# Long-term Follow-up Results of a Pilot Trial of a Fluocinolone Acetonide Implant to Treat Posterior Uveitis

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***Purpose:*** To investigate the safety and efficacy of a fluocinolone acetonide intravitreal implant in the treatment of noninfectious posterior uveitis.

***Design:*** Noncomparative interventional case series, dose randomized, dose masked, prospective.

***Participants:*** Thirty-six eyes of 32 patients with a history of recurrent noninfectious posterior uveitis.

***Methods:*** Patients were randomized to receive either a 0.59-mg or a 2.1-mg fluocinolone acetonide intravitreal implant. Patients were observed every 4 to 6 weeks for the first 3 months and then every 3 months thereafter.

***Main Outcome Measures:*** Preoperative and postoperative ocular inflammation, visual acuity (VA), antiinflammatory medication use, and safety.

***Results:*** Mean follow-up duration was 683±461 days (range, 204–1817). Mean baseline visual acuity for the device-implanted eyes was +1.1 logarithm of the minimum angle of resolution (logMAR) units (20/250), which improved significantly to +0.81 logMAR units (20/125) at 30 months ($P<0.05$). Inflammation was effectively controlled over the follow-up period. The average number of recurrences in the 12 months before implantation was 2.5 episodes per eye. None of these eyes experienced a recurrence for the first 2 years after implantation. There was a reduction in systemic and local therapy use in the device-implanted eyes; of the patients who remained on systemic medication after implantation, dosage was reduced in 68%. The posterior sub–Tenon's capsule injection rate significantly decreased from a mean of 2.2 injections per eye per year to 0.07 injections per eye per year ($P<0.0001$) The most common adverse event was intraocular pressure (IOP) rise. At baseline, 11.0% of eyes used pressure-lowering agents, versus 56.1% over the follow-up period ($P = 0.005$). Filtering procedures were performed in 7 (19.4%) eyes. Four of the 8 phakic eyes, each of which had some level of cataract at device implantation, subsequently underwent cataract extraction. There were no device explantations or patients lost to follow-up during the investigation.

***Conclusion:*** The fluocinolone acetonide intravitreal implant effectively controlled intraocular inflammation in the studied population. Elevated IOP and cataracts that occurred in fluocinolone device–implanted eyes were managed by standard means. The fluocinolone acetonide sustained drug delivery implant seems to be promising in patients with posterior uveitis who do not respond to or are intolerant to conventional treatment. *Ophthalmology 2005;112:1192–1198 © 2005 by the American Academy of Ophthalmology.*

Management challenges of chronic posterior uveitis are well known to the ophthalmic specialist. Corticosteroids, the mainstay of therapy, are the drug of choice to treat inflammation, but treatment success is often hindered by systemic adverse effects.[1] Methods to deliver medications to treat uveitis are plentiful, and all are plagued with limitations. For example, topical delivery is associated with poor posterior segment bioavailability; periocular injections have potential risk of globe perforation, orbital fibrosis, and ptosis; and intravitreal injections are associated with risk of endophthalmitis and/or pseudoendophalmitis.[2] Immunosuppressive agents are generally used as steroid-sparing agents when there is an inadequate response or intolerance to systemic corticosteroids. However, these drugs are often associated with toxic systemic side effects. Moreover, all of these delivery modalities require repeated administration. In

Originally received: December 10, 2004.
Accepted: March 8, 2005. Manuscript no. 2004-391.

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Supported by National Institutes of Health, Bethesda, Maryland (core grant no.: P30 EY05722; Duke Eye Center).

Dr Jaffe has received research support from Control Delivery Systems Inc. Dr Butuner has received consulting fees from Bausch & Lomb Inc. Dr Ashton has business ownership exceeding 1% in Control Delivery Systems Inc.

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ISSN 0161-6420/05/$–see front matter
doi:10.1016/j.ophtha.2005.03.013

the case of systemic and topical therapy, efficacy may be further limited by patient compliance. The chronic nature of posterior uveitis thus has led to the search for a more continuous local method to deliver corticosteroids to the posterior segment.

To overcome the limitations of currently available drug delivery routes, delivery systems for the sustained release of medication within the posterior segment have been developed. These systems offer a promising approach to the treatment of ocular disease in cases where systemic drug administration may be associated with unacceptable toxicity and where repeated intravitreal injection carries unacceptable risk. A nonbiodegradable intravitreal implant (Vitrasert, Bausch & Lomb, Rochester, NY) was approved in 1996 to deliver ganciclovir to the posterior segment for cytomegalovirus retinitis treatment.[3,4] More recently, a nonbiodegradable fluocinolone acetonide intravitreal implant has been developed. In pharmacokinetic studies, drug delivery was linear, with no drug peaks and troughs, and drug release was projected for approximately 1000 days.[5]

In November 2000, we reported results of the first human study to use a fluocinolone acetonide implant to treat 7 eyes of 5 patients with severe posterior uveitis. In that study, 10 months on average after device implantation, visual acuity (VA) was stabilized or improved, and inflammation was controlled in all eyes.[6] In the present study, we expand on the initial investigation and report the results of a long-term prospective study of the fluocinolone acetonide sustained drug delivery implant to treat patients with severe chronic posterior uveitis.

