

Risk of Elevated Intraocular Pressure and Glaucoma in Patients with Uveitis

Results of the Multicenter Uveitis Steroid Treatment Trial

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Objective: To report the 2-year incidence of raised intraocular pressure (IOP) and glaucomatous optic nerve damage in patients with uveitis randomized to either fluocinolone acetonide (FA) implants or systemic therapy. Secondly, we sought to explore patient and eye characteristics associated with IOP elevation or nerve damage.

Design: A randomized, partially masked trial in which patients were randomized to either FA implants or systemic therapy.

Participants: Patients aged ≥ 13 years with noninfectious intermediate, posterior, or panuveitis active within the prior 60 days for which systemic corticosteroids were indicated were eligible.

Methods: Visual fields were obtained at baseline and every 12 months using the Humphrey 24-2 Swedish interactive threshold algorithm (SITA) fast protocol. Stereoscopic optic nerve photos were taken at baseline and at 3-, 6-, 12-, and 24-month follow-up visits. Masked examiners measured IOP at every study visit.

Main Outcome Measures: Glaucoma was diagnosed based on an increase in optic nerve cup-to-disc ratio with visual field worsening or increased cup-to-disc ratio alone, for cases where visual field change was not evaluable, because of missing data or severe visual field loss at baseline.

Results: Most patients were treated as assigned; among those evaluated for glaucoma, 97% and 10% of patients assigned to implant and systemic treatment, respectively, received implants. More patients (65%) assigned to implants experienced an IOP elevation of ≥ 10 mmHg versus 24% assigned to systemic treatment ($P < 0.001$). Similarly, 69% of patients assigned to the implant required IOP-lowering therapy versus 26% in the systemic group ($P < 0.001$). Glaucomatous optic nerve damage developed in 23% versus 6% ($P < 0.001$) of implant and systemic patients, respectively. In addition to treatment assignment, black race, use of IOP-lowering medications, and uveitis activity at baseline were associated with incident glaucoma ($P < 0.05$).

Conclusions: Implant-assigned eyes had about a 4-fold risk of developing IOP elevation of ≥ 10 mmHg and incident glaucomatous optic neuropathy over the first 2 years compared with those assigned to systemic therapy. Central visual acuity was unaffected. Aggressive IOP monitoring with early treatment (often including early filtration surgery) is needed to avoid glaucoma when vision-threatening inflammation requires implant therapy.

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Uveitis frequently results in elevated intraocular pressure (IOP),^{1,2} which has multiple etiologies, but the majority is open angle and presumed to be due to damage to trabecular meshwork function from the chronic inflammatory process. Furthermore, corticosteroid treatment, regardless of route, used to manage uveitis may raise IOP.³⁻⁶ The Multicenter Uveitis Steroid Treatment (MUST) Trial compared the benefits and risks of fluocinolone acetonide (FA) intravitreal implants (0.59 mg; Bausch & Lomb, Rochester, NY) with those associated with systemic treatment as recommended by guidelines⁷ in a randomized, controlled, comparative effectiveness trial of treatment for noninfectious intermediate, posterior, and panuveitis.⁸ The primary results of the trial showed similar visual acuity

outcomes in the 2 groups after 2 years of follow-up, but substantially more ocular complications, including glaucoma, in patients assigned to implants.⁹ Here, we report additional results about the IOP, glaucoma-related, and vision outcomes from this study.

Methods

The MUST Trial was a randomized (allocation ratio 1:1), partially masked, parallel treatment, comparative effectiveness trial (clinicaltrials.gov identifier NCT00132691). All patients provided written informed consent; all governing institutional review boards provided approvals, which were updated annually.

Patients aged ≥ 13 years (only 5 patients were < 18) who had noninfectious intermediate, posterior, or panuveitis in 1 or both eyes active within the prior 60 days for which systemic corticosteroids were indicated were eligible. Those who required systemic therapy for nonocular indications, had uncontrolled diabetes mellitus, had an allergy to study medications, or had uncontrolled glaucoma or advanced glaucoma damage were excluded. Patients were enrolled at 23 centers: 21 in the United States and 1 each in the United Kingdom and Australia. Visits occurred at baseline, 1 month, 3 months, and then every 3 months for ≥ 2 years, with additional visits as needed for clinical care.

Patients were randomized to FA implant or systemic therapy; randomization was stratified by center and site of inflammation (intermediate vs posterior or panuveitis). Patients with bilateral uveitis assigned to the implant group were to receive implants in each eye for which it was indicated. Systemic therapy was guided by expert panel guidelines,⁷ typically starting with high-dose prednisone (1 mg/kg/d up to 60 mg/d) and then tapering to low doses of prednisone (≤ 7.5 mg/d); immunosuppressive drugs were used when indicated.

Study-certified visual acuity examiners measured best-corrected visual acuity as the number of letters read from standard logarithmic visual acuity charts¹⁰; change in visual acuity from baseline to 2 years was the primary outcome. Other important outcomes reported here include IOP, incidence of glaucoma, visual field sensitivity (the Humphrey mean deviation statistic),¹¹ and quality-of-life measures.

