

Discontinuing nasal steroids might lower intraocular pressure in glaucoma

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Background: Topical, intraocular, oral, and parenteral steroids might increase intraocular pressure (IOP), but little is known regarding the effect of nasal steroid spray.

Objective: We sought to examine the effect of discontinuing nasal steroid sprays on IOP in patients with glaucoma.

Methods: A retrospective chart review of patients with glaucoma using nasal steroids was performed. Averaged IOP for each pair of eyes was determined for presteroid use, steroid use, and 2 consecutive poststeroid use (poststeroid 1 and poststeroid 2) examinations.

Results: Twenty-four eyes of 12 patients taking nasal steroids were identified. The mean IOP for each pair of eyes was 15.4 ± 4.3 mm Hg (range, 9-23.5 mm Hg) for the presteroid use examination, 18.0 ± 3.8 mm Hg (range, 12-24.5 mm Hg) for the steroid use examination, 14.5 ± 3.3 mm Hg (range, 9.5-20 mm Hg) for poststeroid use examination 1, and 14.8 ± 3.4 mm Hg (range, 9.5-22.0 mm Hg) for poststeroid use examination 2. Eleven patients experienced decreased averaged IOP at poststeroid use examination 1 after steroid discontinuation at a mean of 35 ± 14 days and continued to maintain this decrease on the poststeroid use examination 2 visit at a mean of 191 ± 150 days. A significant increase between presteroid and steroid use examination IOPs ($P = .007$) and a significant decrease between steroid use and both poststeroid use 1 ($P < .001$) and poststeroid use 2 ($P = .011$) examination IOPs were observed. No significant difference between presteroid use and either poststeroid use examination IOPs ($P = 1.00$) was found. Many patients met their target pressures and were able to avoid or delay additional glaucoma therapy.

Conclusion: A significant reduction in IOP occurred with nasal steroid discontinuation in patients with glaucoma. Nasal steroids might contribute to IOP increase, and inquiry as to whether a patient has glaucoma before medication initiation is warranted. (J Allergy Clin Immunol 2005;116:1042-7.)

Key words: Steroid nasal spray, glaucoma, intraocular pressure, eye

Systemic and topical ophthalmic steroids have long been associated with ocular effects, such as glaucoma or cataracts.¹⁻⁸ Periocular steroid injections^{9,10} and steroids

Abbreviations used

IOP: Intraocular pressure

OHT: Ocular hypertension

POAG: Primary open-angle glaucoma

applied to periocular skin¹¹ also have been associated with increased intraocular pressure (IOP), which is referred to as ocular hypertension (OHT). OHT is a condition in which IOP is increased without signs of optic neuropathy, such as visual field defects and optic nerve head cupping. The presence of these optic neuropathy signs defines glaucoma. Only a fraction of patients with OHT eventually have glaucoma. However, a higher percentage of patients with glaucoma will have an increased IOP response to steroids, risking further glaucomatous damage.¹² Glaucoma, estimated to affect 67 million persons, is the leading cause of irreversible blindness in the world.¹³ Thus far, there has been little evidence to suggest that nasal steroids can cause ocular side effects.

Allergic rhinitis affects up to 30% of adults and 40% of children in the United States.¹⁴ Topical nasal steroids are the most effective treatment option.¹⁵ Nonallergic rhinitis is a common disease that affects approximately 17 million persons in the United States; approximately 22 million have a combination of allergic and nonallergic rhinitis.¹⁶ Topical nasal steroids have demonstrated efficacy in the treatment of nonallergic rhinitis and are considered first-line empiric therapy.¹⁶ With the perceived safety of nasal steroids, their use for the treatment of upper respiratory allergy has become more common.¹⁷ However, inhaled and nasal steroids might be absorbed systemically through the nasal mucosa, gastrointestinal tract through swallowing, or inhaled through the lungs. Although the systemic absorption of inhaled and nasal steroids has been established,^{18,19} the clinically relevant ocular side effects are poorly defined. A large prospective study in 1995 by Samiy et al²⁰ reported no statistically significant increase of IOP in 187 patients without glaucoma taking inhaled steroids for various pulmonary conditions. Similarly, a large case-control study²¹ in 1997 cases suggested that the presence of nasal steroid use in patients with newly diagnosed glaucoma or OHT versus nonglaucomatous patients was not statistically significant (odds ratio, 1.02; 95% CI, 0.59-1.77). However, the number of patients taking continuous high-dose nasal steroids was too small for statistical analysis. In 1998, a small prospective study²² of 26 nonglaucomatous patients revealed no evidence of OHT or cataracts after prolonged use of nasal steroids

