Risk Factors Associated With Intraocular Pressure Increase in Patients With Uveitis Treated With the Fluocinolone Acetonide Implant

Anjali Parekh, MD; Sunil Srivastava, MD; James Bena, MS; Thomas Albini, MD; Quan Dong Nguyen, MD, MSc; Debra A. Goldstein, MD

IMPORTANCE Elevated intraocular pressure (IOP) is a well-known adverse event associated with the fluocinolone acetonide implant (FAI), but no data are available regarding factors associated with increased risk of IOP elevation in patients treated with the FAI.

OBJECTIVE To report risk factors that may predispose patients to elevated IOP after treatment with the FAI.

DESIGN, SETTING, AND PARTICIPANTS Data from 3 multicenter, 3-year, prospective, randomized, phase 2b/3 clinical trials evaluating the safety and efficacy of the FAI were pooled and analyzed. Patients had no underlying glaucoma and at least one eye with a history of recurrent noninfectious uveitis affecting the posterior segment. Patients were treated with 1 or more of the following: systemic therapy (corticosteroids or other immunosuppressive drugs) for at least 3 months before enrollment, 2 or more sub–Tenon capsule corticosteroid injections for uveitis management during the 6 months before enrollment, or systemic corticosteroid or sub–Tenon capsule corticosteroid injection therapy required for at least 2 separate recurrences within 6 months before enrollment.

MAIN OUTCOMES AND MEASURES Factors evaluated as risk factors for IOP elevation included age, sex, lens status, uveitis severity at enrollment, and location of uveitis.

RESULTS Data analyses were based on 641 eyes. A total of 351 eyes did not receive the FAI, whereas 290 eyes had the 0.59-mg FAI placed. An increase in IOP of 10 mm Hg or elevation to 30 mm Hg was seen in 60 untreated eyes (17.1%) and 188 treated eyes (65.1%) (hazard ratio, 5.80; 95% CI, 4.28-7.70; P < .001). A total of 8 untreated eyes (2.3%) required surgical intervention for elevated IOP compared with 93 treated eyes (32.1%) (hazard ratio, 16.48; 95% CI, 8.24-32.96; P < .001). In patients with the FAI, younger age, male sex, and phakic lens status were associated with higher risk of IOP elevation and the need for glaucoma surgery (P = .003, P < .001, and P < .001, respectively).

CONCLUSIONS AND RELEVANCE Patients receiving the FAI are at higher risk of developing an IOP increase of 10 mm Hg or an absolute IOP of 30 mm Hg when compared with patients without the FAI. Patients who are male, younger, and phakic are at an even higher risk for elevated IOP and possibly glaucoma surgery.
The intravitreal fluocinolone acetonide implant (FAI) (Retisert; Bausch & Lomb Inc) is a Food and Drug Administration–approved therapy for the treatment of chronic noninfectious intermediate, posterior, and panuveitis. The efficacy of this implant has been reported in 3 multicenter, 3-year, prospective randomized clinical trials.1,2,3

Elevated intraocular pressure (IOP) is a well-known adverse event secondary to the use of the FAI.2,3 Previous analysis, using pooled data from the aforementioned studies, reported that approximately three-fourths of eyes with uveitis treated with the FAI developed elevated IOP, requiring IOP-lowering agents, whereas one-third required IOP-lowering surgery within 3 years of implantation.4 However, no data are available regarding patient factors associated with increased risk of IOP elevation.

Risk factors for IOP elevation have been characterized for patients receiving intravitreal or sub-Tenon capsule injections of triamcinolone acetonide.3,6 However, to date, no clearly established risk factors for IOP elevation in patients treated with long-acting intravitreal FAIs have been defined. The purpose of this report is to analyze pooled data from 3 multicenter randomized clinical trials, including only eyes with the 0.59-mg FAI (the Food and Drug Administration–approved dose), to describe characteristics that may predispose patients to elevated IOP after implantation of long-acting intravitreal FAIs.

