Outcome of Raised Intraocular Pressure in Uveitic Eyes with and without a Corticosteroid-Induced Hypertensive Response

AHMED SALLAM, HITEN G. SHETH, ZOHAR HABOT-WILNER, AND SUSAN LIGHTMAN

• PURPOSE: To compare the management and outcome of raised intraocular pressure (IOP) in uveitis patients with a corticosteroid hypertensive response and those who are noncorticosteroid responders and to determine the impact of intraocular corticosteroid use on IOP in uveitic eyes.

• DESIGN: Retrospective study.

• METHODS: Eight hundred and ninety-one uveitis patients were observed in a specialized clinic over 3 months. The main outcome measures were frequency, characterization, management, and outcome of uveitis-related ocular hypertension and glaucoma.

• RESULTS: Of 891 patients with uveitis, 191 (275 eyes) had IOP elevation (21.4%). Of these, 95 (34.5%) eyes had glaucoma. IOP elevation attributed to corticosteroid-response (61.1%) was controlled more easily than that resulting from other causes (38.9%), requiring fewer eye drops (mean, 2.06 vs 2.52; $P = .009$) and less filtration surgery (8.9% vs 22.4%). Among eyes with uveitis and raised IOP, elevated IOP developed in 18 eyes (6.5%) after intravitreal triamcinolone, including 64.7% to 30 to 39 mm Hg and 35.3% to 40 mm Hg or more. Prostaglandin analogs were used in 49.2% of 246 eyes; no increase in inflammation was seen in these eyes.

• CONCLUSIONS: In this tertiary center series, most instances of raised IOP were attributable to corticosteroid response. Raised IOP induced by corticosteroid response was controlled more easily and less often resulted in optic nerve or visual field changes of glaucoma. Although intravitreous triamcinolone was associated with substantial risk of corticosteroid-response IOP elevation, all cases were controlled medically without experiencing glaucomatous injury. Prostaglandin-induced uveitis was not observed despite extensive use of prostaglandin IOP-lowering agents. (Am J Ophthalmol 2009;148:207–213. © 2009 by Elsevier Inc. All rights reserved.)

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RAISED INTRAOCULAR PRESSURE (IOP) IS A COMMON problem in patients with uveitis. The proportion of patients in series from tertiary uveitis centers who have been reported to have raised IOP ranges from 10% to 40%,[1–3] being generally more common in chronic uveitis and in patients with Fuchs heterochromic uveitis, Posner–Schlossman syndrome, and uveitis associated with herpes simplex infection.[4–6] The cause may be multifactorial, because both the uveitis itself as well as the treatment with corticosteroids can influence the IOP.[1]

Recently, intravitreal triamcinolone acetonide has become widely used in the treatment of noninfectious uveitis.[7–10] This can be very effective in controlling the inflammation, but also can be associated with a significant rise in IOP, which may be prolonged.[7–9]

The prostaglandin analogs—which include the selective prostaglandin $F_2\alpha$ ($PGF_{2\alpha}$) agonists, latanoprost, travoprost, and bimatoprost—are a new class of potent ocular hypotensive agents that have become one of the major treatments in the management of ocular hypertension and glaucoma.[11] Although some ophthalmologists are wary of their use in patients with uveitis,[12–14] they can be very effective in lowering IOP.[11]

The purpose of this study was to characterize eyes with uveitis and elevated IOP and to compare the management and outcome of raised IOP from when it first occurred in uveitis patients who exhibit corticosteroid-induced ocular hypertension and those who are noncorticosteroid responders. In addition, we aimed to determine if the use of intraocular corticosteroids increased the frequency and severity of raised IOP and whether prostaglandin analogs are safe to use in uveitis patients with raised IOP, as in the primary open-angle glaucoma (POAG) population.