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TABLE I. Patient characteristics

Patient no.	Age (y)	Sex	Diagnosis	Previous surgery	Steroid medication	Target IOP (mm Hg)	Medical history
1	49	M	POAG	None	Fluticasone propionate	≤15	Hypertension, esophagitis, Hyperlipidemia
2	59	M	POAG OS, OHT OD, steroid responder	None	Budesonide	≤20	Diabetes mellitus, hypertension, migraines, osteoarthritis, depression, anxiety
3	61	F	POAG	None	Triamcinolone acetonide	≤15	Parotid adenoma, hypercholesterolemia, psoriasis
4	66	M	OHT	None	Mometasone furoate monohydrate	≤20	Hypothyroid
5	68	F	LTG	TBx OS	Budesonide	≤15	Lipoma, asthma
6	83	F	POAG	None	Fluticasone propionate	≤15	Allergic rhinitis, hyperlipidemia, anemia, heart disease
7	80	F	CACG, uveitic glaucoma	TBx OD, shunt OS	Budesonide	≤15	Arthritis, anemia
8	79	F	POAG, CACG	TBx OD, TBx OS	Budesonide	≤15	Allergic rhinitis, hypertension, hyperlipidemia, depression
9	82	F	LTG	TBx OD, TBx OS	Budesonide	≤15	Hepatitis C, breast cancer, diverticulitis, hypertension, anxiety
10	61	F	LTG	None	Fluticasone propionate	≤15	Allergic rhinitis, depression
11	70	F	POAG	None	Mometasone furoate monohydrate	≤20	Parkinson disease, hypertension, gout
12	35	F	POAG	TBx OD, TBx OS	Unnamed Steroid	≤15	Sinusitis, mitral valve prolapse
66.1 ± 14.4							

OS, Oculus sinister; OD, oculus dexter; LTG, low-tension glaucoma; CACG, chronic angle closure glaucoma; TBx, trabeculectomy.

after endoscopic sinus surgery (mean follow-up, 8.8 ± 3.6 months; range, 3-19 months). A study of 61 patients with seasonal allergic rhinitis taking nasal fluticasone for 1 year showed no increased risk for glaucoma.²³ However, no information was described regarding their glaucoma risk status before steroid use in this study. Six cases²⁴⁻²⁶ of increased IOP associated with combined nasal and inhaled steroid use in nonglaucomatous patients have been reported. To our knowledge, there has been only one case report²⁶ of increased IOP with nasal steroids alone.

The aforementioned studies that have shown no association of nasal steroids with glaucoma were conducted on patients with no previous history of glaucoma. Given that a greater fraction of patients with open-angle glaucoma are steroid responders compared with the general population,⁴⁻⁷ a substantial number of patients with glaucoma taking nasal steroids might be at risk for increased IOP and progressive vision loss. The effect of nasal steroids in patients with glaucoma or OHT remains unclear. We report the results of discontinuing nasal steroids in 12 patients with glaucoma or OHT.

METHODS

Over a 16-month study period (May 2002-September 2003), patients who used nasal sprays were identified prospectively. This was a standard inquiry for patients with glaucoma or OHT over this

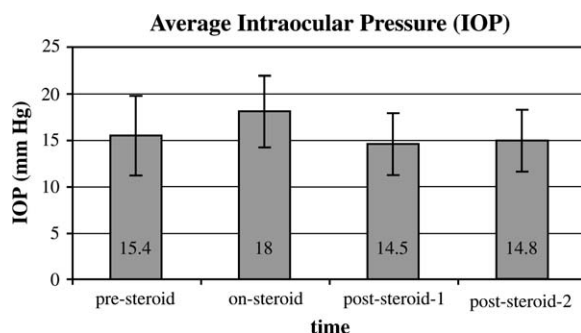
time interval. Patients were included if they had a diagnosis of glaucoma or OHT, were using nasal steroid sprays and agreed to discontinue use, had been seen for at least 1 visit before steroid use, and returned for at least 2 follow-up visits. A retrospective chart review of these patients with glaucoma and OHT using nasal steroids was performed after approval by the Vanderbilt Institutional Review Board. The age, sex, glaucoma diagnosis, history of glaucoma surgery, systemic and topical medication use, type of steroid nasal spray, and IOP for each eye at each time point were recorded. All IOP measurements were taken by 1 ophthalmologist. Data were recorded for presteroid, steroid use, and 2 consecutive poststeroid use (poststeroid 1 and poststeroid 2) clinical examinations. The visual field interpretation was reviewed to determine whether the visual field had deteriorated from the subject's previous visual field. No patient restarted nasal steroids during the period of this study.