Methods

Studies

Data from 3 phase 2b/3, prospective, multicenter randomized clinical trials evaluating the safety and efficacy of the FAI during a 3-year period in eyes with noninfectious intermediate, posterior, and panuveitis were pooled to characterize the risk factors associated with elevated IOP. All patients provided written informed consent; all governing institutional review boards provided approvals, which were updated annually. Two of the 3 studies evaluated both the 0.59-mg and 2.1-mg FAIs. For this analysis, only the 0.59-mg FAI data were included because this is the dose used in clinical practice. Other data from these trials have previously been published.1,2

The first study (NCT00407082) was a 3-year, double-masked, randomized, multicenter, controlled, phase 2b/3 safety and efficacy trial of 278 eyes of 278 patients undergoing treatment with the FAI. The study was performed at sites in the United States (n=26) and Singapore (n=1), and 2 doses of the FAI were compared. The second study (NCT00468871) was a 3-year, randomized, multicenter, phase 2b/3 study of 146 patients with noninfectious posterior uveitis that compared the safety and efficacy of the 0.59-mg FAI with standard-of-care treatment. This study was performed at 43 sites in Europe, Israel, and Saudi Arabia. The third study (NCT00456482) was a 3-year, double-masked, randomized, multicenter, controlled, phase 2b/3 safety and efficacy study that evaluated 2 doses of the FAI in 239 patients. The study was performed at 19 sites in the United States, Canada, China, India, Australia, and the Philippines. Before enrollment, patients were stratified according to their use of systemic or local therapy, such as corticosteroids or other immunosuppressive drugs.

To be eligible for enrollment, patients had at least one eye with a history of recurrent noninfectious uveitis affecting the posterior segment for at least 1 year treated with at least 1 of the following: (1) systemic corticosteroid or other systemic therapy for at least 3 months before enrollment, (2) at least 2 sub–Tenon capsule corticosteroid injections for management of uveitis during the 6 months before enrollment, or (3) systemic corticosteroid or sub–Tenon capsule corticosteroid injection therapy required for at least 2 separate recurrences within 6 months before enrollment. The eye with worse uveitis was enrolled in patients with bilateral disease.

In all 3 studies, ophthalmic examination, including IOP measurements, were conducted on days 1 and 2 and at weeks 1, 4, 8, 12, 18, 24, 30, 34, and 52 after implantation of the FAI. After the 1-year visit, follow-up visits were at 3-month intervals for an additional 2 years. Visual field measurements were conducted at baseline and at selected visits during the postimplantation follow-up. Patients who did not receive implants were treated with local therapy or systemic therapy, depending on the study.

Elevated IOP and Management

Goldmann applanation tonometry was used to measure IOP. The mean of 3 measurements in each eye was recorded as the IOP. The IOP measurements were not corrected for central corneal thickness. In eyes with elevated IOP, topical IOP-lowering medication was used as first-line treatment. Topical IOP-lowering medications included all classes of drugs currently approved by local agencies, with choice of medication at the discretion of the investigator. The use of any IOP-lowering medication was recorded at every study visit. If IOP-lowering medications did not adequately control IOP, IOP-lowering surgery was performed. Surgical intervention, specifically trabeculectomy, glaucoma drainage device implantation, or cyclophotocoagulation for IOP management, was chosen by a glaucoma specialist in most cases. No criteria were specified for the initiation of IOP-lowering surgery or choice of surgery; these were at the discretion of the physician.

Complete success of IOP-lowering surgery was defined as postoperative IOP of 6 to 21 mm Hg that did not require additional IOP-lowering medications. Qualified success was defined as postoperative IOP of 6 to 21 mm Hg that required additional topical IOP-lowering medications.