Certified personnel measured IOP twice using Goldmann applanation tonometry. If the measures differed by > 2 mmHg, a third measurement was performed. If Goldmann IOP could not be obtained then Tono-Pen (Mentor Ophthalmics, Norwell, MA) was used; Tono-Pen measurement were performed twice and, if the measures differed by ≥ 3 mmHg, a third measurement was taken. The mean of the IOP measurements was used in the analysis. Other than visits at 1 and 3 months, when postoperative signs were expected to be visible, visual acuity and IOP examiners were masked.

Visual field assessments were obtained at baseline and every 12 months in a dark room with 1 eye patched with the proper refractive error trial lens using the Humphrey 24-2 Swedish interactive threshold algorithm (SITA) fast protocol. The evaluation was repeated if the results were unreliable or abnormal at baseline or if the visual field, as judged by the study ophthalmologist, had worsened from baseline at any follow-up measurement.

Stereoscopic optic nerve color photographs were taken using reading center-certified cameras and imaging procedures at baseline and at the 3-, 6-, and 12-month follow-up visits and annually thereafter. Because patients with significant media opacities were eligible to enroll in the trial, there were relatively larger proportions of eyes with missing data on characteristics derived from evaluations of fundus photographs.¹² For example, cup-to-disc ratio (CDR) could not be determined at baseline from fundus photographs in 27% of eyes with uveitis, and 10% did not have gradable optical coherence tomography scans.

The National Eye Institute visual function 25-item questionnaire was used to generate a single composite score that ranges from 0 to 100, with 100 being the maximum visual function; a 4- to 6-point difference has been considered clinically meaningful.¹³ The 36-item Short Form responses are coded as scores for 8 domains (physical functioning, bodily pain, general health, vitality, mental health, and physical, social, and emotional role functioning) and summarized using physical and mental component summary scores. The scores are scaled to population norms, with a mean of 50 and a standard deviation of 10; a difference of 3 to 5 points has been considered clinically meaningful for the physical component scale.^{14,15}

When possible, glaucoma was diagnosed from optic nerve photographs taken at 3, 6, and 12 months on the basis of an increase in optic nerve CDR in the setting of documented visual field worsening. In addition, all visual fields were reviewed. In cases where probable glaucomatous worsening of the visual field was present, further assessment of the clinical course was undertaken. We also requested photographs from all visits when the visual field worsened dramatically. In cases where there was no ability to detect visual field change, either because of missing visual field data or severe visual field loss at baseline, increased CDR alone was used to identify incident glaucoma. Because most patients had some visual field loss at baseline—presumably due to damage from uveitis itself and from chronic macular edema¹⁶ and its sequelae—detection of new visual field defects was difficult and glaucoma was diagnosed only if there was a clear optic nerve change based on photography. One hundred eyes with either poor-quality images or no images at baseline were able to be evaluated by the glaucoma specialist at times using the blurry baseline images or subsequent images to identify incident glaucoma and at times relying on stable visual fields to confirm no incident glaucoma if images were missing. One glaucoma specialist (D.S.F.) reviewed the optic nerve photos and all notes on persons with a change in CDR of 0.1 or more for small nerves (those that were < 2 standard deviations in size from the mean of the baseline images) or ≥ 0.2 for normal or large nerves (based on masked fundus photograph reading center evaluations) and categorized the findings as definitely, probably, possibly, or not consistent with glaucoma damage. For this analysis, those graded as definite or probably were classified as glaucoma. A second glaucoma specialist (H.A.) reviewed those found to have definite or probable glaucoma and a 32% random sample of noncases; disagreements were adjudicated by consensus.

The data presented here were collected for up to 2 years after the randomization. Previous reports provide more details on the design and primary results of the trial.^{8,9}

Statistical Analysis

All available data on the outcome measures of interest (eg, IOP elevation, glaucoma surgery, or glaucomatous changes as described) were included in the respective analyses. Because we were able to retrieve previously missing images or visual field data, this report includes evaluations of 13 additional eyes for glaucoma that were not included in the primary publication.⁹ Unless specified otherwise, data were analyzed by assigned treatment. Characteristics of eyes and patients at baseline by treatment assignment were analyzed by Wilcoxon or chi-square tests and, after 2 years of follow-up data, were analyzed by glaucoma status using logistic or linear regression including adjustment for the baseline value for categorical and continuous outcomes, respectively. Associations of events (IOP elevation or glaucoma) in pairs of eyes with uveitis were evaluated with binomial regression models accounting for patient-level clustering.

Associations of baseline characteristics with elevation of IOP by 10 mmHg were evaluated with proportional hazards regression.¹⁷ Race, sex, and age were included in the multivariate models. Other variables selected for inclusion in the multivariate model were chosen using manual forward selection and had a *P* value for inclusion of < 0.10 . Variables with missing values for $> 5\%$ of eyes and variables that were closely associated with the ophthalmologist assessment of active disease were excluded from selection models.

For evaluating the risk of glaucomatous changes, associations were evaluated with Poisson regression.¹⁸ Poisson regression was used because assessments for uveitis were made at discrete time points—1 and 2 years—and all but 1 case were identified at

2 years. Because the number of cases of glaucoma was relatively small (only sufficient to support a small number of variables in a multiple regression model), variables for inclusion in the multivariate model were selected based on inspection of bivariate associations, and variables for which >5% of data were missing were excluded from multivariate models. All models that included data from each eye with uveitis were adjusted for the correlation between eyes from the same participant using generalized estimating equations.¹⁹ Statistical analyses used SAS (version 9.1; SAS Inc, Cary, NC) and Stata/IC 11.1 (StataCorp LP, College Station, TX).

