allergan Inc., Irvine, CA; or Retisert, Bausch & Lomb, Rochester, NY), prescription of oral corticosteroids, or changes in nonsteroidal immunosuppressive agents were recorded. Escalations in glaucoma therapy including prescription of new anti-ocular hypertensive medications or performance of incisional glaucoma surgery were noted. When available, notes of co-managing uveitis specialists were reviewed to ensure that no additional therapies were added.

Identification of uveitis recurrence

Uveitis recurrence was defined as an increase in anterior chamber cells by 2 steps or more, increase in vitreous haze score by 2 steps or more, or any increased inflammation in the study eye as determined by the treating physician that required additional anti-inflammatory therapy. Cystoid macular edema (CME) occurrence was recorded separately and defined as an increase in macular thickening of 10% or more in the central subfield thickness (CST) compared to prior visit or appearance of new retinal cysts on OCT.

Statistical analyses

Summary statistics were used to describe the frequency and duration of follow-up after prospective trial completion. The time to uveitis recurrence and CME occurrence were calculated. Kaplan-Meier survival analysis was used to quantify duration of uveitis remission. Differences between continuous variables were compared using unpaired *t* test with significance set at $P < 0.05$. Statistical analyses were conducted using STATA (Stata Statistical Software, Version 14.1 for Macintosh; Stata Corporation, College Station, TX).

Results

A total of 17 participants with noninfectious intermediate uveitis, posterior uveitis, or panuveitis completed the initial 2-year prospective trial, and results from the first 11 participants have been previously published [9]. Twelve eyes from 12 participants had follow-up at the Duke Uveitis Clinic more than 12 months after completion of the prospective trial and were included in the longitudinal follow-up study. Two participants did not have follow-up at Duke, and 3 participants had fewer than 12 months of follow-up; these participants were excluded.

Patient characteristics are shown in Table 1. The mean patient age was 43 years (range, 25 to 64 years). Of the 12 participants, 10 were women (83%), 6 were black (50%), 6 were white (50%), and 10 had bilateral disease (83%). The average uveitis duration before FAi insertion was 7.7 years (range, 1 to 15 years). Eight participants had anterior and intermediate uveitis, 3 had panuveitis, and 1 had posterior uveitis. Of the participants with associated systemic conditions, 3 had presumed sarcoidosis, 1 had biopsy-proven sarcoidosis, 1 had multiple sclerosis, 1 had juvenile idiopathic arthritis, and 1 had psoriatic arthritis. The participant with posterior uveitis had birdshot chorioretinitis.

Patients were followed after 2-year prospective trial completion for a mean of 34.2 months (range, 12.0 to 56.9 months) with an average of 9.3 visits (range, 2 to 18 visits) (Fig. 1). Nine participants (75%) had office visits at 12 (± 2) months after prospective trial completion, and 7 participants (58%) had office visits at 24 (± 2) months after trial completion. Office visits were completed by GJJ 88% (99/112) or by one of his associates 12% (13/112).

Ocular inflammation

Uveitis recurrences

Of the 12 eyes included in this longitudinal follow-up study, no eyes had a uveitis recurrence during the 2-year prospective trial (24 ± 2 months), but 5 eyes (42%) had a uveitis recurrence during the longitudinal study. The mean time to first uveitis recurrence was 13.8 months (range, 1.8 to 39.9 months) after the 2-year prospective trial completion and 36.1 months after FAi implantation (range, 22.8 to 61.1 months). One participant was diagnosed with a first uveitis recurrence 39.9 months after study completion but after 30.4 months of not being seen. Excluding this participant, the mean time to first recurrence was 7.3 months (range, 1.8–17.3 months) after the 2-year prospective trial was completed and 29.8 months (range, 22.8–42.1 months) after FAi implantation. When evaluating time to uveitis recurrence, only 1 participant out of 12 (8.3%) had a uveitis recurrence by 24 months after FAi implantation, 2 participants (16.7%) by 30 months, 3 (25%) by 33 months, and 4 (33.3%) by 36 months. On Kaplan-Meier analysis, the estimated probability of remaining uveitis free at 36 months was 0.67 (95% confidence interval, 0.34–0.86) (Fig. 2).