Statistical Analysis

Analysis was performed on data from untreated and treated eyes. Treated eyes were those receiving the 0.59-mg FAI, whereas untreated eyes included fellow eyes from treated patients and both eyes from standard-of-care patients. In general, fellow eyes of patients who received the implant were treated with other local therapies. Statistical analysis was used to correct for the inclusion of 2 eyes per study participant. Outcomes for evaluation included IOP elevations of 10, 20, 30, and 40 mm Hg, absolute IOP of 30, 40, and 50 mm Hg, and time to glaucoma surgical intervention. Possible risk factors for IOP elevation included age, sex, lens status, recurrence of disease, and type of uveitis.
Intraocular Pressure Risk Factors

Table 1. Baseline Characteristics of the Cohort by Treated and Untreated Eyes*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Untreated Eyes (n = 351)</th>
<th>Treated Eyes (n = 290)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>338</td>
<td>274</td>
</tr>
<tr>
<td>Mean (SD) age, y</td>
<td>43.0 (14.7)</td>
<td>43.1 (15.4)</td>
</tr>
<tr>
<td>Median (range) age, y</td>
<td>43.5 (7.6-80.9)</td>
<td>43.1 (7.6-84.1)</td>
</tr>
<tr>
<td><strong>Baseline IOP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>350</td>
<td>289</td>
</tr>
<tr>
<td>Mean (SD) IOP, mm Hg</td>
<td>14.8 (3.7)</td>
<td>14.7 (4.1)</td>
</tr>
<tr>
<td>Median (range) IOP, mm Hg</td>
<td>15.0 (2.0-40.0)</td>
<td>15.0 (4.0-31.0)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>124 (35.3)</td>
<td>109 (37.6)</td>
</tr>
<tr>
<td>Female</td>
<td>227 (64.7)</td>
<td>181 (62.4)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>231 (67.2)</td>
<td>157 (54.3)</td>
</tr>
<tr>
<td>Other than white</td>
<td>113 (32.8)</td>
<td>132 (45.7)</td>
</tr>
<tr>
<td><strong>Phakic lenses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>100 (28.5)</td>
<td>117 (40.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>251 (71.5)</td>
<td>173 (59.7)</td>
</tr>
<tr>
<td><strong>Previous recurrence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>222 (63.2)</td>
<td>127 (43.8)</td>
</tr>
<tr>
<td>1</td>
<td>74 (21.1)</td>
<td>71 (24.5)</td>
</tr>
<tr>
<td>2</td>
<td>37 (10.5)</td>
<td>58 (20.0)</td>
</tr>
<tr>
<td>≥3</td>
<td>18 (5.1)</td>
<td>34 (11.7)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate uveitis</td>
<td>117 (33.3)</td>
<td>93 (32.1)</td>
</tr>
<tr>
<td>Panuveitis or posterior uveitis</td>
<td>234 (66.7)</td>
<td>197 (67.9)</td>
</tr>
</tbody>
</table>

Abbreviation: IOP, intraocular pressure.

* Data are presented as number (percentage) of patients unless otherwise indicated.

ease, and location of uveitis. When evaluating age, patients were categorized in groups of younger than 30, 30 through 39, 40 through 49, and 50 through 59 years. Location of uveitis was separated into intermediate uveitis and posterior or panuveitis. Recurrence was defined as uveitis recurrences before study enrollment and as such was viewed as a marker of disease severity at study entry.

For univariate models, categorical factors were summarized using frequencies and percentages, whereas continuous measures were described using means (SDs) and medians (ranges). Time-to-event analyses were used to identify risk factors for the first occurrence of each outcome. Hazard ratios from Cox proportional hazards models, which represent the risk of an outcome event, were presented with 95% CIs. When both eyes of study participants were included in a model, marginal models that included robust SE estimates were used. The proportional hazards assumption was evaluated for each model graphically. Multivariable Cox proportional hazards models were used to identify significant predictors of time to increases in IOP or glaucoma surgery.

Cup-disc ratio and Humphrey visual field mean deviation were also analyzed. Comparisons of treated eyes, untreated eyes, and standard-of-care eyes were performed as were comparisons between treated eyes that required surgical intervention and those that did not. Linear mixed-effect models, assuming a compound symmetry correlation structure for the association of results within eyes over time, were fit using the outcomes of interest as the response variable and time and group as predictors along with their interaction to allow the pattern of measurement change over time to differ by group. Visits for these analyses were restricted to the screening visit, 12-month visit, and 24-month visit. These models adjusted for phakic lens status, age, and sex. Analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc), and R software, version 2.15 (R Foundation for Statistical Computing). All comparisons assumed a significance level of $P < .05$.