Results

Characteristics of the Study Population

A total of 129 persons (245 eyes with uveitis) were randomized to the FA implant, 122 (95%) of whom received ≥ 1 implant, and 126 persons (234 eyes with uveitis) were randomized to standard systemic therapy, 121 (96%) of whom received systemic treatment. Bilateral implants were implanted in 82 patients (64%) assigned to the implant. Fourteen patients assigned to systemic therapy eventually received implants (11%; 23 eyes), 9 of whom received implants in both eyes. Data on elevation of IOP were available for 249 patients (467 eyes with uveitis). Data were available for review of glaucoma status for 120 patients (219 eyes) and 114 patients (207 eyes) assigned to implant and systemic therapy, respectively (Fig 1). There were no meaningful differences in the baseline characteristics of the subgroup of patients who were evaluated for glaucoma versus the entire group of patients.

The 2 treatment groups were similar with regard to age, sex, race, type of uveitis, and baseline ocular characteristics including visual acuity, CDR, and IOP. Eyes with uveitis in patients assigned to implants had borderline poorer visual field sensitivity than those in the systemic group (median, -5.7 vs -4.8 dB, respectively; $P = 0.06$). Over 80% of eyes with uveitis had some diminution of visual field (mean deviation, < -3 dB) at baseline. Conversely, visual acuity was good in most eyes and did not differ substantially between the 2 groups (Table 1).

Use of topical corticosteroid drops was common in both groups; 61% and 66% of patients assigned to the implant and systemic groups, respectively, reported use of topical steroids at baseline. During follow-up, 83% and 79% of patients in the implant and systemic groups, respectively, used corticosteroid drops. Patients assigned to systemic therapy were more likely to receive periocular corticosteroids (48% vs 25%; $P < 0.001$) and intravitreal corticosteroids (18% vs 6%; $P = 0.004$) than patients assigned to implants.

IOP Elevation

As reported previously,⁹ the incidence of IOP elevation and surgical treatment for elevated IOP was higher in patients (and eyes) assigned to the implant group (Table 2; Fig 2). Overall, 65% versus 24% of patients assigned to implant versus systemic therapy, respectively, experienced an elevation of ≥ 10 mmHg above the baseline measurement within the first 2 years of follow-up. The mean peak IOP for those who experienced an increase in IOP of ≥ 10 mmHg regardless of treatment assignment was 36 mmHg (range, 14–70 mmHg). Over the 2 years, 69% of patients assigned to the implant received IOP-lowering therapy compared with 26% in the systemic treatment arm ($P < 0.001$), and 32% versus 5% received a surgical intervention ($P < 0.001$).

Nearly half of the patients assigned to implants (49%) developed an IOP of ≥ 30 mmHg compared with 11% of patients

assigned to the systemic group ($P < 0.001$). Among patients who had a spike in IOP to ≥ 30 mmHg, similar percentages underwent surgery to lower IOP in the implant and systemic groups (50% vs 38%, respectively; $P = 0.62$). Nineteen patients (15%) assigned to the implant and 4 (3%) assigned to systemic treatment had an IOP spike to ≥ 40 mmHg; about half of those patients in both groups (53%) subsequently had IOP-lowering surgery.

We restricted some analyses to patients who received their assigned treatment to investigate the timing of events relative to implant surgery. Elevations in IOP were common in the first year for patients assigned to and receiving implants (Fig 3); 58% (70 patients) of those assigned to and receiving implants experienced an elevation of ≥ 10 mmHg within 12 months of implant surgery compared with 15% (17 patients) assigned to and receiving systemic treatment. Incident IOP elevation of ≥ 10 mmHg occurred in 8 additional patients after 12 months in the implant group compared with 7 additional patients in the systemic group. The median time from implant surgery to an IOP increase of ≥ 10 mmHg was 9 months (95% confidence interval [CI], 5–12) in patients assigned to and receiving implants.

The risk of IOP elevation or of undergoing IOP-lowering surgery was higher in the fellow eye of patients with bilateral implants once an event occurred in 1 eye. Among the 81 participants assigned to the implant group who received implants in both eyes, 22% had a ≥ 10 mmHg increase in IOP in 1 eye, whereas 49% developed an increase in both eyes. In participants with bilateral implants the risk for an increase in IOP in a fellow eye once an IOP elevation occurred in 1 eye was high (relative risk [RR], 2.9; 95% CI, 1.7–4.9; $P < 0.001$). Ten patients (12%) with bilateral implants underwent surgery for IOP-lowering in 1 implanted eye and 20 patients (24%) underwent IOP-lowering surgery in both implanted eyes. The risk of undergoing surgery was markedly increased for the fellow eye once 1 eye had surgery (RR, 10.1; 95% CI, 4.7–21.8; $P < 0.001$).