METHODS

CONSECUTIVE CASE NOTES OF ALL UVEITIS PATIENTS ATtending a tertiary referral uveitis clinic over a 3-month period were reviewed. For patients attending clinic during this interval, all clinic notes since initial presentation were reviewed and the first documented episode of raised IOP was identified. Patients were excluded if they had transient elevation of IOP because of transient postoperative uveitis, a clinic follow-up time of less than 6 months, or if they had

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TABLE 1. Characteristics of Eyes with Raised Intraocular Pressure in Uveitic Eyes with and without Corticosteroid Hypertensive Response

Eye-Specific Characteristics	Corticosteroid Responder Eyes	Noncorticosteroid Responder Eyes with Elevated IOP	*P* value
No. of eyes	168	107	
Mean follow-up ± SD, yrs	6.69 ± 6.13	7.67 ± 8.62	.305[a]
Mean age ± SD (range), yrs	47.5 ± 15.3 (21 to 84)	55.7 ± 15.9 (21 to 91)	<.0001[a]
No. male (%)	75 (44.6)	46 (42.9)	.788[b]
Race, no. (%)			
White	102 (60.8)	60 (56.1)	
Indian origin	36 (21.4)	30 (28)	
Black	18 (10.7)	13 (12.1)	
Middle Eastern	4 (2.4)	2 (1.9)	
South East Asian	6 (3.6)	2 (1.9)	
Unknown	2 (1.2)	0	
Uveitis distribution, no. (%)			
Anterior uveitis	52 (30.9)	31 (28.9)	
Acute anterior uveitis	17	13	
Posner–Schlossman syndrome	1	2	
Others[c]	16	11	
Chronic anterior uveitis	35	18	
Herpetic uveitis	0	3	
Fuchs heterochromic uveitis	3	3	
Others[d]	32	12	
Intermediate uveitis	63 (37.5)	27 (25.2)	
Posterior and panuveitis	53 (31.5)	49 (45.8)	
Toxoplasmosis	1	5	
Idiopathic retinal vasculitis	14	4	
VKHS and SO	2	7	
Others[e]	36	33	

IOP = intraocular pressure; SD = standard deviation; SO = sympathetic ophthalmia; VKHS = Vogt–Koyanagi–Harada syndrome; yrs = years.

Table 1 is by eye rather than by patient because some patients had 1 eye in the corticosteroid responder group and the other eye in the noncorticosteroid responder group. Patient-level characteristics apply to eyes.

[a]Independent samples *t* test.

[b]Chi-square test.

[c]HLA-B27 uveitis, Behçet syndrome, sarcoid uveitis, and idiopathic acute anterior uveitis.

[d]Sarcoid uveitis, HLA-B27 uveitis, juvenile idiopathic arthritis-associated uveitis, and idiopathic chronic anterior uveitis.

[e]Behçet syndrome, birdshot retinochoroidopathy, acute retinal necrosis, multifocal choroiditis and idiopathic posterior, and panuveitis.

a so-called masquerade syndrome or glaucoma that was diagnosed before the onset of uveitis. For patients with a raised IOP, additional data regarding clinical course and treatment were collected.

Uveitis was classified as anterior, intermediate, or posterior or panuveitis, depending on the anatomic site of intraocular inflammation. The uveitis was considered acute if the duration of active inflammation lasted less than 3 months, and as chronic uveitis if longer than this.[15] IOP at each clinic visit since presentation was recorded. Raised IOP was defined as an IOP of more than 21 mm Hg on 2 or more consecutive occasions (Goldmann applanation tonometry) at any time during the follow-up. Among the patients with raised IOP, those observed to have IOP elevation of 6 mm Hg or more above baseline in relation to the use of any form of corticosteroid treatment were considered to have corticosteroid-related IOP elevation. A diagnosis of glaucoma was made on the basis of glaucomatous optic disc or visual field (VF) changes, or both.

Raised IOP requiring treatment refers to eyes with IOP of 30 mm Hg or more without optic disc and field changes, or IOP of more than 21 mm Hg with glaucomatous optic discs, VF changes, or both. Patients with an IOP of less

than 30 mm Hg were not treated if they had normal optic discs and VFs but were monitored closely for signs of the onset of glaucoma. For this study, medical treatment to control elevated IOP was coded in the analysis as intermittent or sustained. Cases were classified as having intermittent treatment if IOP-lowering medications were continued for less than 50% of their follow-up and were classified as sustained otherwise. Controlled IOP was defined as IOP of 21 mm Hg or less in eyes with ocular hypertension or IOP equal to or less than the defined target pressure (12 to 14 mm Hg) for eyes with uveitic glaucoma.