## Materials and Methods

Five eyes of 4 patients were included from the original report (1 patient from the original report was not operated on by the first author and, hence, was not included in the current report). Each of these eyes received a 2.1-mg device. One eye from this initial series received a 15-mg device, projected to release the drug over 18 years. The remaining 4 eyes received a 2.1-mg device designed to release fluocinolone acetonide at a targeted initial release rate of 2 $\mu$g/day over 1000 days. The average duration of follow-up for this initial cohort of eyes has been extended from 11.8 months (range, 4.5–19) to 57.4 months (range, 47–62). Thirty-one additional eyes of 28 patients (not included in the original report) were randomized to receive either a 0.59-mg or a 2.1-mg fluocinolone acetonide implant, designed to release the drug at a targeted initial release rate of 0.6 $\mu$g/day or 2 $\mu$g/day, respectively, over a 1000-day period. All patients were recruited nonconsecutively to the Duke University Eye Center between November 1998 and March 2003, and surgeries were done by a single surgeon (GJJ). Patients were deemed eligible to receive an implant if they met all of the following criteria: a history of recurrent noninfectious posterior uveitis or intermediate uveitis with or without iridocyclitis; incomplete therapeutic response or treatment-limiting side effects to oral, periocular corticosteroid, and/or immunosuppressive agents; VA of at least light perception; intraocular pressure (IOP) controlled at $\leq$21 mmHg with no more than 1 topical ocular antihypertensive agent; and ability to comprehend informed consent and comply with follow-up examinations. Patients were excluded if they had an allergy to fluocinolone acetonide or any component of the delivery system, presence of a toxoplasmosis scar in the study eye, or peripheral retinal detachment (RD) in the area of implantation or tested positive for human immunodeficiency virus. Also excluded were female patients who were pregnant or lactating or not taking precautions to avoid pregnancy. An investigator-sponsored investigational new drug application was submitted to the Food and Drug Administration. Approval to conduct the study was granted by the Food and Drug Administration and the Duke Institutional Review Board. Informed consent was obtained from all patients. In patients with bilateral disease, the study eye was the more severely affected eye meeting entry criteria. In patients with unilateral disease, the affected eye was the study eye. At the investigator's discretion, patients with bilateral disease who met the study eligibility criteria could be considered for an implant in the fellow eye once the original study eye was stable for a period of 6 months. Both the investigator and the patient were masked to the implant dose at patient enrollment and throughout the study.

Follow-up visits after the first week took place at least every 4 to 6 weeks for 6 months, and every 3 months thereafter. Assessments included best-corrected VA, measured by an Early Treatment Diabetic Retinopathy Study chart; Goldman tonometry; slit-lamp biomicroscopy; indirect ophthalmoscopy; and, when possible, bilateral fundus photography, fluorescein angiography, Humphrey visual field testing, and optical coherence tomography. Prespecified safety measures included IOP increase and/or cataract development requiring surgical intervention, endophthalmitis, RD, hypotony ($<$7 mmHg on 3 consecutive visits), suprachoroidal and/or severe vitreous hemorrhage, and any event that necessitated device explanation. Detailed results of fluorescein angiography and optical coherence tomography will be reported in a separate article.

In the event of clinical recurrence in either eye (defined as an end point), patients were treated based on the clinician's medical judgment. The protocol did not specify recurrence treatment guidelines. Recurrence was deemed to have occurred when any of the following conditions were met: an increase in the number of anterior chamber cells by 2 grades (grading scale previously described[6]), new chorioretinitis at the margin of an area of chorioretinal atrophy (in the case of a patient with serpiginous chorioretinopathy), or administration of a posterior sub–Tenon's capsule triamcinolone acetonide injection. Posterior sub–Tenon's capsule injections could be given to the device-implanted or fellow eye for a 2-grade increase in anterior chamber cells, a decrease in VA, or an increase in cystoid macular edema (CME), or whenever the investigator felt that it was clinically necessary. Systemic therapy with corticosteroids or other immunosuppressants was initiated when an ocular recurrence could not be controlled with periocular steroid injections or after a flare-up of systemic disease.

Statistically significant differences in the change from mean baseline VA and comparisons of before and after posterior sub–Tenon's capsule injections and before and after ocular antihypertension medication use rates were determined by paired-sample *t* tests. When the *P* value for the associated Shapiro–Wilk test for normality was $<$0.01, an appropriate signed rank test was utilized. *P* values for the mean logarithm of the minimum angle of resolution (logMAR) VA comparisons between the device-implanted and fellow eyes were determined by the Wilcoxon signed rank test. Kaplan–Meier survival analyses were used to estimate the percentage of eyes that were recurrence free, ocular antihypertensive medication free, and filtering surgery free after device implantation. *P* values of $<$0.05 were considered statistically significant.

### Surgical Procedure

The pupil was dilated with cyclopentolate 1% and neosynephrine 2.5%. Most patients were given a retrobulbar or peribulbar block that consisted of 4% lidocaine and 0.75% bupivacaine 1:1 (vol-