The primary end point for the study was to examine whether the nasal steroid spray contributed to IOP increase in patients with glaucoma or OHT. We examined the changes in IOP and whether patients met their target IOPs during steroid use and after steroid discontinuation. The mean IOP for each pair of eyes was calculated. Then the percentage change from presteroid use was calculated for the steroid use examination, poststeroid use examination 1, and poststeroid use examination 2. The restricted/residual maximum likelihood-based mixed effects model was used to compare averaged IOP, percentage IOP changes for each pair of eyes, and the target IOP for each eye to adjust the intracorrelation effect for patients who had multiple measurements. The generalized estimating equations method was used for the analysis of binary IOP target outcomes. For the pairwise multiple comparisons of averaged IOP and averaged

TABLE II. IOP of each eye during the presteroid, steroid, and poststeroid use examinations

Patient no.	Presteroid IOP (mm Hg)			Steroid use IOP (mm Hg)			Poststeroid 1 IOP (mm Hg)			Poststeroid 2 IOP (mm Hg)		
	OD	OS	Average	OD	OS	Average	OD	OS	Average	OD	OS	Average
1	11	13	12	16	14.5	15.25	12	12	12	14.5	13	13.75
2	17	17	17	19	22	20.5	17	18	17.5	15	18	16.5
3	14	16	15	16	19.5	17.75	15	16	15.5	17	16	16.5
4	19	17	18	26	23	24.5	21	18	19.5	18.5	17	17.75
5	14	12	13	18	20	19	14	13	13.5	15	13	14
6	16	14	15	18	16	17	16	13	14.5	16	13	14
7	24	23	23.5	19.5	18	18.75	15	14	14.5	15	14	14.5
8	24	15	19.5	16	12	14	16	13	14.5	14.5	18	16.25
9	7	11	9	8	21	14.5	8	14	11	7	11	9.5
10	9	10	9.5	12	12	12	9	10	9.5	10	12	11
11	17.5	22	19.75	26	22.5	24.25	20	20	20	20	24	22
12	15	12	13.5	20	18	19	12	11	11.5	13	10	11.5
Mean $\pm$ SD	15.4 $\pm$ 4.3			18.0 $\pm$ 3.8			14.5 $\pm$ 3.3			14.8 $\pm$ 3.4		

Shading indicates previously operated eyes.
OD, Oculus dexter; OS, oculus sinister.

**FIG 1.** Graph of averaged IOP before, during, and after steroid nasal spray use.

IOP percentage change from presteroid use, *P* value was adjusted by using the Bonferroni procedure. All tests of significance were 2 sided, and differences were considered statistically significant at a *P* value of less than .05. SAS version 8.2 software (SAS Institute, Cary, NC) was used for the analyses.

RESULTS

Twenty-four eyes of 12 patients (11 with glaucoma and 1 with OHT) met the inclusion criteria (Table I). One patient was excluded because he desired to continue his steroid nasal spray to control sinus drainage. He had an increase in IOP after the nasal spray and short-term oral steroids subsequently were administered. His IOPs have remained controlled in the midteens with the addition of a topical β -blocker. A second patient was excluded because a glaucoma medication was added at the time of stopping steroid use, which would confound subsequent IOP measurements. No patients included in the study were taking systemic or topical steroids at the time of nasal steroid use. One patient (patient 2) was classified as a

steroid responder because his IOP had increased in response to steroids before our study.

Patients were taking various combinations of glaucoma medications. No subject included in the study received additional medical or surgical glaucoma therapy at the time of nasal steroid discontinuation or the subsequent 2 follow-up visits. All study patients were unaware that their nasal spray was a steroid. Subjects dosed the nasal sprays a variable 1 to 2 sprays several times daily to every other day for weeks to months before their ocular examination. The subjects had no interval systemic steroids, iritis, or traumas that could cause an IOP spike. Their past and current medical histories are listed in Table I.