All analyses were conducted using the statistical package SPSS for Windows version 11.0 (SPSS Inc, Chicago, Illinois, USA). The independent samples *t* test was used to assess differences between independent means in corticosteroid responder eyes and noncorticosteroid responder eyes with elevated IOP (patient's age, length of follow-up, and number of IOP-lowering drops). The association between corticosteroid response in eyes with elevated IOP and factors related to IOP control (need for sustained medical treatment and use of acetazolamide) and raised IOP outcome (frequency of glaucoma and need for IOP-lowering surgery) was tested with the chi-square test. In both tests, *P* values less than .05 were considered significant.

RESULTS

• **STUDY POPULATION:** The study included 891 uveitis patients who had at least 6 months of follow-up. One hundred and ninety-one patients met the criteria for raised IOP (21.4%) with 275 eyes included. There were 30 eyes with acute uveitis (10.9%) and 245 eyes with chronic uveitis (89.1%). Patients noted to have had raised IOP had been followed up for a mean of 7 years (range, 0.5 to 47 years). Table 1 shows the demographic features of the eyes with uveitis and elevated IOP.

Of the 275 eyes with raised IOP, 180 (65.5%) had ocular hypertension and 95 eyes (34.5%) had glaucoma. The mean maximum IOP was 34.3 ± 8.01 mm Hg (range, 22 to 62 mm Hg). IOP-lowering treatment was needed in 151 (83.9%) of 180 eyes with ocular hypertension and in all eyes (100%) with glaucoma. In total, raised IOP requiring treatment was present in 246 (89.5%) of 275 eyes with elevated IOP, with intermittent treatment required in 125 (50.8%) of 246 eyes and sustained treatment in 121 (49.8%) of 246 eyes. IOP was elevated but required no treatment in 29 (10.5%) of 275 eyes. Of eyes with acute uveitis, 83.3% (25/30) required IOP-lowering agents, as compared with 90.2% (221/245) of eyes with chronic uveitis ($P = .284$, Chi-square test).

• **CORTICOSTEROID TREATMENT AND THE STEROID HYPERTENSIVE RESPONSE:** Corticosteroids were used in the management of uveitis in all eyes. In Fuchs heterochromic uveitis, the use of topical corticosteroids was transient, and only as a challenge test, to confirm the diagnosis when a lack of response occurred. Corticosteroid use was subdivided according to the route of administration. Of the eyes with raised IOP, 257 eyes (93.5%) were managed with topical corticosteroids, 37 (13.5%) required periocular injections, and 29 eyes (10.6%) were treated with intravitreous triamcinolone. Oral prednisolone was given in 126 eyes (45.82%).

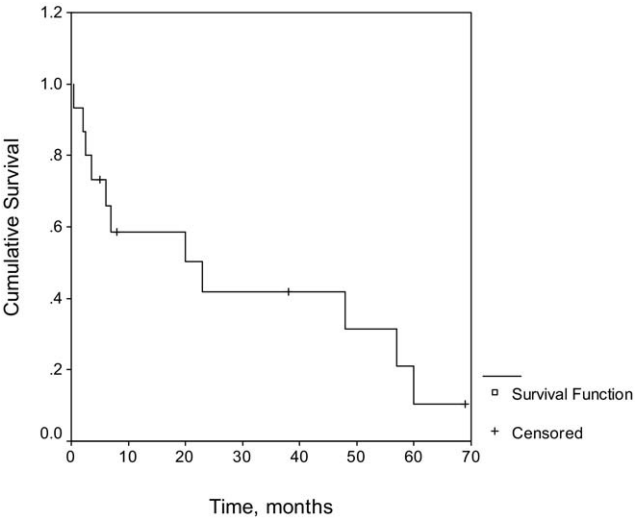

FIGURE. Kaplan-Meier curve showing time-to-discontinuation of intraocular pressure (IOP)-lowering therapy among eyes in which raised IOP developed after intravitreous triamcinolone therapy.

