Corticosteroid-induced ocular hypertension and glaucoma: a brief review and update of the literature
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Purpose of review
The purpose of this article is to briefly review the literature of corticosteroid-induced ocular hypertension and glaucoma, its risk factors, the pathophysiology, and treatment options. In particular, literature pertaining to glaucoma in response to intravitreal triamcinolone acetonide will be reviewed.

Recent findings
Primary open-angle glaucoma, status as a glaucoma suspect, and a family history of glaucoma are risk factors for an ocular hypertensive response with the use of corticosteroid therapy. Recent studies suggest that younger age may also be a risk factor in patients treated via the intravitreal route with cortico-steroids. The mechanism of elevated intraocular pressure is increased aqueous outflow resistance owing to an accumulation of extracellular matrix material in the trabecular meshwork.

Summary
Corticosteroid-induced ocular hypertension and glaucoma has been recognized for more than 50 years. Knowing the risk factors, prevalence, and pathophysiology can help the clinician prevent, monitor, and treat corticosteroid-induced ocular hypertension and glaucoma.

Keywords
intravitreal triamcinolone, ocular hypertension, review, steroid-induced glaucoma

Introduction
Increased intraocular pressure (IOP) can occur as a consequence of oral, intravenous, inhaled, topical, perilunar, or intravitreal corticosteroid therapy [1–6,7,8**, 9–11]. If the ocular hypertension is of a significant magnitude, not recognized, and not treated, subsequent glaucomatous optic neuropathy can develop (that is, steroid-induced glaucoma). Steroid-induced ocular hypertension was first reported in 1950 when McLean [12] reported an increase in IOP associated with the systemic administration of adrenocorticotropic hormone (ACTH). The first report of increased IOP caused by the local administration of cortisone occurred four years later [13]. Since those initial reports, corticosteroid-induced glaucoma has been studied intensively. A number of predisposing risk factors have been identified [14–23,24**]. The intraocular potency and mode of administration have been shown to be important in initiating an ocular hypertensive response [1–6,7,8**,9,25]. Recently, the popular use of intravitreal triamcinolone acetonide (IVTA) for subretinal fluid, macular edema, and adjunctive therapy in the treatment of choroidal neovascularization has led to an increased incidence of corticosteroid-induced ocular hypertension from IVTA [7,**8,26–28,29**]. The molecular biological factors contributing to increased IOP are beginning to be better understood and these findings may lead to additional management options in the future [30–41]. We will review selected studies with an emphasis on glaucoma elevations associated with IVTA.

Predisposing risk factors for corticosteroid-induced glaucoma
When treated with topical steroids for 4–6 weeks, 5% of the population demonstrates a rise in IOP greater than 16 mmHg and 30% have a rise of 6–15 mmHg [10,11]. Several variables have been identified as predisposing risk factors for steroid-induced ocular hypertension. Patients with predisposing risk factors should be followed more diligently when receiving corticosteroids.

Primary open-angle glaucoma (POAG) patients and glaucoma suspects were shown to be at an increased risk for elevated IOP after treatment with corticosteroids. Studies by Armaly [14,15] revealed that approximately one-third of glaucoma suspects and more than 90% of POAG patients responded with an IOP elevation greater than 6 mmHg after receiving a 4-week course of
topical dexamethasone 0.1%. The effect was noted to be more prominent in the eyes of older adult patients compared with the eyes of younger adult patients. A study by Becker and Mills [16] also indicated that patients with pre-existing glaucoma and glaucoma suspects demonstrated large, highly significant increases in IOP in 2–4 weeks with the use of topical betamethasone 0.1% and exhibited decreased outflow facility during the treatment period. The IOP returned to baseline or normal in approximately 1 week with discontinuation of steroid treatment. Moreover, other studies showed that simply having a first-degree relative with POAG could make one susceptible to being a steroid-responder [18, 19].

