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Effect of an Injectable Fluocinolone Acetonide Insert on Recurrence Rates in Chronic Noninfectious Uveitis Affecting the Posterior Segment

Twelve-Month Results

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Purpose: To assess the safety and efficacy of an intravitreal fluocinolone acetonide (FA) insert to manage inflammation associated with chronic noninfectious posterior uveitis.

Design: Multicenter, randomized, prospective, doubled-masked, sham-controlled, 3-year phase 3 clinical trial.

Participants: One hundred twenty-nine participants with recurrent noninfectious posterior uveitis were assigned randomly to FA insert (n = 87) or sham injection (n = 42). The more severely affected eye in participants with bilateral disease was designated as the study eye.

Methods: The insert (FA, 0.18 mg) was injected into the vitreous cavity; sham injection mimicked the insert delivery procedure. Ophthalmic examinations, OCT, and ocular tolerability and discomfort assessments were conducted; study visits were on days 7 and 28 and months 2, 3, 6, 9, and 12. Uveitis recurrence was treated as needed. The 6-month recurrence rate was the primary outcome measure.

Results: The 6-month (28% and 91%) and 12-month (38% and 98%) uveitis recurrence rates were significantly lower ($P < 0.001$) with FA insert vs. sham, respectively. Fewer recurrences per study eye (mean, 0.7 vs. 2.5), lower incidence of 15-letter or more decrease in best-corrected visual acuity (14% vs. 31%), and reduced systemic (19% vs. 40%) and local (7% vs. 62%) uveitis adjunctive treatments were observed with FA insert vs. sham, respectively. The FA insert group showed higher rates of cataract. Intraocular pressure-lowering treatment use was similar between groups. No deaths, treatment-related study discontinuations, or unanticipated safety signals were observed through 12 months.

Conclusions: Chronic noninfectious posterior uveitis was managed successfully in this study population; FA insert eyes experienced fewer uveitis recurrence episodes, required fewer adjunctive treatments, and demonstrated less visual acuity loss compared with sham eyes. The FA insert treatment group showed higher rates of cataract; delivery by injection was not associated with an increase in ocular adverse events or any other safety measures not typically associated with local steroid use, suggesting the procedure is appropriate for an office setting. *Ophthalmology 2019;126:601-610 © 2018 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.aaojournal.org.

Current treatment for chronic noninfectious uveitis of the posterior segment of the eye includes systemic, local, or topical corticosteroids alone or in combination with systemic immunosuppressants or with immunosuppressants alone when corticosteroids are not indicated, provide insufficient inflammation control, or are not well tolerated. Topical corticosteroids generally are ineffective for treating intermediate or posterior uveitis resulting from poor intravitreal absorption, and systemic treatments often have treatment-limiting side effects.[1,2]

Recurrent bouts of inflammation occurring in chronic uveitis, if left untreated or undertreated, can damage surrounding tissue, leading to reduced vision in the afflicted eye.[3,4] The treatment goals for noninfectious uveitis are to induce disease quiescence, to limit involvement of structures adjacent to the disease site, and to preserve or improve vision.[5] The ideal treatment, which targets the disease site and limits systemic exposure in the absence of uveitis-associated systemic disease, is a low dose to reduce known ocular side effects of corticosteroid treatments, is long lasting to reduce

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the dosing frequency, and is applied easily to reduce patient inconvenience and side effects associated with application methods.[4,6,7] Intravitreal drug delivery systems, newly available or currently in clinical development, may help clinicians meet these goals.[7,8]

Ozurdex (Allergan, Irvine, CA) is an injectable 0.7-mg dexamethasone-containing intravitreal insert available to treat noninfectious uveitis affecting the posterior segment of the eye. A prospective, sham-controlled, randomized study[9,10] evaluated the effects of 0.7-mg or 0.35-mg dexamethasone inserts compared with a sham injection on ocular inflammation and vision-related functional outcomes. Improved visual acuity and lower rescue medication use, but higher rates of increased intraocular pressure (IOP) and cataract, were observed over the 26-week period after implantation for study eyes treated with Ozurdex compared with sham injection. If clinically indicated, Ozurdex may be readministered; however, there is limited information on repeated administration in uveitis patients.[11]

Retisert (Bausch & Lomb, a division of Valeant Pharmaceuticals North America, LLL, Bridgewater, NJ) is a surgically placed intravitreal fluocinolone acetonide (FA)-containing (0.59 mg) implant to treat posterior uveitis. It delivers drug for up to 3 years, thereby eliminating the need for frequent repeat applications. In a randomized 2-year trial,[12] uveitis was controlled better with an FA insert (0.59 mg) than standard systemic steroid treatment at 24 months (88% vs. 71% controlled; $P = 0.001$); however, visual acuity was similar between groups and higher rates of increased IOP, cataract, and cataract surgery were seen with the FA insert. In 2 separate 3-year studies,[13,14] eyes treated with 0.59- or 2.1-mg implants showed significantly reduced recurrence rates at 3 years (range, 20%−26%) compared with that observed in the 1-year period before implantation (range, 42%−62%). At 3 years after implantation, study eyes showed greater gains in best-corrected visual acuity (BCVA) and reduced rescue medication requirements compared with the year before implantation and with the nonimplanted fellow eye. Increased IOP occurred in approximately 2 of 3 implanted study eyes, and cataract surgery was required in nearly all phakic implanted eyes.