Risk Factors for IOP Elevation

In bivariate analyses, factors associated with an increased risk of a ≥ 10 mmHg elevation in IOP in eyes with uveitis were assignment to implant, age < 50 years, male sex, and baseline use of IOP-lowering drugs ($P < 0.05$; Table 3). Phakic lens status and mean deviation of -3 dB or worse were marginally ($0.05 < P < 0.10$) associated with IOP elevation risk (Table 4, available at <http://aojournal.org>). Duration of disease, topical steroid use, bilateral disease, macular thickness, and several other disease characteristics were not associated with altered risk of IOP elevation. Vogt-Koyanagi-Harada disease was positively associated ($P < 0.001$), whereas sarcoid-associated uveitis was negatively associated ($P = 0.04$; Table 4). In the multivariate model that included adjustments for treatment assignment, age, race, sex, receiving IOP medications at baseline, and current inflammation activity, only implant assignment, younger age, and baseline IOP medications were significantly associated; sex, mean deviation, and lens status were no longer associated (Table 3). Measures of vitreous cells, haze, and macular thickness were not included in multivariate exploratory analysis because of missing data.

Incidence of Glaucoma

One glaucoma specialist reviewed all patient data (D.S.F.) and a second (H.A.) reviewed all classified as having incident glaucoma as well as 119 sets (32%) of photographs that had been diagnosed as “not glaucoma” by the initial reviewer. Only 2 (1.7%) of these were recategorized as glaucoma upon review, making it unlikely that many cases were missed during the initial assessment.

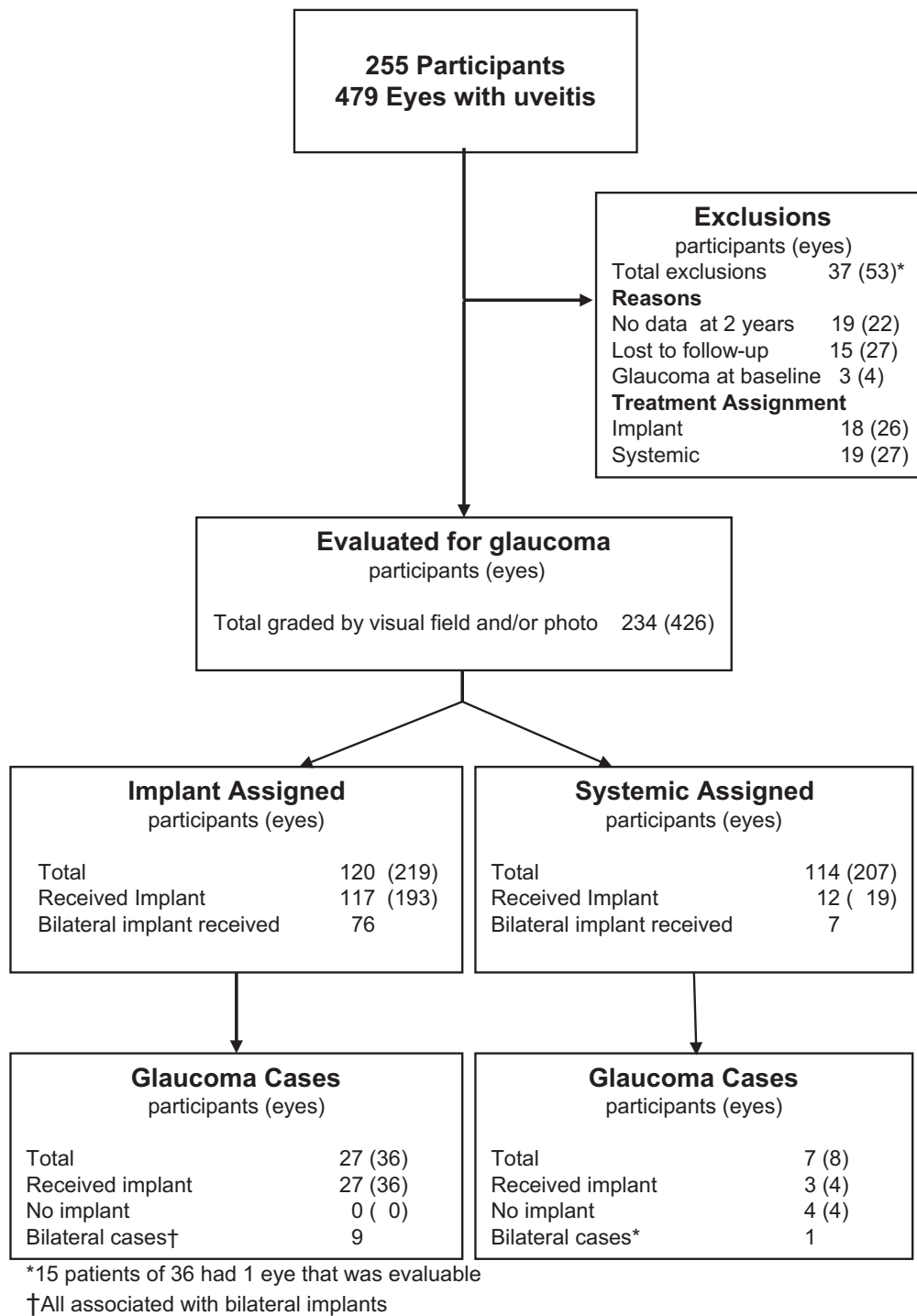


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. VF = visual field.