Although older patients are at increased risk, the frequency of steroid responsiveness with age may occur in a bimodal distribution. Children as a group have been shown to be greater steroid-responders as compared with adults. A recent study by Lam et al. [24] showed that 71.2 and 59.2% of children receiving topical dexamethasone 0.1% (four times per day and two times per day, respectively) responded with an IOP rise greater than 21 mmHg. Additionally, 36.4 and 21.1% of those same two groups had an IOP rise greater than 30 mmHg. Among children under 6 years old who received dexamethasone 0.1% four times per day, the peak IOP was greater, the net increase in IOP was greater, and the time required to obtain the peak IOP was less. Children greater than 6 years old (children up to age 10 were included in the study) had a similar net increase in IOP, but did not show a significant difference in peak IOP or the time required to reach the peak IOP.

Gatson et al. [20] showed that patients with connective-tissue disease tend to be steroid-responders. Men with connective-tissue disease tended to be greater responders, although gender is not typically considered a risk factor in people without connective-tissue disease. Additionally, patients with type-1 diabetes mellitus [20] and high myopia [22] have also been shown to be at increased risk to be steroid-responders.

In summary, pre-existing POAG, status as a glaucoma suspect, or a first-degree relative with POAG are important risk factors for corticosteroid-induced ocular hypertension and glaucoma. Age may be a risk factor; increased risk appears to occur in a bimodal distribution peaking first at age 6. As one progresses through adulthood age may not be a factor until late adulthood when the risk again rises. Finally, those with connective-tissue disease, type-1 diabetes mellitus, and high myopia should all be considered high risk, and prudent follow-up should be pursued during periods of corticosteroid use.

Types of preparations and modes of administration
Corticosteroids have been shown to exert an ocular hypertensive response relative to the intraocular potency of the steroid [25]. Aside from the relative ability to inhibit inflammation, the other main determinant of intraocular potency is chemical structure. Acetates are more lipophilic and penetrate through the cornea better than phosphates, which are relatively hydrophilic. Medrysone 1.0% caused a 1.0 mmHg rise in IOP, while more potent steroids such as prednisolone acetate 1.0% and dexamethasone acetate 0.1% caused a 10 and 22 mmHg rise in IOP, respectively.

Corticosteroids have been shown to cause a elevation in IOP through all modes of administration [1–6,7,8,9]. The rise of IOP usually occurs over a period of weeks if used topically [15,16,25] and years if used systemically [1]. There have been some reports of an elevation of IOP within hours of initiating intensive topical steroid use [42].

The mode of therapy becomes important when considering corticosteroid use in individuals with pre-existing risk factors for an ocular hypertensive response. Some modes of therapy can be discontinued easily, thereby reducing or reversing any untoward effects on IOP. Other modes of therapy, however, such as subtenon’s, periocular, or intravitreal injections, are not as easily reversed if problems are encountered.