Recently, Jaffe et al[15] reported results of a double-masked, long-term, dose-comparator study of an 0.18-mg FA-containing intravitreal injectable insert in eyes with chronic noninfectious intermediate uveitis, posterior uveitis, or panuveitis. The insert continuously administered FA microdoses at 1 of 2 rates to achieve a high- and low-dose regimen, each of which were less than the dose delivered by Retisert. After 24 months, all 11 implanted eyes showed improved signs of intraocular inflammation, preserved or improved visual acuity, and reduced requirements for local or systemic anti-inflammatory therapies compared with the 24-month preimplantation period. There were no significant differences in outcomes between dose regimens. Compared with the fellow eye, treated eyes showed a trend toward increased IOP requiring medical intervention: 5 study eyes required at least 1 treatment with eye drops, and 2 study eyes underwent surgical filtration. Although the study was small, the results showed the potential for lower rates of increased IOP compared with the higher FA dose delivered with Retisert.

Based on the positive results of this initial FA insert study, the current clinical trial was initiated to evaluate the effect of a low-dose, single-application FA insert to prevent recurrent episodes of inflammation in participants with chronic noninfectious intermediate uveitis, posterior uveitis, and panuveitis. With a larger study population and longer exposure period than previously evaluated, the current study planned to define further the benefit-to-risk profile in this patient population. The FA insert delivers a low daily corticosteroid dose for 3 years and is injected during an office-based procedure. Accordingly, we hypothesized that the FA insert would control inflammation; would reduce vision-threatening, corticosteroid-related ocular adverse events; and would compare favorably with currently approved intraocular sustained delivery systems. Herein, we report the prespecified primary outcome end point of the study (6-month analyses) and 12-month results of this phase 3 controlled study of an FA insert to treat noninfectious uveitis affecting the posterior segment of the eye (clinicaltrials.gov identifier, NCT01694186).

Methods

The study is a 3-year, prospective, randomized, doubled-masked, sham-controlled clinical trial evaluating the efficacy and safety of a preloaded, injectable FA insert to prevent recurrence of noninfectious uveitis that affects the posterior segment of the eye. Thirty-three clinical sites in the United States, Europe, Israel, and India enrolled participants. All site institutional review boards or institutional ethics committees reviewed and approved the study protocol and other relevant study-related documents, including the site-specific informed consent form (Table S2, Appendix 1, available at www.aaojournal.org, for a list of participating study sites). The study complied with the Declaration of Helsinki, United States Code 21 of Federal Regulations, and all other local regulations.

Study Participants

All participants provided written informed consent; those eligible for study participation were at least 18 years of age, had a diagnosis of noninfectious uveitis affecting the posterior segment of at least 1 eye (with or without anterior uveitis) for a minimum of 1 year, had experienced at least 2 separate recurrences of uveitis requiring systemic corticosteroid or immunosuppressant treatment or intraocular or periocular corticosteroid injections, or had received in the 12 months preceding study entry (1) systemic therapy (corticosteroid or other systemic treatment) for a minimum of 3 months or (2) at least 2 intraocular or periocular corticosteroid injections to manage uveitis (see Appendix 1, available at www.aaojournal.org, for additional eligibility criteria).

Fluocinolone Acetonide Inserts

Fluocinolone acetonide (0.18 mg) was contained in the core of a polyamide polymeric cylinder (3.5-mm long with a 0.37-mm outer diameter) with an impermeable silicon cap on one end and a permeable polyvinyl alcohol membrane on the other end. A preloaded sterile applicator with a 25-gauge needle was used to inject the implant through the pars plana into the vitreous cavity. After placement, drug was delivered through the permeable end of the cylinder at an approximate initial rate of 0.2 μg FA daily, decreasing to 0.1 μg daily over the 36-month study period. The sham applicator was an empty 1-ml syringe to which a blunt 18-gauge needle was attached.

Insert Injection Procedure

The FA insert and sham injectors were packaged identically. Study eyes were pretreated with a topical antibiotic (1 drop every 5 minutes for a total of 3 drops); the FA insert was injected into the intravitreal space as described previously.[15] Study eyes in the sham injection group underwent the same procedures, except that rather than administering an injection, the investigator placed the blunt needle of the sham injector against the sclera of the study eye and then exerted pressure to mimic the injection procedure and to mask the participant to treatment assignment.

Study Design

Treatment was assigned in a 2:1 ratio (FA insert-to-sham injection). Treatment randomization was stratified by systemic treatment for uveitis control at study entry and was stratified further by type of treatment (corticosteroid or immunosuppressant). An independent statistical group generated the randomization code, which was accessed for participant assignment through a central interactive voice response system. At each site, one unmasked investigator administered study treatment and performed day 1 assessments, and one masked investigator performed all study assessments after day 1. The injected insert typically remains in a peripheral location within the vitreous base and is not detected easily on routine ophthalmologic examination. Regardless, we cannot exclude the possibility that the insert could have been visible in some study participants. All other study personnel and participants were masked to treatment assignment and remained so throughout the study. The primary analysis was planned at 6 months; secondary analyses were planned at 12 and 36 months. The affected eye in unilateral uveitis, the more seriously affected eye in bilateral uveitis, and the right eye in equally affected, symmetrical uveitis were identified as the study eyes. Standard systemic or topical treatment to manage uveitis at study entry was allowed so long as such treatment was withdrawn within 3 months of the day 1 study visit, in a manner consistent with the recommended dose reduction schedule for the treatment being administered.