One hundred and sixty-eight (61.1%) of 275 eyes exhibited corticosteroid-induced IOP rise during the follow-up (mean ± standard deviation [SD], 6.69 ± 6.13 years) in relation to topical, periocular, oral, or intravitreous corticosteroid therapy. Among 18 eyes with intravitreous triamcinolone-related ocular hypertension, 14 (77.8%) had received prior topical, periocular, or systemic corticosteroid treatment. Of these, only 1 eye had a history of previous corticosteroid-induced ocular hypertension, which was seen after an orbital floor injection of corticosteroids. Regarding the number of intravitreous triamcinolone injections in eyes with triamcinolone-related IOP rise, 11 (61.1%) eyes had a single injection, 5 (27.8%) eyes received 2 injections, and 2 (11.1%) eyes received a total of 3 injections. In eyes that had multiple injections, a corticosteroid response was recorded after the first injection in 5 eyes, after the second of 2 injections in 1 eye, and after the third of 3 injections in another eye. Only 2 (11.1%) of these 18 eyes required additional short-term acetazolamide treatment, with all eyes otherwise (16 eyes; 88.9%) managed with ocular antihypertensive drops only (mean number of drops ± SD, 1.95 ± 1.16). In the 5 eyes that had further injections after IOP elevation with their first intravitreous triamcinolone injec-

TABLE 2. Outcome of Raised Intraocular Pressure in Uveitic Eyes with and without Corticosteroid Hypertensive Response

Factor in Analysis	No. of Eyes (%)		
	Corticosteroid Responder Eyes (n = 168)	Noncorticosteroid Responder Eyes with Elevated IOP (n = 107)	*P* value[a]
Need for sustained IOP-lowering medications	56 (33.3%)	65 (60.8%)	<.0001
Use of oral acetazolamide	23 (13.7%)	25 (23.4%)	.039
Frequency of glaucoma	38 (22.6%)	57 (53.3%)	<.0001
Need for aqueous filtering surgery	15 (8.9%)	24 (22.4%)	.002

IOP = intraocular pressure.
[a]Chi-square test.

tion, IOP-lowering drops were given at the time of repeated injections in anticipation for further IOP rise. At a median follow-up of 48 months from the time of the initial intravitreous triamcinolone injection, in no eye did a change in optic disc appearance develop as evidenced on fundus examination, nor did any eye require IOP-lowering surgery. IOP was controlled in all 18 eyes (100%), with 14 eyes (77.8%) being off all IOP-lowering treatment (median time to discontinuation of IOP-lowering therapy, 23 months) and 4 eyes (22.2%) continuing to receive ocular antihypertensive drops only (Figure).

• **MANAGEMENT OF ELEVEATED INTRAOCULAR PRESSURE:** β-Blockers were the most common agents prescribed for management of elevated IOP in this study, being used in 224 (91.1%) of 246 eyes that required IOP reduction. β-Blockers were used either as monotherapy (58/246; 23.6%) or in combination with other ocular hypotensive drops (brimonidine, dorzolamide, and prostaglandin analogs). In total, 77 (31.3%) of 246 eyes were managed with 1 antiocular hypertension drop, 47 eyes (19.1%) needed a combination of 2 drops, 65 (26.4%) needed 3 drops, and 57 (23.2%) required more than 3 drops. Short-term treatment with oral acetazolamide was indicated in 48 (19.5%) of 246 eyes when raised IOP was not controlled with 3 to 4 topical antihypertensive agents.