Of the 12 study patients, 75% were female, and 25% were male. The average age was 66.1 ± 14.4 years, with an average female age of 68.8 ± 15.3 years and an average male age of 58.0 ± 8.5 years. Of the 15 eyes that had not undergone previous glaucoma surgery, all experienced a pressure increase (range, 0.5-8.5 mm Hg) after starting nasal steroids and a pressure decrease (range, 1-6 mm Hg) after nasal steroid discontinuation at poststeroid use examination 1 (Table II). Nine eyes had undergone previous glaucoma surgery (8 trabeculectomy and 1 Ahmed shunt). Of these previously operated eyes (indicated by shading in Table II), 4 eyes (patients 5, 9, and 12) responded similarly to the nonsurgical eyes with an IOP increase (range, 5-10 mm Hg). One eye (patient 10) had a stable IOP (<13 mm Hg) throughout the study period. Four previously operated eyes had a decrease in IOP during steroid use. These responses occurred after the addition of a glaucoma medication (patient 7) and poor medication compliance (patient 8) at the presteroid use visit.

The mean IOP for each pair of eyes was calculated for each time point. Then the average of all 12 patients' mean IOP was determined for the presteroid use (15.4 ± 4.3 mm Hg; range, 9-23.5 mm Hg), steroid use (18.0 ± 3.8 mm Hg; range, 12-24.5 mm Hg), poststeroid use 1 (14.5 ± 3.3

TABLE III. Averaged IOP percentage change from baseline

Patient	% Increase on steroid	% Decrease at poststeroid 1 examination	% Decrease at poststeroid 2 examination
1	27.1	0.0	14.6
2	20.6	2.9	-2.9
3	18.3	3.3	10.0
4	36.1	8.3	-1.4
5	46.2	3.8	7.7
6	13.3	-3.3	-3.3
7	-20.2	-38.3	-38.3
8	-28.2	-25.6	-16.7
9	61.1	22.2	0.0
10	26.3	0	15.8
11	22.8	1.3	11.4
12	40.7	-14.8	-14.8
	22.0 ± 25.4	-3.3 ± 16.0	-1.5 ± 15.7

mm Hg; range, 9.5-20 mm Hg), and poststeroid use 2 (14.8 ± 3.4 mm Hg; range, 9.0-22.0 mm Hg) examinations (Table II).

The restricted/residual maximum likelihood-based mixed effects model demonstrated a significant increase between presteroid use and steroid use IOPs ($P = .007$, Fig 1). There was a significant decrease between the steroid use examination and both poststeroid use examination 1 ($P < .001$) and poststeroid use examination 2 ($P = .011$) IOPs. No significant difference between the presteroid use IOP and either poststeroid use IOP ($P = 1.00$) was noted.

Ten of 12 patients experienced an increase in averaged IOP after starting nasal steroids. Eleven of 12 patients experienced a decreased averaged IOP on poststeroid use examination 1 at a mean of 35 ± 14 days (range, 21-59 days) after discontinuation of the nasal steroids. They continued to maintain a decreased averaged IOP on poststeroid use examination 2 at a mean of 191 ± 150 days (range, 84-645 days). The averaged IOP percentage change from presteroid values was a $22.0\% \pm 25.4\%$ increase with nasal steroid spray. There was only a $3.3\% \pm 16.0\%$ decrease at poststeroid use examination 1 and a $1.5\% \pm 15.7\%$ decrease at poststeroid use examination 2 compared with the baseline presteroid use IOP values (Table III).

The clinical significance of nasal steroid discontinuation was defined in eyes having IOPs greater than the target level during steroid nasal spray use, with the need for additional glaucoma therapy if the IOP did not decrease to the target level or less. The IOP was greater than the target level in 18 eyes during nasal steroid use (Tables I and II). Three of the 12 subjects had visual field deterioration in at least one of their eyes while taking nasal steroids (Table IV). Right and left eye visual fields (Fig 2) from 1 subject demonstrate the dense loss in the central 30° that occurs with significant primary open-angle glaucoma (POAG). Fourteen ($P \leq .001$) of these eyes at poststeroid use examination 1 and 13 ($P = .001$) of these eyes at poststeroid use examination 2 met the target IOP after discontinuation of nasal steroids (Table II). This enabled these patients to delay additional medical or surgical therapy.