Study Visit Assessments

Participants were evaluated at a screening visit within 30 days before the day 1 visit. Thereafter, they were assessed as shown in the schedule of assessments by study visit found in Table S1 (available at www.aaojournal.org). Additional visits occurred if medically necessary. Medical treatment of elevated IOP was at the investigator's discretion but was required if IOP was more than 30 mmHg. Treatment continued as medically necessary; unresponsive increased IOP was treated using other interventions (e.g., glaucoma drainage procedure). Cataract removal by extracapsular extraction with phacoemulsification, as with any other elective ocular procedure, was performed no less than 4 weeks before a scheduled study assessment day. Fluocinolone acetonide insert could be removed in cases of drug or insert intolerance, endophthalmitis, or partial insert extrusion or exposure.

Outcome Measures

Efficacy End Points. The primary outcome, which was performed on the intent-to-treat population, was the difference between study groups in the proportion of participants who showed recurrence of uveitis by month 6. To avoid attributing an inflammatory response to the implantation procedure, assessments for uveitis recurrence began after day 7. The clinical definition of uveitis recurrence used in the study was (1) a 2-step or more increase in the number of cells in the anterior chamber per high-powered field (×1.6 using a 1-mm beam),[16] (2) a 2-step or more increase in vitreous haze,[17] or (3) a deterioration in visual acuity of 15 letters or more of BCVA using Early Treatment Diabetic Retinopathy Study chart visual acuity (Lighthouse 2nd edition [Light House Low Vision Products, Long Island City, NY] or Precision Vision ETDRS [Precision Vision, Villa Park, IL]). In each instance, the cause of the change must have been attributable only to noninfectious uveitis. Further, a recurrence event was imputed if, for a previously nonrecurrent study eye, the study eye was treated with a prohibited local or systemic medication, or the participant had a missing ophthalmic assessment at the 6- or 12-month visit. Prohibited medications were defined as follows: (1) oral, systemic, injectable, or topical corticosteroids or (2) systemic immunosuppressants.

Secondary end points included treatment-group comparisons through 12 months of recurrence rate, cumulative number of recurrences, time to first recurrence, BCVA change from baseline, resolution of macular edema (clinical assessment based on OCT imaging), and number of adjunctive treatments used. Uveitis recurrence was treated with periocular or intraocular corticosteroid injections or topical medications; systemic immunosuppressants or corticosteroids were reserved for use if topical or local treatments had failed.

Safety End Points. Safety assessments included changes in visual acuity, anterior chamber cells,[16] vitreous haze,[17] IOP, and cataract status; IOP- or cataract-related medical or surgical procedures; tolerability and discomfort assessments; adverse events; vital signs; laboratory tests; and concomitant medication use (adverse event definitions are available in Appendix 1, available at www.aaojournal.org).

Statistical Analyses

The primary efficacy analysis was the treatment-group comparison of the proportion of participants with a recurrence of uveitis in the study eye by the 6-month time point. The study sample size of 120 participants (80 and 40 patients for FA insert and sham treatment groups, respectively) was calculated based on the primary end point; treatment groups were not sized to detect statistically significant differences in secondary end points (additional details are available in Appendix 1, available at www.aaojournal.org).

Results

Participant Disposition

A total of 129 participants with noninfectious uveitis affecting the posterior segment were randomized to treatment in 6 countries (56 participants in the United States, 42 participants in Europe and the Middle East [United Kingdom, Germany, Hungary, and Israel], and 31 participants in India). A list of participating sites is found in Table S2 (available at www.aaojournal.org), with 87 participants randomized to FA insert and 42 to sham injection (Fig 1). The first participant was enrolled on August 8, 2013, and the last participant was enrolled on March 30, 2015. Data cutoff for the primary analysis at 6 months was September 21, 2015, and that for the 12-month analysis was April 16, 2016. Three participants discontinued the study before the 12-month data cutoff date. Mean ± standard deviation number of days on study was 357±24.4 days (FA insert) and 354±29.4 days (sham injection).

Treatment group mean age was similar, and predominantly female participants were included (Table 3). At study entry, similar proportions of participants in each group were receiving systemic corticosteroid or immunosuppressive therapy. Overall, average