Glaucoma developed within 24 months in 16% versus 4% (RR, 4.5; 95% CI, 1.9–10.3) of eyes assigned to implant and systemic treatment, respectively (Table 2). With the exception of 4 eyes in 4 patients, all the cases of glaucoma observed were in eyes that received an implant (regardless of original treatment assignment). Twenty-seven patients (23%) assigned to implant developed glaucoma, 9 in both eyes, compared with 7 patients (6%) assigned to systemic treatment, with only 1 case of bilateral glaucoma in that group. Among the eyes that developed glaucoma there were a few

with dramatic worsening of the optic nerve damage over follow-up. Four eyes with a CDR of ≤ 0.5 at baseline developed a worsening in CDR of ≥ 0.4 . This occurred in 4 patients (of 99 patients with CDR < 0.5 at baseline), all of whom had bilateral disease, and all the affected eyes had been treated with an implant.

All cases of bilateral glaucoma were diagnosed in patients with bilateral implants. In the subset of patients with bilateral implants, the risk of glaucoma was increased in the fellow eye once glaucoma was identified in the first eye (RR, 7.9; 95% CI, 3.4–18.9; $P < 0.001$).

Table 1. Baseline Characteristics of Participants and Eyes With Uveitis by Assigned Treatment

Characteristic	Systemic (n=126)	Implant (n=129)	Total (n=255)
Demographics			
Age, mean years (SD)	46.9 (15.1)	45.8 (15)	46.3 (15.0)
Female sex, n (%)	100 (79)	91 (71)	191 (75)
Race/ethnicity, n (%)			
White	70 (56)	72 (56)	142 (56)
Hispanic	15 (12)	18 (14)	33 (13)
Black	31 (25)	35 (27)	66 (26)
Other	10 (8)	4 (3)	14 (5)
VFQ-25, mean score (SD)	62.6 (20.7)	58.4 (21.4)	60.5 (21.1)
Clinical characteristics			
Patient specific			
Unilateral uveitis, n (%)	17 (13)	12 (9)	29 (11)
Site of uveitis, n (%)			
Intermediate	47 (37)	50 (39)	97 (38)
Posterior or panuveitis	79 (63)	79 (61)	158 (63)
Systemic disease present, n (%)	33 (26)	36 (27)	69 (27)
Using glaucoma medications, n (%)	17 (13)	23 (17)	40 (16)
Eye specific*			
	n = 234	n = 245	n = 479
Visual acuity, standard letters, median (25th, 75th percentile)	71 (53, 81)	68 (46, 79)	70 (49, 80)
Visual field, mean deviation (dB), median (25th, 75th percentile) [†]	-4.8 (-8.7, -2.8)	-5.7 (-9.9, -3.2)	-5.2 (-9.6, -3.0)
IOP mmHg, mean (SD) [†]	14 (4.5)	14.1 (4.8)	14 (4.7)
Cup-to-disc ratio, mean (SD) [†]	0.32 (0.13)	0.31 (0.12)	0.31 (0.12)
Aphakic/pseudophakic, n (%)	105 (45)	102 (42)	207 (43)
Ciliary body involved, n (%)	97 (41)	114 (47)	211 (44)
Anterior chamber involved, n (%)	48 (21)	48 (20)	96 (20)
History of hypotony, n (%)	12 (5)	12 (5)	24 (5)
History of elevated IOP, n (%)	36 (15)	33 (13)	69 (14)
On glaucoma medication, n (%)	28 (12)	37 (15)	65 (14)

dB = decibels; IOP = intraocular pressure; SD = standard deviation; VFQ-25 = 25-item Visual Function Questionnaire.

*Eye-specific characteristics are summarized for the 479 eyes with uveitis at enrollment.

[†]Missing data: 12 (5%) implant and 8 (3%) systemic therapy eyes for mean deviation score; 2 implant eyes IOP; and 81 (33%) and 43 (18%) systemic therapy eyes for cup-to-disc ratio.

Risk Factors for Glaucomatous Optic Nerve Damage

Baseline risk factors for glaucomatous optic nerve damage were assignment to implant, active uveitis, black race, and IOP-lowering medication use (Table 3; $P < 0.05$). In addition, CDR > 0.5 and presence of anterior chamber cells of $+0.5$ or higher at baseline²⁰ were marginally associated with increased glaucoma risk in bivariate models ($0.05 < P < 0.10$; Table 4). Duration of disease, topical steroid use, bilateral disease, macular thickness, and several other disease characteristics were not associated with development of glaucoma. In the multivariate model, which included adjustments for treatment assignment, age, race, sex, use of IOP-lowering medications, and uveitis activity, only implant assignment, black race, use of IOP-lowering medications, and uveitis activity were significantly associated (Table 3). We did not include anterior cells in the multivariate model because it was strongly associated with uveitis activity, and the presence of haze at baseline was not included because of missing data. Missing data (unable to see fundus) for the haze variable were associated with glaucoma diagnosis (Table 4). As reported, elevated IOP during follow-up was common (Table 2) and it was a strong risk factor for subsequent optic nerve damage; 24% of eyes with elevation of IOP of ≥ 10 mmHg during follow-up went on to develop glaucoma and 30% of eyes that developed IOP elevation to ≥ 30 mmHg developed optic nerve damage.