Of the 5 total uveitis recurrences, 5 had increased anterior chamber cells, and 3 of these also had increased vitreous haze. Four of these patients had a diagnosis of anterior and intermediate uveitis (of which 1 was associated with multiple sclerosis and 1 probable sarcoidosis) and 1 with panuveitis (associated with probable sarcoidosis). All eyes were initiated on additional anti-inflammatory therapy as determined by GJJ or DSG. Participants with a uveitis recurrence after FAi did not differ from those who did not by baseline CST, duration of uveitis, or age.

CME occurrences

Three eyes (25%) had an occurrence of CME during the prospective trial. In the longitudinal follow-up study, two eyes (17%) had an occurrence of CME, without an increase in anterior chamber cell or vitreous haze score, and required additional anti-inflammatory therapy (topical corticosteroids for one case and topical ketorolac for the other). These patients had a diagnosis of anterior and intermediate uveitis (1 associated with sarcoidosis and 1 with juvenile idiopathic arthritis). The mean time to CME recurrence was 13.3 months (range, 9.3 to 17.3 months) after the 2-year prospective trial completion and 36.9 months (range, 36.1 to 42.1 months) after FAi implantation. Participants with a CME occurrence had a thicker mean baseline CST at the start of the longitudinal study compared to those who did not (572 μM and 356 μM, respectively, one-tailed $P < 0.05$), but otherwise did not differ by duration of uveitis or age.

Recurrence-free group

Five eyes (42%) did not have a documented uveitis recurrence or CME occurrence during the longitudinal, follow-up study. These participants had an average of 6 office visits (range, 1 to 15 visits) with average follow-up of 29.8 months (range, 12.3

Table 1 Study participant characteristics

Patient no.	Age (years)	Gender	Ethnicity	Uveitis diagnosis	Associated systemic disease	Uveitis duration (years)	Laterality	Lens status	Glaucoma surgery	Systemic corticosteroids[α]	Nonsteroidal immunosuppressive[ß]	Length of follow-Up (months)[γ]
1	61	Female	White	Anterior and intermediate	Multiple sclerosis	11	Bilateral	Pseudophakic[*]				24.6
2	35	Female	Black or African American	Panuveitis	Probable sarcoid	15	Bilateral	Pseudophakic[*]		Prednisone 15 mg/day	MTX 25 mg/week	12.0
3	40	Male	Black or African American	Anterior and intermediate		11	Bilateral	Pseudophakic[*]				47.7
4	25	Female	Black or African American	Anterior and intermediate		1	Bilateral	CE/IOL (with FAi)[†]	Yes[§]		MTX 20 mg/week	56.9
5	50	Female	White	Panuveitis		11	Bilateral	CE/IOL (during)[‡]		Prednisone 10 mg/day	MMF 3000 mg/day	52.9
6	28	Female	White	Anterior and intermediate	Psoriatic arthritis	2	Unilateral	Pseudophakic[*]	During trial[‡]			23.3
7	64	Female	White	Anterior and intermediate	Probable sarcoid	4	Bilateral	CE/IOL (with FAi)[†]			Previously on MTX	13.7
8	47	Female	Black or African American	Anterior and intermediate	Sarcoid	14	Unilateral	Pseudophakic[*]				47.0
9	29	Female	Black or African American	Anterior and intermediate	JIA	4	Bilateral	CE/IOL (with FAi)[†]	Yes[§]		Previously on MTX	36.2
10	44	Female	White	Posterior		9	Bilateral	CE/IOL (after)[§]		Prednisone 5 mg/day	Previously on MMF	46.6
11	33	Male	Black or African American	Anterior and intermediate	Probable sarcoid	3	Bilateral	CE/IOL (with FAi)[†]	During trial[‡]			37.4
16	62	Female	White	Panuveitis		7	Bilateral	Pseudophakic				12.3