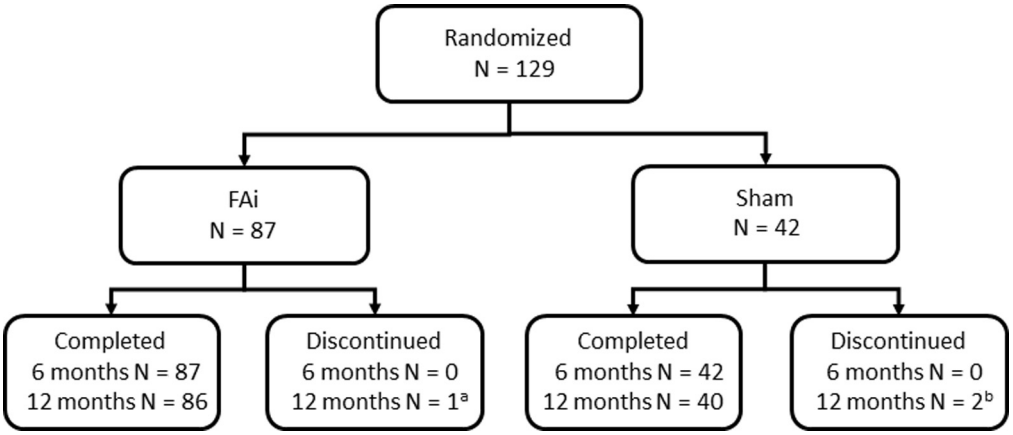

Figure 1. Flowchart showing the disposition of study participants at 12 months. [a]Voluntary withdrawal; [b]lost to follow up; FAi = fluocinolone acetonide insert.

disease duration was greater in the FA insert group when compared with the sham group (7.8 vs. 5.6 years, respectively), and the proportion of FA insert group participants with disease duration greater than 5 years was nearly twice that observed in the sham group. A lower proportion of FA insert than sham injection study eyes (45% vs. 50%, respectively) had a vitreous haze severity of 1/2+.

Recurrence of Uveitis

The 6-month uveitis recurrence rate, the primary study end point, was significantly lower in FA insert eyes than sham injection eyes (27.6% vs. 90.5%, respectively; Table 4). Between 6 and 12 months, the recurrence rates increased in both treatment groups but remained significantly lower for FA insert (37.9%) than sham injection study eyes (97.6%). At both time points, the uveitis recurrence rate was significantly lower ($P < 0.001$) for FA insert study eyes. The mean number of recurrences per study eye was lower with FA insert than with sham injection through 12 months (0.7±1.22 vs. 2.5±1.67, respectively). In either treatment group, most of the recurrence events were imputed rather than observed, although by 6 months, higher rates of observed events occurred with sham injection (12 of 38 [32%]) than with FA insert (1 of 24 [4%]).

The median time to the first recurrence episode was 378.0 days (95% confidence interval, 362.00 days—not evaluable) for FA insert study eyes and 70.5 days (95% confidence interval, 57.00—91.00 days) for sham injection study eyes. The likelihood of a recurrent uveitis episode was greater for sham injection compared with FA insert through the first 12 months of the study (Fig 2). Post hoc analyses of uveitis recurrence risk showed hazard ratios of 7.08; similar results were seen when the data were stratified by baseline systemic uveitis therapy and by type of therapy (data shown in Fig S3, available at www.aaojournal.org).

Adjunctive Treatments for Inflammation Control

Through 12 months, 19% of FA insert group participants and 40% of sham injection group participants had undergone at least 1 systemic corticosteroid or immunosuppressant treatment. Topical corticosteroid treatment was administered to 21% of FA insert and 48% of sham injection study eyes; 7% and 62%, respectively, of study eyes had undergone at least 1 intraocular or periocular steroid treatment. A post hoc analysis of systemic uveitis treatment use through 12 months stratified by baseline use showed a significant treatment-group difference favoring FA insert in the cohort that was being treated systemically at baseline (Fig 4).

Visual Acuity

The mean BCVA change from baseline at 12 months was greater in the FA insert group (5.8±14.36 letters) than the sham injection group (3.3±12.78 letters), but the treatment-group difference was not statistically significant ($P = 0.353$). A loss of 15 letters or more at any assessment was less common in FA insert study eyes compared with sham injection study eyes through month 12 (14% vs. 31%; $P = 0.021$; Fig 5). Only study eyes with a baseline BCVA of 70 letters or fewer could reasonably be expected to realize a 15-letter gain during the study (85 letters are the equivalent of 20/20 visual acuity). Baseline BCVA of 70 letters or fewer was reported for 62% of FA insert study eyes and 76% of sham injection study eyes, suggesting a lower proportion of FA insert eyes could reasonably be expected to realize a 15-letter improvement over baseline. However, nearly twice the percentage of FA insert vs. sham injection study eyes (22% vs. 10%; $P = 0.110$) showed a 15-letter improvement from baseline at the 12-month visit.

Macular Edema

The pro vs. portion of study eyes with macular edema decreased from baseline over the first 12 months of the study in both treatment groups. Among study eyes that were evaluated by OCT at both baseline and 12 months, 71% (35/49) of FA insert and 48% (13/27) of sham injection study eyes with macular edema reported by the investigator at baseline had no macular edema reported at 12 months. Study eyes in both treatment groups without baseline macular edema remained free of macular edema at 12 months.

Baseline mean central subfield thickness (CST) was 368.0±145.0 μm and 369.5±165.4 μm for FA insert and sham injection study eyes, respectively. In the FA insert study eyes, mean CST decreased by 61.3 μm at day 28 and it remained stable through 12 months, whereas in the sham study eyes, CST increased by 7.5 μm at day 28 and decreased more gradually through 12 months. At 12 months, the mean CST was 285.5±75.6 μm and 303.7±113.1 μm for FA insert and sham injection study eyes, respectively (Fig S6, available at www.aaojournal.org).

Vitreous Haze and Anterior Chamber Cell Count

Vitreous haze stabilized or improved with FA insert during the first 12 months of the study (Fig S7, available at www.aaojournal.org).