Compared with eyes that did not develop glaucoma over 2-years of follow-up, eyes diagnosed with glaucoma had higher peak

IOPs during follow-up as well as a higher IOP at the 2-year visit (Table 5; Fig 4 available at <http://aojournal.org>). As expected, because the diagnosis relied on CDR and, less so, on visual field, eyes diagnosed with glaucoma had greater impairment of visual field and increased CDR (Table 5). However, mean best-corrected visual acuity in the eyes that developed glaucoma was not lower than those that did not (Table 5; Fig 5 available at <http://aojournal.org>); 52% of eyes diagnosed with glaucoma and 60% of eyes without glaucoma had a best-correct visual acuity of $\geq 20/40$ at 2 years ($P = 0.36$).

There were no differences in vision-related quality-of-life scores at 2 years between patients who developed glaucoma and those who did not (mean, 68 vs 70, respectively; $P = 0.61$). Nor were there differences in the 36-item Short Form physical component score (mean, 47 vs 47, respectively; $P = 0.92$) or the mental component score (mean, 51 vs 48, respectively; $P = 0.06$) between those who developed glaucoma and those who did not.

Discussion

Fluocinolone acetonide implant therapy is associated with a high risk of substantial IOP elevation, often requiring glaucoma surgery.³ As in prior drug licensing trials,^{21–23} IOP elevation was common in eyes of MUST Trial participants receiving an implant, with nearly two thirds requiring

Table 2. Outcomes Related to Glaucoma by Treatment Assignment

	Systemic		Implant		Risk Ratio (95% CI) [†]
	Events (n/N)	Percent at 2 Years* (95% CI)	Events (n/N)	Percent at 2 Years* (95% CI)	
Eyes with uveitis					
IOP elevation (mmHg increase)					
≥10	35/230	15 (11–21)	121/235	52 (46–58)	4.3 (2.8–6.6)
≥30	14/229	6 (4–10)	76/236	32 (27–39)	6.0 (3.3–11.0)
≥40	5/230	2 (1–5)	22/236	9 (6–14)	4.4 (1.4–13.6)
Treatment for elevated IOP					
IOP-lowering drugs	40/202	20 (15–26)	122/200	61 (55–68)	4.2 (2.7–6.5)
IOP-lowering surgery	8/226	4 (2–7)	60/233	26 (21–33)	8.3 (3.4–20.5)
Glaucoma diagnosis	8/207	4 (2–8)	36/219	16 (12–22)	4.5 (1.9–10.3)
Patients					
IOP elevation (mmHg increase)					
≥10	29/124	24 (17–33)	80/124	65 (57–73)	3.6 (2.4–5.6)
≥30	13/124	11 (6–18)	60/125	49 (40–58)	5.6 (3.1–10.3)
≥40	4/124	3 (1–9)	19/125	15 (10–23)	4.7 (1.6–14.0)
Treatment for elevated IOP					
IOP-lowering medications	28/112	26 (18–35)	75/109	69 (60–78)	3.9 (2.6–6.1)
IOP-lowering surgery	6/124	5 (2–11)	39/123	32 (25–42)	7.8 (3.3–18.0)
Glaucoma diagnosis	7/114	6 (3–12)	27/120	22.5 (16–31)	3.7 (1.7–8.1)

CI = confidence interval; IOP = intraocular pressure.

*Cumulative percentage of eyes or patients with event over 2 years of follow-up.

[†]Hazard ratio or relative risk from proportional hazards model or Poisson model—respectively—accounting for correlation between eyes from the same patient—if applicable.

IOP-lowering therapy within 2 years and one quarter requiring surgery to control IOP. The estimated number needed to harm was 5 (95% CI, 3 to 9), that is, just about 1 of 5 patients treated with an implant rather than systemic treatment will have an IOP elevation of ≥10 mmHg that would not have occurred with systemic treatment. Our

findings demonstrate that, within the first 2 years, these elevations can lead to glaucomatous optic nerve damage, which affected 23% of patients (16% of eyes) assigned to receive an implant. The corresponding number needed to harm for glaucoma was 8 (95% CI, 5–21), that is, there will be 1 additional case of glaucoma for every 8 patients treated with an implant rather than systemic treatments. Within the 2-year period of follow-up, we did not see an effect of glaucoma on visual acuity or vision-related or general health-related quality of life. The long-term prognosis for these individuals is uncertain and requires further study.

Elevation of the IOP mostly occurred in the first year after implantation (median, 9 months). However, new cases continued to occur in the second year, highlighting that the risk of IOP elevation is ongoing in these implanted eyes. Possible explanations for incident cases in the second year may be cumulative corticosteroid response, variability in the release of steroid from the implant over time, and the natural history of treated uveitis. Extreme IOP elevations were seen in several instances, predominantly in patients assigned to the implant group. If left untreated, such elevations can result in rapid vision loss, suggesting that patients with implants should be evaluated for IOP elevation frequently (the consensus of the MUST Research Group is that patients should be seen at least every 6 weeks and possibly more frequently). In patients with bilateral implants, the risk of a spike in IOP was markedly higher in the fellow eye after 1 eye had a spike; such patients would benefit from close observation and rapid intervention or, in some cases, preemptive IOP-lowering therapy.