CE cataract extraction; *IOL* intraocular lens; *JIA* juvenile idiopathic arthritis; *MMF* mycophenolate mofetil, *MTX* methotrexate

[α] At the start of the longitudinal follow-up study

[ß] At the start of the longitudinal follow-up study

[γ] After 2-year prospective trial

[*] Eye was pseudophakic at the time of fluocinolone acetonide implant insertion

[†] Surgery was performed at the time of fluocinolone acetonide implant insertion

[‡] Surgery was performed after fluocinolone acetonide implant insertion but during the prospective trial

[§] Surgery was performed after the prospective trial for fluocinolone acetonide implant

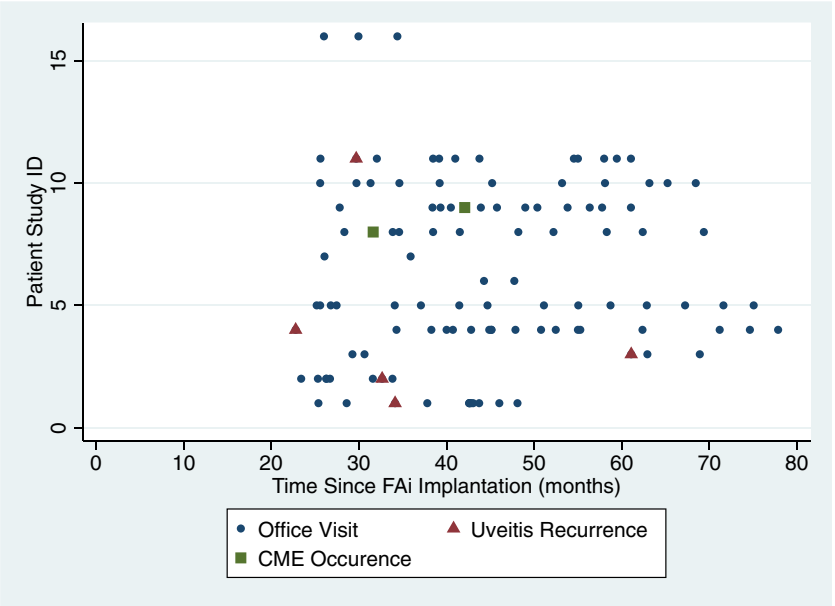

Fig. 1 Plot of each office visit (circle) after completion of the 2-year prospective trial. The first uveitis recurrence and CME occurrence are denoted separately (triangle and square, respectively)

to 52.9 months). Two participants received systemic corticosteroids—one for treatment of uveitis flare in the non-study eye and the other for an unrelated rash. In both patients, the treatment started around 3 months after study completion, but both patients were followed for a total of 46.6 to 52.9 months with 11 to 15 visits, respectively.

Anti-inflammatory therapy

Systemic therapy

The use of systemic corticosteroids and nonsteroidal immunosuppressive were overall reduced for most participants. For systemic corticosteroids during the longitudinal study, 1 participant had a reduced dose from 10 to 1 mg, 2 received it temporarily (less than 3 months) for uveitis recurrences in the study eye but otherwise were not on corticosteroids, 1 received an increased dose for an unrelated rash and then returned to the maintenance dose of 5 mg, and 1 stayed on the same dose of 15 mg/day for control of uveitis in the non-study eye.

For systemic nonsteroidal immunosuppressive medication, 6 of 12 participants were either on mycophenolate mofetil (2 participants) or methotrexate (4 participants) at the time of FAi implantation. The mycophenolate mofetil was discontinued in 1 participant by the end of the prospective trial who stayed off