Table 3. Demographics and Baseline Characteristics

	Treatment Groups			
	Fluocinolone Acetonide Insert	*Sham*	*Total*	**P Value***
No. of participants	87	42	129	
Mean age (SD), yrs	48.3 (13.9)	48.3 (13.7)	48.3 (13.8)	>0.9999†
<60	65 (74.7)	32 (76.2)	97 (75.2)	0.8555‡
≥60	22 (25.3)	10 (23.8)	32 (24.8)	
Female gender	50 (57.5)	29 (69.0)	79 (61.2)	0.2060‡
Race				0.8241§
White	60 (69.0)	26 (61.9)	86 (66.7)	
Black	4 (4.6)	3 (7.1)	7 (5.4)	
Asian	21 (24.1)	12 (28.6)	33 (25.6)	
Other	2 (2.3)	1 (2.4)	3 (2.3)	
Mean duration of uveitis (SD), yrs	7.8 (6.69)	5.6 (6.82)	7.1 (6.79)	0.0844†
<2	15 (17.2)	14 (33.3)	29 (22.5)	0.0178‡
2–5	25 (28.7)	16 (38.1)	41 (31.8)	
>5	47 (54.0)	12 (28.6)	59 (45.7)	
Mean BCVA (SD), letters	66.9 (15.49)	64.9 (15.53)	66.3 (15.47)	0.4936†
Vitreous haze severity				0.5810‡
0/0.5+	48 (55.2)	21 (50.0)	69 (53.5)	
1/2+	39 (44.8)	21 (50.0)	60 (46.5)	
Severity of macular edema (μm)				0.3147‡
CST <300	37 (42.5)	14 (33.3)	51 (39.5)	
CST ≥300	48 (55.2)	27 (64.3)	75 (58.1)	
Systemic treatment for uveitis control				0.9973‡
None	43 (49.4)	21 (50.0)	64 (49.6)	
Corticosteroid therapy	27 (31.0)	13 (31.0)	40 (31.0)	
Immunosuppressive therapy	17 (19.5)	8 (19.0)	25 (19.4)	

BCVA = best-corrected visual acuity; CST = central subfield thickness; SD = standard deviation.
Data are No. (%) unless otherwise indicated.
*Post hoc analysis.
†Two-sample *t* test.
‡Chi-square test.
§Fisher exact test.

Vitreous haze also improved in the sham injection group, but as with BCVA changes, at a lower rate than that observed with FA insert. Improvements in anterior chamber cell counts followed a similar pattern, with improvements observed in both treatment groups, but proportionally more study eyes showed improvements with FA insert (Fig S8, available at www.aaojournal.org).

Intraocular Pressure

At each study visit through 12 months, the mean change from baseline IOP was slightly greater in FA insert than sham injection study eyes (Fig S9, available at www.aaojournal.org); at the 12-month visit, mean IOP generally was unchanged in sham injection eyes (0.2±4.17 mmHg), whereas a slight mean increase

Table 4. Uveitis Recurrence Rates at 6 and 12 Months

	Fluocinolone Acetonide Insert	Sham	Odds Ratio (95% CI)
No. of participants in intention-to-treat population	87	42	
6 mos*	24 (27.6)	38 (90.5)†	24.94 (8.04–77.39)
Observed	1 (1.1)	12 (28.6)	
Imputed	23 (26.4)	26 (61.9)	
12 mos	33 (37.9)	41 (97.6)†	67.09 (8.81–511.06)
Observed	3 (3.4)	12 (28.6)	
Imputed	30 (34.5)	29 (69.0)	

Data are no. (%) unless otherwise indicated. *P* value based on rates of no recurrence.
CI = confidence interval.
*Primary end point.
†$P < 0.001$.