Corticosteroid-induced ocular hypertension associated with triamcinolone acetonide
IVTA has become a useful therapy for many conditions including uveitis, veno-occlusive disease, diabetes, and choroidal neovascularization. When given intravenously, triamcinolone acetonide is 35 times more potent as an anti-inflammatory agent than cortisol. As the list of indications and use of IVTA increases, the incidence of corticosteroid-induced glaucoma associated with IVTA will be more common and more likely to be encountered by ophthalmologists. In a recent meta-analysis, Jonas found that intravitreal dosages of approximately 20 mg (the dose more commonly used in Europe) are associated with a 41% prevalence of an IOP elevation greater than 21 mmHg [29]. All but one patient was managed with topical glaucoma medications and medications were no longer needed about 6 months after the injection. The one patient that required surgery underwent trabeculectomy 9 months after injection and fluid aspirations obtained during surgery contained soluble triamcinolone [43]. It was concluded that IVTA may last 9 months or longer and this fact should be considered prior to repeating the injection.
Another study, by Smithen and colleagues [7], of 89 patients with a mean baseline IOP of 14.9 mmHg analyzed the prevalence of IOP elevation following IVTA injection. All patients had received a 4 mg (the dosage more commonly used in the United States) of IVTA and were followed for 6 months. The mean pressure increase was 8.0 mmHg and 40.4% experienced a pressure elevation of 24 mmHg or higher; the pressure elevation occurred at a mean of 100.6 days. Patients were also stratified into the categories of ‘no history of glaucoma’ and ‘glaucoma patient’. The patients in these two categories were subsequently divided into two additional categories based on their baseline IOP. Patients without a history of glaucoma and a baseline IOP of at least 15 mmHg had a 60% chance of developing a pressure of at least 24 mmHg, whereas those with a baseline IOP less than 15 mmHg had a 22.7% chance of developing an IOP of at least 24 mmHg. Patients with a history of glaucoma had a 50% chance of developing an IOP of at least 24 mmHg. Of these patients, 50% had a baseline IOP of at least 15 mmHg. In this series, patients who received multiple IVTA injections did not experience an increased incidence of elevated IOP, and there was no correlation between IOP elevation and the disease process being treated by the injection. All patients who experienced an IOP elevation had their pressure controlled with a mean of one glaucoma medication. Individuals who were already taking one glaucoma medication required an average of one additional medication. No patients in this study required surgical intervention to control their elevated IOP.

Singh and colleagues [8] reported a case series of early and rapid increases in IOP following an IVTA injection in three individuals. In all three cases, a significant rise in IOP occurred within 1 week of IVTA for macular edema. All of the individuals required subsequent surgical intervention to control the elevated IOP. A peculiar finding was the presence of a white material in the angle of one individual on gonioscopy, probably from the injection. A common finding was that all three of these patients were pseudophakic, which may have allowed the medication to move into the anterior segment causing a decrease in the breakdown of substances in the trabecular meshwork. To prevent these complications, Vedantham [44] suggested that pseudophakic patients and those with prior vitrectomies be followed with greater scrutiny. In addition, he suggested that filtering the triamcinolone and instructing patients to sleep on their backs might prevent this complication.

Most patients with elevated IOP after IVTA are successfully managed with topical glaucoma medications. Traditional glaucoma surgical techniques can successfully control elevated IOP and are generally required in less than 2% of cases. Filtration surgery is not the only option. One group reported vitrectomy with removal of the intraocular triamcinolone acetonide from the vitreous cavity to treat the elevated IOP [45]. This procedure alone was capable of controlling the ocular hypertension and could also be considered as an alternative if traditional glaucoma treatments are not an option or fail to control the IOP.

IVTA appears to be increasingly popular to treat those with visual loss from macular edema; thus the prevalence of its associated corticosteroid-induced ocular hypertension will continue to rise. Clinicians should be aware that an elevated IOP may occur in nearly half of all cases following a single injection of IVTA. After an injection, they should be followed with greater scrutiny. Postinjection examinations should occur 1 day later and approximately 1 week later for high-risk patients. Regular follow-up examinations should continue for greater than 6 months. Weinreb et al. [42] showed that, rarely, some patients with a prior history of glaucoma could develop elevated IOP in a matter of hours following topical administration. Examinations should include monitoring of the IOP and gonioscopy for pseudophakes and patients with prior vitrectomies to detect mechanical obstruction of the trabecular meshwork by the medication. If the IOP cannot be managed with the addition of glaucoma medications, subspecialty care from a glaucoma specialist should be sought as some patients may go on to require surgical intervention.

The pathophysiology of corticosteroid-induced ocular hypertension and glaucoma

The mechanism of corticosteroid-induced ocular hypertension is increased aqueous outflow resistance. There are a number of observations that can be simplified into three broad categories: corticosteroids can induce physical and mechanical changes in the microstructure of the trabecular meshwork; cause an increase in the deposition of substances in the trabecular meshwork, thereby causing decreased outflow facility; and inhibit proteases and trabecular meshwork endothelial cell phagocytosis causing a decrease in the breakdown of substances in the trabecular meshwork.