### Results

Data analyses were based on 641 eyes. A total of 351 eyes were treated with systemic (corticosteroids or immunomodulatory therapy) or local therapy (topical or periocular corticosteroids) but did not receive the implant, whereas 290 eyes were treated with the 0.59-mg FAI. For clarity, patients who received the FAI are referred to in this discussion as treated, and those who received only systemic or local therapy and did not have the FAI are referred to as untreated. Table 1 gives the demographic comparisons between all treated and untreated eyes. Untreated eyes had fewer recurrences and were more likely to be from patients who were white and patients who were phakic.

In the 351 untreated eyes, an IOP increase of 10 mm Hg or elevation to 30 mm Hg was seen in 60 eyes (17.1%) compared with 188 (65.1%) of 290 treated eyes (hazard ratio, 5.80; 95% CI, 4.28-7.70; $P < .001$). Only 8 untreated eyes (2.3%) required surgical intervention for elevated IOP compared with 93 treated eyes (32.1%) (hazard ratio, 16.48; 95% CI, 8.24-32.96; $P < .001$). Because only 8 untreated eyes (2.3%) required glaucoma surgery, risk profiling of this group was based on small numbers and was not statistically significant.

Evaluation of risk factors (age, sex, lens status, recurrence of disease before study enrollment, and location of disease) revealed that elevation of IOP of 10 mm Hg or reaching an absolute threshold of 30 mm Hg was more likely in younger treated
patients (patients younger than 30 years or in the 30- to 39-year age group; \( P = .003 \)). Similarly, treated male patients and phakic patients were more likely to have IOP increases of 10 mm Hg or reach an absolute threshold of 30 mm Hg \( (P < .001) \). Race, disease severity at time of enrollment, and location of uveitis were not associated with risk of IOP elevation (Table 2).

Multivariable models among treated eyes revealed that male sex and phakic lens status were predictors of an increase in IOP of 10 mm Hg or reaching a threshold of 30 mm Hg. The risk of an increase of 10 mm Hg or reaching 30 mm Hg in phakic patients was nearly twice that of pseudophakic patients (hazard ratio, 1.97; 95% CI, 1.42-2.73; \( P < .001 \)). In addition, the hazard ratio for an increase in IOP of 10 mm Hg or reaching 30 mm Hg by patient age increments of 5 years was 0.96 (95% CI, 0.91-1.01; \( P = .13 \)). Moreover, female patients had 60% of the risk of an increase relative to male patients (hazard ratio, 0.60; 95% CI, 0.44-0.80; \( P < .001 \)) (eTable in the Supplement).

Table 3 gives the comparison evaluating the cup-disc ratio and Humphrey visual field mean deviation in treated eyes, untreated eyes, and standard-of-care eyes. Treated eyes at 24 months had significant changes from baseline in cup-disc ratio \( (P < .001) \). The change seen in the treated group was different from the untreated and standard-of-care eyes \( (P < .001) \). However, no significant differences were found in Humphrey visual field mean deviation.

### Discussion

Increases in IOP have been observed after all routes of corticosteroid administration.\(^8,9\) Patients with uveitis receiving intravitreal triamcinolone therapy appear to be at greater risk of IOP elevation than patients treated with intravitreal triamcinolone for other conditions.\(^8,10-14\) This finding could be because patients with uveitis may have cellular debris blocking the trabecular meshwork (TM) structures\(^2-15\) or have synchiae mechanically blocking normal aqueous flow.\(^7\) It is difficult to compare the results of this study with other publications because few studies have looked specifically at the FAI. However, despite the fact that the FAI delivers constant corticosteroid exposure to the eye as opposed to intravitreal triamcinolone for which levels decrease, it is likely that many of these explanations for elevated IOP with intravitreal triamcinolone apply to the FAI.