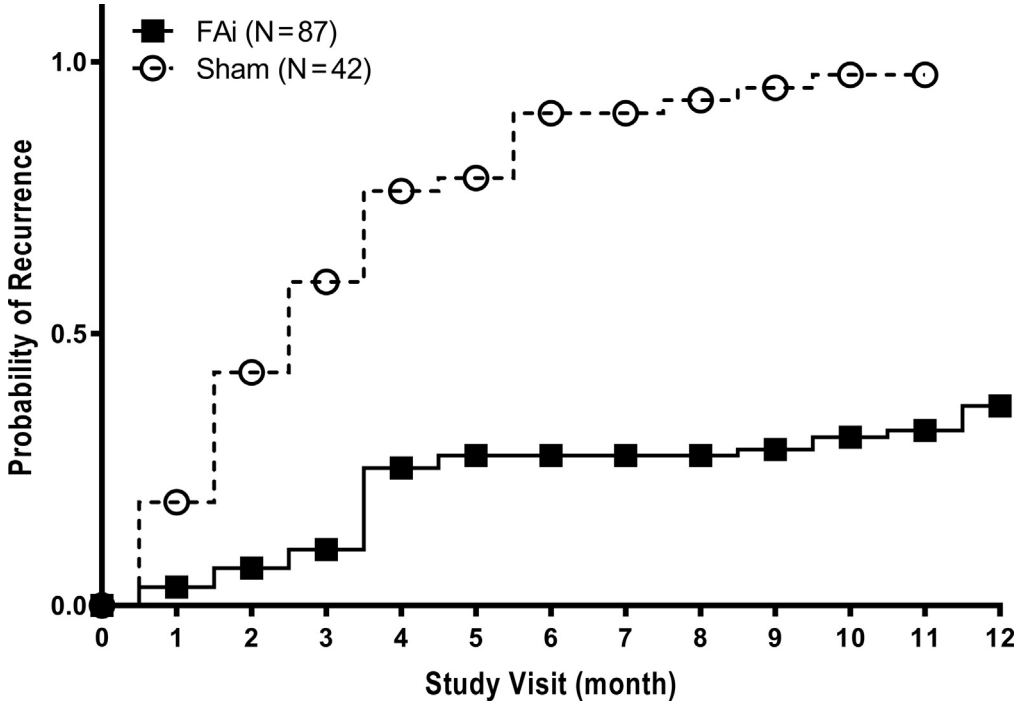

Figure 2. Kaplan–Meier time-to-event analysis of cumulative recurrence rates by treatment (fluocinolone acetonide insert [FAi] and sham) over the 12-month period.

was noted for FA insert eyes (1.3±3.57 mmHg). Through the first 12 months of the study, the FA insert was associated with higher rates of IOP of 25 mmHg or more, or 30 mmHg or more, and an increase of more than 5 mmHg or more than 12 mmHg over baseline values compared with sham injection (Table 5). Intraocular pressure-lowering medication was used in similar proportions of study eyes in both treatment groups during the first 12 months of the study (26% of FA insert study eyes and 26% of sham injection study eyes). More FA insert than sham study eyes required more than 1 medication for increased IOP through

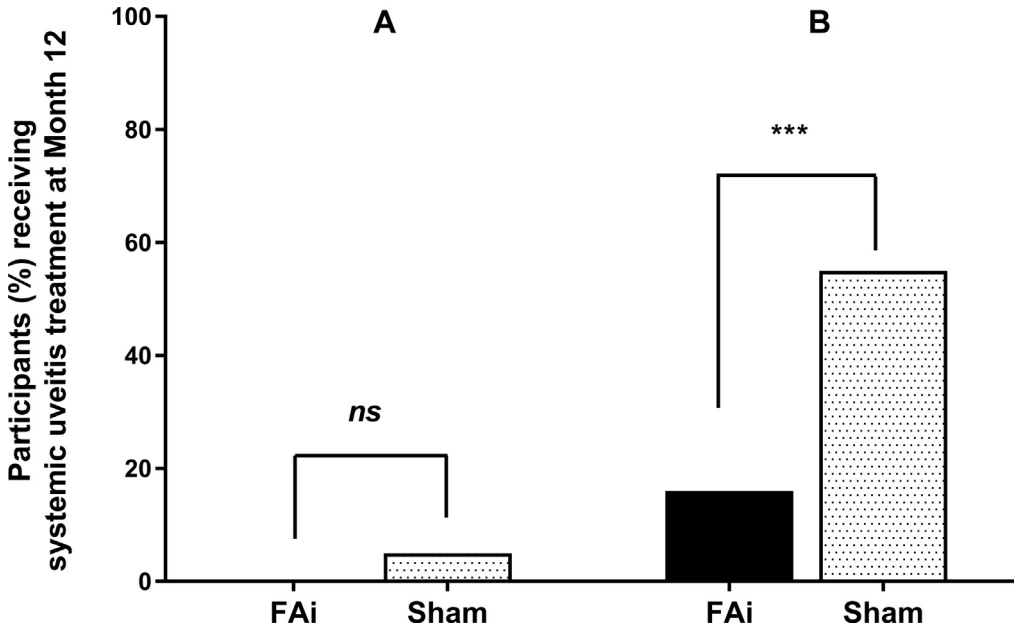

Figure 4. Bar graphs showing the proportion of study eyes receiving systemic treatment for uveitis during the first 12 months of the study by systemic treatment at baseline: (**A**) cohort not receiving systemic corticosteroids or immunosuppressant uveitis at baseline (fluocinolone acetonide insert [FAi], n = 41; sham, n = 20), and (**B**) cohort receiving systemic corticosteroids or immunosuppressant uveitis treatment at baseline (FAi, n = 44; sham, n = 20). ns = not significant. ***$P < 0.001$.