Early elevations in IOP were expected because previous studies have documented that most cases occur in the first year,³ but recent publications indicate that sometimes

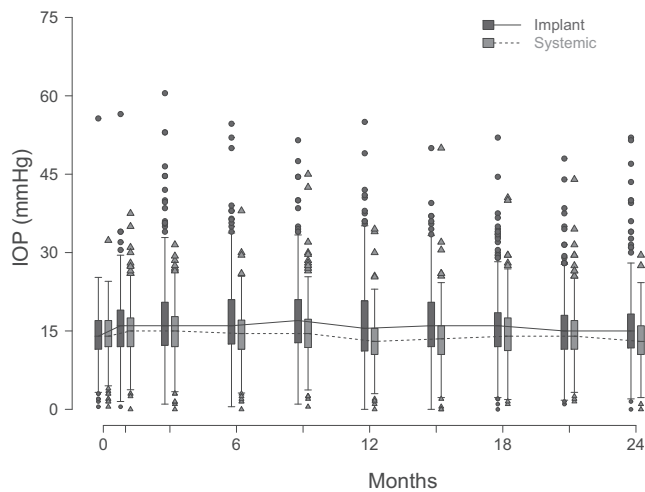


Figure 2. Box plots of intraocular pressure (IOP) measurements from eyes with uveitis during the trial by treatment assignment. Data for the implant group are in black and data for the systemic group are in grey. The middle bar of the boxes represents the median; the lower and upper ends of the boxes are the first and third quartiles, respectively. The whiskers represent values within 1.5 times the interquartile range from the upper or lower quartile (or the minimum and maximum if within 1.5 times the interquartile range of the quartiles), and data more extreme than the whiskers are plotted individually as outliers (circles for implant group and triangles for systemic group).

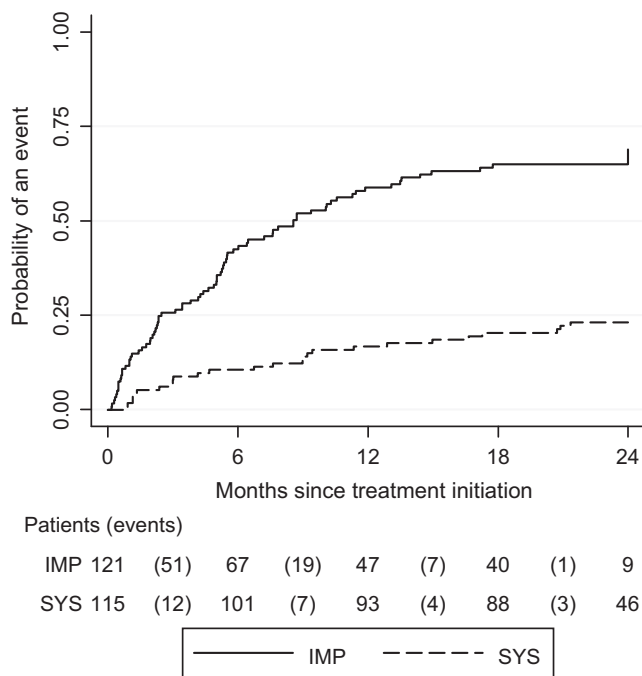


Figure 3. Kaplan–Meier curve of time from treatment initiation to increase in intraocular pressure ≥ 10 mmHg by treatment assignment among patients who received their assigned treatment. The numbers below the graph represent the number of patients in the risk set at each time point and, in parentheses, the number of events that occurred within the 3-month time intervals. IMP = implant treatment assignment; SYS = systemic treatment assignment.

extreme elevations can occur as late as the third year after implantation,²⁴ consistent with our observations of high spikes in the second year after implantation.

Baseline factors associated with IOP elevation, after adjustment for confounding, included implant treatment assignment, younger age, and use of glaucoma medications at baseline. The association of younger age is consistent with the findings from an earlier study of intravitreal triamcinolone in persons with uveitis²⁵ and clinical impression, but it is difficult to explain. Perhaps younger eyes have greater aqueous secretion than older eyes, but an equal degree of corticosteroid-induced compromise of drainage, leading to greater likelihood of an IOP spike.

Our results confirm that the excess IOP elevation seen in patients receiving implants does translate into a higher risk of glaucomatous optic neuropathy. The incidence of glaucoma in this study may not be generalizable to other settings where interventions may have been initiated earlier or later for elevations in IOP.

Similar to the pattern observed with IOP elevation, the risk of glaucoma was markedly increased if the fellow eye was identified as having glaucoma. Patient’s eyes were not evaluated independently, so the grading of the first eye may have influenced the evaluation of the second eye and hence the increase in risk noted in this study may be an overestimate of the risk in the fellow eye. Furthermore, the diagnosis was challenging in this patient population, who frequently had visual field defects at baseline, and worsening of the visual field could have been due to progressive cataract, glaucoma, or the disease process itself. Nevertheless, the effect size associated with implant treatment, and second eye involvement in patients with 1 eye affected, is so great that it remains unlikely that these associations are spurious.