TABLE IV. Visual field deterioration

Patient	OD	OS
1	N	N
2	N	N
3	N	N
4	N	N
5	N	Y
6	N	N
7	N	Y
8	N	N
9	Y	Y
10	N	N
11	N	N
12	N	N

OD, Oculus dexter; OS, oculus sinister; Y, yes; N, no.

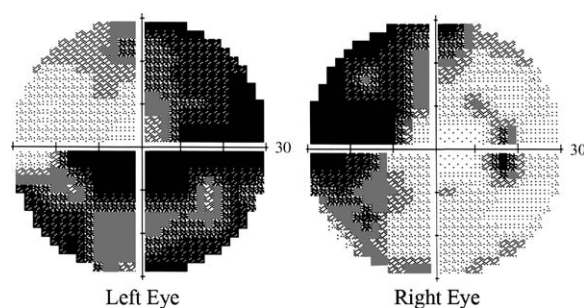


FIG 2. Computerized central 30° visual fields of subject 12 with POAG demonstrate severe loss of peripheral vision encroaching on central fixation, especially in the left eye.

DISCUSSION

Although large studies have shown no substantial risk of inhaled and intranasal steroids in patients without ocular pathology, the effect of nasal glucocorticoids in those with glaucoma or OHT remains unclear. Topical nasal steroids have demonstrated efficacy and are considered first-line empiric therapy in the treatment of allergic and nonallergic rhinitis.^{15,16} The increase in nasal steroid spray use for sinusitis and allergic rhinitis was the impetus for this study. Nonallergic rhinitis might occur more frequently in women than in men.¹⁶ This female predominance might be one reason for the higher percentage of women in our study. Although intranasal steroids are considered to have few systemic side effects, Knutsson et al²⁷ reported suppressed serum cortisol levels and downregulated peripheral lymphocyte glucocorticoid receptor mRNA in healthy subjects after 2 weeks of twice-daily intranasal budesonide or fluticasone, suggesting systemic absorption does occur. The intranasal corticosteroids do vary in their systemic bioavailability, with budesonide well absorbed through the nasal mucosa into the systemic circulation and mometasone furoate with almost undetectable levels systemically at prescribed doses. The quantification limit of this assay was 50 ng/L.²⁸ We found that a clinically and statistically significant reduction in IOP can be achieved with discontinuation of nasal steroid spray in patients with glaucoma or OHT. Reduction of

IOP after nasal steroid discontinuation was maintained for at least several months. Many patients met their target IOP by simply discontinuing their nasal steroid alone and were able to avoid or delay additional glaucoma therapy.

Exogenous topical steroids can produce an IOP increase in normal eyes.⁶ Becker and Mills⁴ found topical corticosteroids increased the IOP from baseline levels an average of 15.2 mm Hg in patients with glaucoma and an average of 4.6 mm Hg in healthy patients. It is estimated that 18% to 36% of the general population will eventually have an increase of IOP with corticosteroid therapy, with a much higher response rate in patients with POAG.¹² An increase of even 3 mm Hg could cause the IOP of patients with glaucoma to become higher than their maximal target IOP, necessitating additional glaucoma medication or surgery. Corticosteroids increase outflow resistance through the trabecular meshwork, with a preceding upregulation of several genes, including the well-studied GLC1A (myocilin/TIGR) gene.²⁹ The delay in myocilin upregulation corresponds to the delay in IOP after steroid initiation.³⁰ Mutations in this gene alone have been associated with most familial juvenile glaucoma and approximately 5% of adult open-angle glaucoma cases.¹³ Additional knowledge is expected as more genes, along with their products, functions, and mutations, are discovered.¹³

The mechanism of steroid-induced increase of IOP is multifactorial, with a major effect on reduction of aqueous outflow. Target cells for glucocorticoids were identified in the trabecular meshwork of human glaucomatous and nonglaucomatous eyes, suggesting that steroid-specific receptors might play a role in steroid-induced increase in IOP.^{12,31,32} One proposed mechanism suggested that steroids might inhibit degradation of glycosaminoglycans in the trabecular meshwork, causing an accumulation of these substances, which increases outflow resistance.^{12,33-35} Degenerative changes in the trabecular meshwork of glaucomatous eyes might account for the greater effect of steroids in those with glaucoma compared with normal eyes.^{6,7} A second theory suggested that steroid-induced outflow resistance is related to an increase in the expression of elastin³⁶ or fibronectin^{37,38} or to an alteration in collagen synthesis^{38,39} in the extracellular matrix.