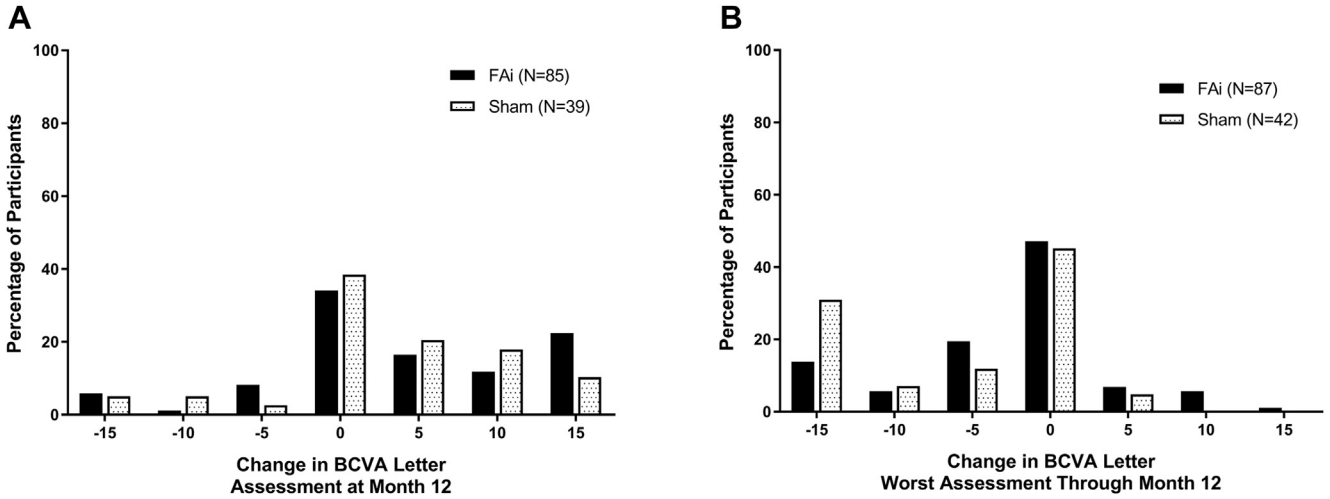

Figure 5. Bar graphs showing the proportion of study eyes with gains or losses from baseline in (**A**) best-corrected visual acuity (BCVA) at month 12 (fluocinolone acetonide insert [FAi], n = 85; sham, n = 35) and (**B**) worst BCVA through month 12 (FAi, n = 87; sham, n = 42). For the month 12 time point, only data from study eyes with an assessment at both baseline and month 12 are included. For the worst BCVA calculation, only data from study eyes with a baseline assessment and at least 1 assessment after baseline are included (safety population data set).

the first 12 months of the study (Table S6, available at www.aaojournal.org). Three FA insert and 2 sham injection study eyes required surgical intervention to treat elevated IOP. New-onset glaucoma was reported in the study eye of 1 participant in each treatment group.

Cataract

Of the 42 FA study eyes that were phakic at baseline, 14 (33%) required cataract surgery during the first 12 months of the study. Over the same period, 1 phakic sham injection eye (5%) required cataract surgery. Post hoc analysis showed a significant increased risk for cataract development among study eyes treated with FA insert compared with those treated with sham injection (33% vs. 12%, respectively; odds ratio, 3.7; $P < 0.01$).

Treatment-Emergent Adverse Events

The incidence of at least 1 treatment-emergent ocular adverse event (AE; Medical Dictionary for Regulatory Activities [MedDRA] preferred terms) through 12 months was 80% in FA insert and 93% in sham injection study eyes. Approximately half of the participants in both treatment groups experienced a nonocular AE during the first 12 months of the study. Nasopharyngitis was the most common nonocular AE in both groups. Table S7 (available at www.aaojournal.org) includes a list of ocular AEs (study eye only) and nonocular AEs that occurred in at least 5% of participants in either treatment group.

Sixteen participants, 9 (10.3%) in the FA insert group and 7 (16.7%) in the sham injection group, experienced protocol-defined serious ocular AEs (Table S8, available at www.aaojournal.org). The most common serious ocular AEs were increased IOP (2 participants [2.3%]) and cataract (4 participants [4.6%]) in FA insert study eyes and macular edema, noninfectious endophthalmitis, and uveitis (each experienced by 2 participants [4.8%]) in sham injection study eyes. Serious AEs, ocular or nonocular, were manageable and did not result in either treatment or study discontinuation. No deaths were reported during the first 12 months of the study.

Discussion

During the first 12 months of this 3-year study, the insert provided effective management of intraocular inflammation associated with chronic noninfectious posterior uveitis as evidenced by significantly lower recurrence rates noted at 6 months and sustained through 12 months ($P = 0.001$), fewer uveitis recurrences per study eye, and a longer time to onset of recurrence compared with sham injection. Efficacy results were consistent across subgroups. No unexpected safety findings were observed with the minimally invasive FA insert (0.18 mg).

The study protocol included a 3-month anti-inflammatory medication taper and then a comparison against sham of uveitic recurrence rate at 6 months. This tapering strategy was the result of regulatory discussions with the Food and Drug Administration on study design. The rationale for the tapering protocol was to determine whether sustained FA release achieved with the FA insert would result in delayed uveitis recurrence rates in patients with no concomitant use of steroids by the time of the primary efficacy readout at 6 months. The tapering strategy was similar to that used in a phase 3 adalimumab study to treat noninfectious intermediate posterior and panuveitis, in which systemic corticosteroids were tapered over 15 weeks.[18]

At the start of the study, half of participants in either treatment group were receiving systemic corticosteroids or immunosuppressants (3:2 ratio) to manage uveitis; these medications were tapered and discontinued over the first 3 months of the study. At both the 6- and 12-month time point, the proportion of sham injection participants requiring systemic corticosteroids or immunosuppressants to treat uveitis increased, whereas use in the FA insert group decreased over the same period, consistent with the lower rate of study eye recurrences observed in the FA insert group. The treatment-group disparity in adjunctive therapy

Table 5. Intraocular Pressure at Any Visit after Baseline through 12 Months*

Intraocular Pressure	Fluocinolone Acetonide Insert (n = 87)	Sham (n = 42)	Odds Ratio†	P Value†
≥25 mmHg	17 (19.5)	5 (11.9)	1.7971	0.2799‡
≥30 mmHg	11 (12.6)	2 (4.8)	2.8947	0.2197§
Increase from baseline >5 mmHg	42 (48.3)	14 (33.3)	1.8667	0.1086‡
Increase from baseline >12 mmHg	16 (18.4)	4 (9.5)	2.1408	0.1923‡