Prostaglandin analogs (latanoprost, bimatoprost, and travoprost) were used to control elevated IOP in 121 (49.2%) of 246 eyes that required topical antihypertensive treatment either as monotherapy (11 of 246 eyes; 4.5%) or, more commonly, in combination with other ocular antihypertensive agents. Prostaglandin analog drops were stopped in 60 eyes (49.6%) for various reasons. In 17 (28.3%) of 60 eyes, IOP elevation was short-lived and topical antihypertensives could be stopped after the control of inflammation, 20 eyes (33.3%) were controlled by other drops, and 16 (26.7%) of 60 had surgically controlled IOP, of which 14 eyes required no further treatment and 2 eyes required additional topical treatment with β-blockers. In 4 eyes (4/60; 6.7%), ocular irritation developed necessitating cessation of prostaglandin therapy. Prostaglandin analogs also were stopped in 3 more eyes (5%) that were receiving long-term latanoprost treatment (range, 4 to 24 months). Of these eyes, 2 pseudophakic eyes had increased anterior chamber inflammation, and 1 eye with intermediate uveitis developed cystoid macular edema (CME) 6 weeks after an uneventful cataract and intraocular lens implantation surgery.

Surgery to control elevated IOP was needed in 14.5% (40/275) of the eyes with elevated IOP. Of these, 30 (55%) of 40 underwent trabeculectomy with antimetabolite augmentation (mitomycin C in 22 eyes and 5-fluorouracil in 8 eyes), 3 eyes (7.5%) had trabeculectomy surgery without wound modulators, and 6 eyes (15%) underwent glaucoma shunt surgery. Surgical iridectomy was required in 1 eye only.

Table 2 shows the control and outcome of raised IOP in eyes with uveitis and elevated IOP that demonstrated a hypertensive corticosteroid response (168/275; 61.1%) and those that were noncorticosteroid responders (107/275; 38.9%). Corticosteroid-induced hypertensive response was associated with a lower need for aqueous filtering surgery, with 15 (8.9%) of 168 corticosteroid-responder eyes having surgery as compared with 24 (22.4%) of 107 in the noncorticosteroid-responder group ($P = .002$, Chi-square). Looking at the number of IOP-lowering drops the first time IOP came under control, a significant difference in the number of drops use was noted between corticosteroid-responder eyes (mean ± SD, 2.06 ± 1.46) and noncorticosteroid-responder eyes with raised IOP (2.52 ± 1.41; $P = .009$, independent samples t test; 95% confidence interval [CI], 0.116 to 0.812).

DISCUSSION

ELEVATION IN IOP CAN OCCUR AS A CONSEQUENCE OF corticosteroid treatment, and this has been demonstrated with all methods of administration.[7–10,16–20] Corticosteroids increase the IOP by increasing the resistance of the aqueous humor outflow facility, which is mediated by alteration of the mechanical structure of the trabecular meshwork, extracellular matrix deposition in the trabecular meshwork, and reduction of the functional and phago-

cytic activity of the trabecular cells.[21–23] In the present study, we demonstrated that a significant proportion (61.1%) of the IOP elevation in uveitic eyes at our tertiary center was corticosteroid induced. Although Armaly previously demonstrated that in only 35% of the normal population does a hypertensive corticosteroid response develop, the corticosteroid response rate increases dramatically in situations where conventional aqueous outflow pathway is thought to be compromised already.[16,24] Similar to eyes with POAG, where 90% respond to corticosteroids with a rise in IOP,[24] eyes with uveitis may have an increased outflow resistance and thus are at a high-risk for corticosteroid-induced ocular hypertension and glaucoma developing.[25]

Intravitreous triamcinolone represents an important and recent adjunct in the management of uveitic macular edema and vitreitis. Our data showed that intravitreous triamcinolone-related ocular hypertension accounted for 6.5% of the total number of eyes with IOP rise secondary to uveitis (18/275 eyes). However, all eyes were controlled with medical treatment, and IOP elevation generally was short lived and did not result in optic nerve damage. In addition, intravitreous triamcinolone did not seem to be associated with an increase in the overall risk of elevated IOP in uveitic eyes. In fact, the risk of raised IOP seemed to be lower in the current series than in our previous series,[1] despite the use of intravitreous triamcinolone in a substantial number of eyes in the current series. Although caution generally is applied in retreating eyes with previously documented triamcinolone-induced corticosteroid response, alternative treatment options sometimes are limited in patients who have contraindications to or did not respond to systemic therapy previously and where initial intravitreous triamcinolone resulted in significant visual improvement. In these cases, repeating the intraocular corticosteroid injection with prophylactic use of ocular antihypertensive agents and careful IOP follow-up provided favorable results in our hands.