Changes in the microstructure of the trabecular meshwork may cause a decrease in outflow facility and an increase in IOP. Clark and colleagues [30] showed that the actin stress fibers were reorganized into actin networks that resembled geodesic-dome-like polygonal lattices in human trabecular meshwork cells cultured in the presence of dexamethasone. Upon discontinuing dexamethasone, cross-linking of the actin networks was reversible. The effect was thought to be mediated via trabecular meshwork glucocorticoid receptors. In perfu-
sion-cultured human eyes, Clark and colleagues [31] found that steroid treatment had similar microstructural changes and was associated with an increased outflow resistance. The accumulated extracellular matrix (ECM) has the potential to affect both the paracellular (that is, the flow in-between trabecular meshwork endothelial cells) and transcellular (that is, the flow through pores created within a single and or between two inner wall Schlemm’s canal cells) levels.

Corticosteroids also increase the deposition of ECM in the trabecular meshwork leading to decreased outflow facility. A study by Wilson et al. [32] found an increased deposition of ECM material altering the ultrastructure of the juxtacanicular region. The corticosteroid dexamethasone increases glycosaminoglycan, elastin, and fibronectin production in cultured trabecular meshwork; the glycosaminoglycan deposition increases further with prolonged steroid exposure [33,34]. Myocilin is a 55 kDa protein that has also been shown to be induced in cultured human trabecular meshwork cells after exposure to dexamethasone for 2–3 weeks [35]. Mutations in myocilin have been shown to be associated with juvenile-onset and adult-onset POAG [36]. Controversy exists as to if myocilin causes an increase or a decrease in outflow facility. In studies of perfused human trabecular meshwork cell cultures, recombinant myocilin decreased outflow facility, while studies of viral-mediated transfer of myocilin in trabecular meshwork cells caused an overexpression of myocilin and increased outflow facility [37].

Finally, decreased outflow facility may be caused by reduced degradation of substances in the trabecular meshwork. Levels of tissue plasminogen activator, stromelysin [34], and metalloproteases [38,39] have been shown to decrease in trabecular meshwork cultures treated with dexamethasone. Furthermore, dexamethasone treatment inhibits trabecular meshwork cell arachidonic acid metabolism [40] and reduces the phagocytic properties of the cells [38,41]. Because these cells function to remove debris deposited in the meshwork, reduced functional activity may lead to reduced outflow facility.

**Conclusion**

Corticosteroid-induced ocular hypertension and glaucoma has been recognized for more than 50 years. A number of risk factors have been identified for the development of corticosteroid-induced ocular hypertension and glaucoma, including a personal or family history of glaucoma, young children, older adults, type-1 diabetes mellitus, connective-tissue disease, and high myopia. The intraocular pressure and mode of administration are also important risk factors. Increasing use of IVTA will probably lead to a greater probability that ophthalmologists will encoun-

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 213–214).


Ocular hypertension and glaucoma

Jones and Rhee


This study investigated the ocular hypertensive and anti-inflammatory responses to two different dosage schedules of 0.1% topical dexamethasone. The authors showed that the ocular hypertensive effect of topical 0.1% dexamethasone is dose and age dependent in children. Children 6 years and under were at especially high risk. This becomes clinically relevant, especially when treating children with uveitis and other conditions that necessitate the use of corticosteroids. Most studies investigating steroid-induced glaucoma examined an elderly patient population.


This study investigated the IOP response after IVTA injections and found that, when 25 mg of triamcinolone acetonide is used intravitreally, an IOP elevation can develop in about 50% of eyes. This was similar to that reported in [7]. For patients receiving this higher dose of IVTA, IOP elevation was noted about 1–2 months after the injection (slightly less than the 100 days reported in [7]). Likewise, IOP was normalized by topical medications in the vast majority of patients and returned to normal values without further medication about 6 months after the injection.