Data are no. (%) unless otherwise indicated.
*Participants with an intraocular pressure reading at both baseline and the study visit are included in the analysis.
†Post hoc analysis.
‡Chi-square test.
§Fisher exact test.

use was not unexpected and indicates that the FA insert reduced the requirement for rescue therapy through the 12 months of follow-up compared with sham injection. Nearly half of participants who received sham injection required rescue therapy because of uveitis recurrence. Consequently, treatment-group differences in efficacy end points and general safety measures, such as visual acuity, macular edema, and changes in IOP or cataract status, were confounded by adjunctive steroid or immunosuppressant therapy use during the study period through month 12.

The typical disease course of chronic uveitis is recurrence, treatment, and quiescence, and then the cycle repeats; with each successive episode of inflammation, there is a risk for incremental vision loss.[19] Our data suggest that extended uveitis control offered by the intravitreal delivery of daily submicrogram FA doses may prove beneficial to minimize the cumulative damage that results from repeated cycles of recurrence. In this 12-month analysis, visual acuity was preserved or improved more often with FA insert, with fewer 15-letter BCVA reductions and more 15-letter improvements compared with sham injection. The FA insert resulted in greater proportional shifts to letter gains at both 6 and 12 months, and fewer FA insert study eyes showed letter losses. In contrast, at 6 months, half of sham injection study eyes showed a decrease in BCVA; this proportion of participants with reduced BCVA was smaller by the 12-month visit, likely because of the high percentage of sham injection participants who were given adjunctive therapies to control uveitis. At 12 months after implantation in the Multicenter Uveitis Steroid Treatment (MUST) trial,[12] eyes treated with Retisert (0.59 mg) had a group mean improvement in BCVA of 4.6 letters (standard error, 1.38 letters) compared with a group mean of 5.8 letters (standard deviation, 14.36 letters) at 12 months in the current study. The FA insert treatment effect on BCVA improvements may be underestimated in our study because proportionally more FA insert study eyes than sham injection study eyes showed baseline BCVA of more than 70 letters, limiting the degree to which visual acuity could improve.

Our study excluded participants using IOP-lowering medication in the study eye at study entry. During the first 6 months of the study, 18% of FA insert study eyes required IOP-lowering medication, a rate that compares favorably with that reported in the 26-week Ozurdex study (25% with 0.35 mg and 22% with 0.70 mg).[9] The IOP medication use rate in FA insert study eyes was 26%, a lower rate than that reported for Retisert (0.59 mg) over the same period (58%).[20] The observed lower use of IOP-lowering medication with the FA insert in the present study may be the result of including participants with a lower risk of IOP elevation at study entry, exposure to a lower corticosteroid release rate during the study, or both.

Nearly all phakic eyes treated with Retisert are expected to demonstrate cataract and require surgical correction within 3 years after implantation.[21] Among phakic eyes treated with Ozurdex, 61% required cataract surgery, generally between months 18 and 39.[22] In the present study, 33% of phakic eyes treated with FA insert required cataract surgery beyond 12 months after implantation. We anticipate that there will be an increase in the incidence of both cataract and cataract surgery with increased study follow-up, but the magnitude of increase remains to be established.

Direct comparisons of results in noninfectious posterior uveitis studies are difficult because of different study design, inclusion or exclusion criteria, definition of recurrence, severity of baseline disease, duration of treatment, dose and dosing regimen, study end points, and timing of assessments. These caveats notwithstanding, the inflammation control observed during the first 12 months of our study compares favorably with that of Retisert,[12,14] Ozurdex,[9] and adalimumab.[19,23] Consistent with previous reports, the injectable FA insert application was generally well tolerated, without any nonocular serious sequelae.

Study limitations include enrollment of participants without severe active inflammation at the time of the initial study treatment and lack of stratification by uveitis etiology. Evaluation of the therapeutic effect of FA insert in uveitic eyes with more significant active ocular inflammation than that included in the current study and in the uveitis subset stratified by anatomic location, cause, or both likely would yield additional useful information to the practicing clinician, particularly considering the ceiling effect for possible visual acuity improvements based on BCVA letters gained, a constraint that likely disproportionately affected the FA insert treatment group.

Our data suggest that the 0.18-mg intravitreal FA insert is a promising treatment to control inflammation associated with noninfectious uveitis affecting the posterior segment over an extended period. The FA insert can be administered in an office-based setting. Few adverse events associated with the treatment were observed, and those that were observed generally were consistent with known effects of

corticosteroids administered intravitreally. Insert removal was not required during the first 12 months of the study. These data represent the early results of a pivotal trial. Analysis of the study data through 36 months, as well as additional randomized well-controlled studies, are needed to confirm these 12-month results and to quantify the benefits of continuous long-term control of intraocular inflammation.

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Abbreviations and Acronyms:
AE = adverse event; **BCVA** = best-corrected visual acuity; **CST** = central subfield thickness; **FA** = fluocinolone acetonide; **IOP** = intraocular pressure; **ITT** = intent-to-treat; **SD** = standard deviation.

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