In addition to assignment to implant and IOP elevation during follow-up, other risk factors for glaucoma included black race, use of IOP-lowering medications at baseline, and

Table 3. Association of Baseline Characteristics with Intraocular Pressure (IOP) Increase of 10 mmHg from Baseline and Glaucoma Diagnosis

Characteristic	Events/Eyes	IOP Increase ≥ 10 mmHg				Glaucoma Diagnosis				
		Crude RR	(95% CI)	Adjusted* RR (95% CI)	P Value*	Crude RR	(95% CI)	Adjusted* RR (95% CI)	P Value*	
Treatment assignment										
Systemic	35/230	Ref				8/207	Ref			
Implant	121/235	4.28	(2.79–6.57)	4.24 (2.87–6.25)	<0.001	36/219	4.47	(1.95–10.25)	4.09 (1.80–9.28)	<0.001
Age (yrs)										
<50	104/261	Ref				30/242	Ref			
≥ 50	52/204	0.59	(0.39–0.88)	0.49 (0.34–0.70)	<0.001	14/184	0.62	(0.31–1.24)	0.65 (0.34–1.27)	0.21
Race										
Other	116/342	Ref				25/316	Ref			
Black	40/123	0.96	(0.62–1.47)	0.88 (0.60–1.28)	0.49	19/110	2.10	(1.09–4.08)	1.91 (1.01–3.62)	0.05
Sex										
Female	109/353	Ref				34/321	Ref			
Male	47/112	1.50	(1.00–2.24)	1.30 (0.89–1.89)	0.17	10/105	0.93	(0.43–2.02)	0.88 (0.40–1.92)	0.74
Glaucoma medications										
No	123/400	Ref				31/367	Ref			
Yes	33/65	2.08	(1.29–3.36)	2.62 (1.69–4.08)	<0.001	13/59	2.44	(1.29–4.63)	2.24 (1.20–4.18)	0.01
Uveitis activity										
Not active	25/94	Ref				4/86	Ref			
Active	129/363	1.42	(0.89–2.27)	1.35 (0.89–2.06)	0.16	40/336	3.60	(1.14–11.40)	3.22 (1.11–9.29)	0.03

CI = confidence interval; Ref = reference group; RR = relative risk.

*Adjusted for treatment assignment, age, sex, race, baseline IOP medications, and uveitis activity.

Table 5. Outcomes at 2 Years by Glaucoma Status in Eyes With Uveitis

	Glaucoma		No Glaucoma		P Value
	n	Mean (95% CI)	n	Mean (95% CI)	
IOP (mmHg)					
At 2 years	44	18.7 (15.6–21.7)	374	14.2 (13.6–14.8)	0.004
Maximum observed	44	36.5 (32.3–40.6)	382	23.2 (22.0–24.3)	<0.001
Cup-to-disc ratio	38	0.52 (0.46–0.57)	324	0.35 (0.34–0.36)	<0.001
Visual field (mean deviation, dB)	40	-11.9 (-14.7–-9.1)	370	-6.5 (-6.9–-6.0)	<0.001
Visual acuity (standard letters)	44	64.1 (58.1–70.0)	375	69.6 (67.7–71.4)	0.072

CI = confidence interval; dB = decibels; IOP = intraocular pressure.

*Means—95% CIs, and P values estimated from linear regression with general estimating equations adjusted for characteristic at baseline.

active uveitis at baseline. Patients already using IOP-lowering medications may have had less outflow facility at the outset, and hence may have suffered earlier or more pronounced IOP elevation, with a greater risk of glaucoma. A number of patients with active uveitis at baseline also may have had impaired aqueous secretion initially, which might have been restored with control of inflammation at about the same time aqueous outflow was impaired, leading to similar IOP effects and downstream effects on glaucoma risk. However, an evaluation of cases of uveitis likely to have ciliary body involvement did not show a consistent association (Table 4). Furthermore, because of relatively high rates of missing data, many anatomic characteristics of the eyes could not be included in multivariate models.

The high risk of IOP elevation and glaucoma should be considered when evaluating the appropriateness of FA implant for patients with uveitis, particularly those with any prior evidence of IOP control issues, glaucoma, or large CDR. Patients taking any IOP-lowering medication at enrollment were at notably higher risk for optic nerve damage, and those taking ≥ 2 medications were even more vulnerable. One prior report has suggested the approach of performing simultaneous filtering surgery in such patients²⁶ if FA implant therapy would otherwise be highly desirable. The MUST Trial excluded persons with unmanageable IOP and those with advanced glaucomatous optic nerve injury, so our results likely underestimate the IOP and glaucoma risk after implant therapy in populations including such patients.

In conclusion, patients assigned to receive FA implant had a 4- to 5-fold greater risk of developing large IOP elevations over the first 2 years compared with those assigned to receive systemic therapy, and about 1 in 6 uveitic eyes in the implant group developed glaucomatous optic neuropathy in the context of at least quarterly monitoring in a clinical trial. The attributable risk of implant therapy on glaucoma was 12.6% in the MUST Trial, with 1 excess case of glaucoma for every 8 patients assigned to implant therapy. Those who initially were taking IOP-lowering therapy were at greater risk, as were those with active uveitis. Frequent monitoring for incident IOP elevation is indicated in patients receiving implant therapy, which potentially could mitigate much of this risk; the consensus of the MUST Research Group is that these patients should be followed at least every 2 months for IOP monitoring. Preemptive filtering surgery at the time of

implantation²⁶ should be considered in higher risk cases, and early use of filtration seems justified in patients experiencing substantial IOP elevations after implantation, given that a large proportion will not be controllable with eye drops alone. These risks should be weighed against the benefits of implant therapy, which usually is successful in obtaining sustained control of inflammation in cases where other many options have failed, when determining the ideal therapy for patients with uveitis.

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