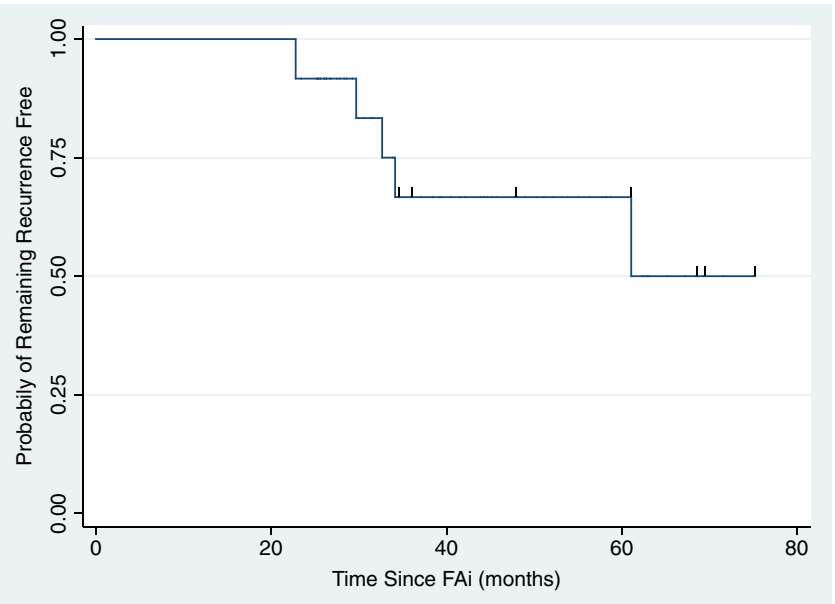

Fig. 2 Kaplan-Meier analysis of cumulative recurrence rates over the follow-up period. Censored data are indicated with vertical tick marks

of it during longitudinal follow-up. In the other participant, the mycophenolate mofetil was reduced from 3000 to 1000 mg/day during the prospective trial and was discontinued 15 months after trial completion. Of the 4 participants on methotrexate, 2 were weaned off the medication during the prospective trial. One participant stayed on the same dose of methotrexate 25 mg/week throughout the prospective trial and longitudinal follow-up. One participant initially had the dose of methotrexate increased from 20 to 25 mg/week immediately after the completion of the prospective trial but was eventually weaned off the medication 50 months later.

Safety

Visual acuity

The mean logarithm of the minimum angle of resolution (logMAR) visual acuity at the beginning of the longitudinal follow-up study was 0.32 (range 0 to 1.51) (Snellen equivalent 20/31.4, range 20/20 to 20/640). At 12 (± 2) months after the prospective trial, the mean logMAR visual acuity was 0.47 (range 0 to 1) (Snellen equivalent 20/42, range 20/20 to 20/200) and at 24 (± 2) months 0.59 (range 0 to 1.2) (Snellen equivalent 20/47, range 20/20 to 20/320). At the end of the longitudinal follow-up study, the visual acuity was 0.37 (range 0 to 0.9) (Snellen equivalent 20/37.7, range 20/20 to 20/160).

Elevated intraocular pressure

Two eyes underwent Ahmed Glaucoma Valve (New World Medical, Rancho Cucamonga, CA, USA) implantation to control IOP elevations during the prospective trial, as previously reported. During the longitudinal follow-up study, 4 eyes had IOP elevations above 21 mmHg. One was attributed to measurement variability, and the other 3 (25%) were successfully managed with topical anti-ocular hypertensive medication. Two eyes eventually received incisional glaucoma surgery, but the indication was to decrease the topical medication burden rather than uncontrolled IOP.

Cataracts

All eyes were pseudophakic at the start of the longitudinal follow-up period; 6 eyes were pseudophakic at the start of the prospective trial, 4 underwent cataract extraction and intraocular lens placement at time of FAi insertion for existing cataract, and 2 eyes underwent cataract extraction during the course of the prospective trial or immediately thereafter.

Adverse events

During the 2-year prospective trial, 3 eyes had transient hypotony (IOP < 7 mmHg) on the first and seventh days after FAi implantation that resolved spontaneously without sequelae. None had hypotony during the longitudinal follow-up study. No eyes during the prospective trial or follow-up afterward had endophthalmitis, retinal tear, retinal detachment, severe vitreous hemorrhage, or suprachoroidal hemorrhage.