Our analyses indicate that eyes at maximum risk of elevated IOP in this cohort are those of younger patients. Previous reports\(^12,16-18\) have found that younger patients are at increased risk of experiencing IOP elevation after intravitreal triamcinolone therapy. The TM in eyes treated with corticosteroids has demonstrated a marked increase in the accumulation of type IV collagen and fibronectin.\(^9,19\) Thickening of fibers of the TM can lead to a decrease in size of the pores and thus affect aqueous outflow.\(^8\) Because there is a steady decrease in TM cells throughout life,\(^15\) the induced changes in microstructure of the TM in a young eye, with a larger number of TM cells, may explain why younger patients are more sensitive to corticosteroid-induced elevations in IOP. Another possible explanation could be related to the status of the vitreous in older vs younger patients. In elderly patients, vitreous is more liquefied and may allow for more diffusion of the drug with subsequently less corticosteroid-induced IOP elevation.

Sex as a risk factor for IOP response has been more inconsistently described.\(^9,20\) Studies have found that triamcinolone\(^6\) and difluprednate\(^21\) can have more profound IOP effects on male patients than female patients, which is consistent with the results of this study. Possible explanations could be related to differences in TM function between men and woman, differences in size of eyes and as such the TM, or even hormonal differences between the sexes.

Phakic patients were more likely to have an IOP response and require surgery in this cohort. This finding may be related to angle function after cataract extraction. Removing the lens may open a patient’s angle structures and allow for better outflow. It is also possible that irrigation and aspiration during cataract extraction may clean inflammatory debris from angle structures, allowing them to function more efficiently.

Another possible explanation for this could be that the lens in the eyes with the FAIs increases in size from steroid-induced cataractous changes, resulting in a subtle effect on angle structures and outflow facility.

A previously published study\(^22\) described risk factors associated with IOP elevation secondary to the FAI. The data analyzed in this study were collected during the Multicenter Uveitis Steroid Treatment Trial (MUST) in which patients were randomized to receive the FAI or systemic therapy. The bivar-
Intraocular Pressure Risk Factors

Parekh.

ARTICLE INFORMATION

Submitted for Publication: October 6, 2014; final revision received December 16, 2014; accepted December 19, 2014.

Published Online: February 26, 2015.


Author Contributions: Dr Srivastava had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Parekh, Srivastava, Goldstein.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Parekh.

Critical revision of the manuscript for important intellectual content: Srivastava, Bena, Albini, Nguyen, Goldstein.

Statistical analysis: Srivastava, Bena, Albini.

Obtained funding: Srivastava.

Administrative, technical, or material support: Parekh.

Study supervision: Srivastava, Nguyen, Goldstein.

Conflict of Interest Disclosures: Dr Srivastava reported working as a consultant for Bausch & Lomb Inc and receiving financial support from Bausch & Lomb Inc, Novartis, and Allergan. Dr Albini reported working as a consultant for Bausch & Lomb Inc, Allergan, and Eleven Biotherapeutics and receiving financial support from Genetech. Dr Nguyen reported receiving financial support from Genetech, Regeneron, Lux Biosciences, Abbott, GSK, Santen, Opts, and Heidelberg Engineering and working as a consultant for Santen and Bausch & Lomb Inc. Dr Goldstein reported working as a consultant for Bausch & Lomb Inc, Xoma, Clearside Biomedical, and Abbvie. No other disclosures were reported.

Funding/Support: This study was supported in part by an unrestricted grant from Research to Prevent Blindness (Dr Goldstein).

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

In this series, patients receiving the FAI had a higher risk of having an IOP increase of 10 mm Hg or an absolute IOP of 30 mm Hg when compared with patients without the FAI. Male patients and those who were young and phakic were at an even higher risk for elevated IOP and glaucoma surgery. This information may be helpful in counseling patients about their risks before placement of the FAI. Close monitoring is advised to reduce the risk of progression to glaucoma.
Intraocular Pressure Risk Factors

Original Investigation Research


REFERENCES