Although there have been anecdotal small case series suggesting a causal relationship between prostaglandin analogs and the development of anterior uveitis or macular edema, all reported cases had 1 or more risk factors independent of prostaglandin treatment such as previous intraocular surgery, pseudophakia, or a history of uveitis.[12–14] Moreover, there is no evidence from controlled clinical trials and experimental studies to support a direct association between prostaglandin analogs and intraocular inflammation or CME. In a prospective, randomized, crossover study conducted with a laser flare meter, latanoprost, travoprost, and bimatoprost had no statistically significant effect on the blood-aqueous barrier of phakic patients with POAG and ocular hypertension after 1 month use of the prostaglandin analog that was followed by a 4-week washout period between each drug.[26] A long-term study of latanoprost treatment also has demonstrated the absence of any clinically significant effect on the permeability of the blood-aqueous barrier in patients treated for as long as 12 months.[27] Additionally, data from the multicenter, controlled, phase III latanoprost trials[28–31] showed that CME attributable to prostaglandin treatment did not occur in more than 1,000 patients treated with latanoprost.

We do not believe the 3 cases with uveitis or CME in which latanoprost was stopped represent prostaglandin-induced uveitis. These eyes were pseudophakic with a previous history of CME, and their uveitis previously was stable with the administration of prostaglandin analogs. Corticosteroid therapy already had been increased in these eyes at the time of latanoprost cessation, making it difficult to judge the exact relationship between latanoprost and intraocular inflammation or CME. However, even if these were cases of prostaglandin-induced uveitis, such cases would be rare (upper bound of a one-sided 97.5% CI, 3.0%). Our findings also are supported by the results of a retrospective study that compared the frequency of anterior uveitis and CME in 280 eyes with uveitis and raised IOP treated with and without prostaglandin analogs.[32] Results showed no significant difference in the frequency of anterior uveitis (odds ratio [OR], 0.94; $P = .87$) or CME (OR, 0.48; $P = .19$) in eyes treated with prostaglandin analogs and those treated with nonprostaglandin agents. Other factors such as drug costs may limit the use of these drugs as first-line agents in these uveitis patients.

An important objective of the study was to look at the adequacy of elevated IOP control in corticosteroid responders as compared with those whose IOP elevation is related to the intraocular inflammation rather than to corticosteroid use. Our results confirm anecdotal clinical experience that compared with eyes that have uveitis-related ocular hypertension and glaucoma, IOP elevation in corticosteroid responders is associated with a significantly less sustained need for medical treatment and a lower rate of secondary glaucoma. Although a corticosteroid response complicates the management of uveitis, IOP control seems to be easier and more effective in this cohort, with a lower need for topical and systemic IOP-lowering medications or surgical intervention. We believe that these results reflect the different underlying mechanisms for uveitis-related ocular hypertension and glaucoma. Although corticosteroid-induced damage is more related to acute and potentially reversible changes in the microstructure of the trabecular meshwork,[21–23] damage resulting from intraocular inflammation tends to be more insidious, with development of permanent changes in the trabecular system and hence a more sustained IOP elevation and glaucoma.[33]

In summary, this study suggests that a significant proportion of elevated IOP with uveitis is the result of a corticosteroid hypertensive response. IOP seems to be controlled more effectively in these eyes than in those in which the IOP rise is secondary to intraocular inflammation, rather than to the use of corticosteroids. Intravitreous triamcinolone acetonide use is associated with a

substantial risk of developing ocular hypertension, but this currently accounts for less than 10% of cases with hypertensive uveitis in our practice, with IOP rise being transient in most cases and only requiring medical treatment. Although larger controlled trials would be needed to investigate more precisely the association between prostaglandin analogs and the development of anterior uveitis or CME, our data suggest that the routine use of prostaglandin analogs is not contraindicated in the uveitis population.

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Biosketch

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