Discussion

As a novel therapeutic agent in the armamentarium for the treatment of noninfectious uveitis, FAi has unique advantages over existing implants in that it can be administered in an office-based procedure and is designed to last longer than both Retisert (30 months) and Ozurdex (3 months). This study is the first to demonstrate the effect of FAi through nearly 5 years of follow-up after implantation. Our real-world experience suggests that the effect of the injectable FAi can be maintained on average for 36 months, with the first recurrences occurring 23 months after implantation. Although direct comparisons of results from various uveitis treatment trials are inexact due to different study designs, initial experience with FAi, including this study, suggests comparable if not better inflammation control compared to other sustained-release corticosteroids including Retisert and Ozurdex [2, 6, 7, 9].

The uveitis recurrence rates observed in this study are lower than initial results from the phase 3, prospective, randomized, double-masked, sham-controlled clinical trial of FAi. The recurrence rates found in this population were 0% versus 27.6% at 12 months and 33.3% versus 56.3% at 36 months [10]. Differences between the studies could be the result of a different patient population included in this study; for example, there were more women and African Americans in the present study when compared to the randomized study. Another key difference was the definition of uveitis recurrences. The addition of systemic medications (i.e., steroids) without a 2 step increase in inflammation in the study eye was not defined as a uveitis recurrence. This circumstance occurred in 2 participants, both in the recurrence-free group. Moreover, in addition to documented increases in anterior chamber or vitreous inflammation, the clinical trial defined missing designated ophthalmic assessments as a uveitis recurrence. In this study, we did not impute recurrences on the basis of missed study visit since the intervals between follow-up visits were variable at the discretion of the treating physician, and there were no pre-specified study visits at which a missed visit would have been recorded. As indicated above, one study participant presented with a recurrence nearly 40 months after study completion but after 30 months of not being seen. However, even when this study participant was excluded, the mean time to first uveitis recurrence was nearly 30 months after FAi implantation.

As with other sustained corticosteroid delivery systems, there are safety concerns with FAi, including cataract formation and elevated IOP. Consistent with the existing data, a high percentage

of patients in this study were pseudophakic by 24 months after FAi, and all eyes had undergone cataract extraction soon after the 2-year prospective trial. Similarly, elevated IOP was also observed after the initial 24-month period, but these elevations appeared transient, and each incident was adequately controlled on topical anti-ocular hypertensive medication. Long-term elevations of IOP requiring incisional glaucoma surgery for adequate intraocular pressure control were nonexistent. By contrast, with Retisert implants, rates of incisional glaucoma surgery are as high as 36.6% with a mean time to surgery from device implant of 2.4 years. [13] The reason for the favorable side effect profile of the FAi compared to the Retisert on IOP elevation is not entirely clear. However, we hypothesize that a lower corticosteroid release rate with FAi (0.25 mcg/day) compared to Retisert (0.6 mcg/day), a difference in inclusion criteria for the study, and/or closer proximity of the Retisert to the ciliary body and trabecular meshwork might have contributed to this difference. The visual acuity at the end of the follow-up compared to the beginning was slightly decreased (20/37.7 compared to 20/31.4). This apparent decline could just reflect the variability in obtaining visual acuity in the regular office setting outside the context of a clinical trial.

This study has several limitations, including its retrospective nature and variable follow-up intervals. Although the number of patients included is relatively small, this study provides real-world data on the duration of effect of the FAi, uveitis recurrences with the implant, and the first to include data for patients beyond 3 years after implantation. Data after 2 years of FAi implantation were collected retrospectively, with varying follow-up intervals at the discretion of the treating uveitis specialist and treatment decisions made by a single investigator, and thus, the results may not necessarily be generalizable. Despite these limitations, this study is the first to quantify average time to uveitis recurrence with the FAi. The results in this study and the completed but not yet published prospective 3-year study of FAi will be valuable to guide management decisions when using FAi for noninfectious uveitis.

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Compliance with ethical standards

Conflict of interest CXC: none
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GJJ: EyePoint Pharmaceuticals, Inc. (consultant)

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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