Relatively few studies have examined the effects of nasal steroids on IOP in healthy subjects. Garbe et al²¹ reviewed a Canadian insurance database of almost 10,000 patients given a new diagnosis of OHT or POAG to calculate an odds ratio of increased pressure with inhaled or nasal steroids relative to control subjects. Although the odds ratio of 1.44 (95% CI, 1.01-2.06) of the previously healthy subjects suggested a higher risk of increased IOP relative to prolonged use of high-dose inhaled steroids, there were an insufficient number of patients taking continuous high-dose nasal steroids for analysis. The presence of any reported nasal steroid use was not statistically significant in the patients given a new diagnosis of OHT or POAG (odds ratio, 1.02; 95% CI, 0.59-1.77). Seven other studies were identified that evaluated the effect of steroid nasal spray on the IOP of healthy patients.

Three investigations reported that there were no significant changes in IOP or that glaucoma did not develop, but no actual IOP measurements were listed.^{22,23,40} Four studies noted no statistically significant increase in mean IOP after nasal steroid use, but 3 included cautionary statements. In 2000, Bross-Soriano et al⁴¹ stated, "There were some modifications in the IOP, but without exceeding the normal parameters." In 2004, Bross-Soriano et al⁴² reported, "Variations were found in the IOP of patients who used local steroid, with discreet elevations in the beclomethasone dipropionate and mometasone furoate groups; however, variations were always within normal limits." Neither study included individual response information. Samiy et al²⁰ reported that no healthy subject had an IOP increase of greater than 4 mm Hg. One abstract noted no IOP of greater than 22 mm Hg in 42 healthy patients taking fluticasone propionate.⁴³ Of greater importance, there has been no study evaluating the effects of nasal steroids on IOP in patients given a previous diagnosis of juvenile glaucoma or POAG. These groups are more susceptible to IOP spikes from steroids delivered through any other route of administration¹² and are more likely to experience vision loss from IOP increases than healthy subjects.

The one case report of nasal steroid-induced glaucoma indicated that nasal spray use occurred for 5 months.²⁶ One limitation of our retrospective study is the absence of information on steroid duration and dosage. Study patients were taking a wide variety of nasal steroid sprays with different relative potencies. In addition, patients were not rechallenged with their nasal spray to absolutely establish the spray as the sole causative factor for the IOP increase. An additional potential source of bias is that this study was not blind, which might cause the examiner to err toward a higher IOP in the steroid use measurement and toward a lower IOP in the poststeroid measurements. Of the patients whose pressure did not respond predictably to steroid use and discontinuation, all had a history of prior glaucoma surgery. A well-functioning trabeculectomy was present in the eye that maintained a stable controlled IOP throughout the study. Trabeculectomies will diminish in their capability to control IOP over time and require adjunctive glaucoma medications and might not overcome a steroid challenge. A well-designed prospective clinical trial to evaluate IOP responsiveness in patients with glaucoma might be warranted.

In our report of 12 patients, discontinuation of nasal steroids resulted in an improvement of IOP in most eyes, enabling those patients to avoid or delay additional medical or surgical therapy. We suggest that prescribing providers inform all patients that the nasal spray is a steroid. Providers should consider inquiring about a history of glaucoma before prescribing a steroid intervention and consider alternative therapy for patients given a diagnosis of glaucoma or recommend monitoring the IOP by the patient's ophthalmologist. Likewise, ophthalmologists should consider questioning patients with glaucoma regarding specific use of nasal sprays, as well as steroids, because patients might not be aware that nasal sprays can contain steroids. Many of the 12 subjects

reported in this study would have declined the nasal spray for their symptoms if they had been aware that it was a steroid. Patients with glaucoma should be educated regarding the risk of IOP increase with steroids and be informed to have an eye examination in 2 to 3 weeks if they require steroid administration for their health so that any uncontrolled IOP can be treated. Some patients with glaucoma who have severe respiratory or collagen vascular disease benefit greatly from steroids. Although a few points of IOP increase might be insignificant for healthy patients, it might have significant long-term visual field and vision consequences in individual patients with severe loss from glaucoma. If the IOP is greater than the maximal targeted IOP in patients requiring steroid therapy, then additional glaucoma medications or surgical glaucoma procedures are required to prevent visual field deterioration.

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