Update on Steroid-Induced Glaucoma

A review of the literature and tips on managing patients.

BY HOUMAN D. HEMMATI, MD, PHD, AND ALAN L. ROBIN, MD

Based on many promising clinical outcomes, the use of corticosteroids to treat ophthalmic disease has expanded rapidly during the last decade. Applications include diseases such as neovascular age-related macular degeneration (AMD), diabetic macular edema, ocular surface and intraocular inflammatory disease, and retinal vein occlusion. Intravitreal steroids are also useful in detecting vitreous in the anterior chamber following trauma or the inadvertent breakage of the posterior capsule during cataract surgery. As a result, preservative-free steroids for intravitreal injection were recently introduced to the US market. The systemic use of steroids to treat primary or secondary inflammatory diseases is widespread. Although systemic corticosteroids have traditionally been equated with significant adverse effects such as diabetes, osteoporosis, and cataract, the local delivery of these agents to the eye through topical, periorbital, or intravitreal means is not without risks.[1]

Recently, advances in molecular biology and genetics have generated considerable interest in the mechanisms and management of corticosteroid-induced ocular hypertension and glaucoma.[2,3] This article reviews the literature on the subject and offers some advice on prevention and management.

BACKGROUND

The connection between steroids and glaucoma was first demonstrated in the early 1950s, when the systemic administration of ACTH was shown to increase IOP.[4] A decade later, Armaly and Becker reported elevations in IOP after the topical administration of corticosteroids.[5-7] Specifically, they showed that both glaucoma suspects and patients with primary open-angle glaucoma (POAG) were at higher risk than normal controls for increases in IOP after treatment with topical corticosteroids. Approximately 90% of the patients with POAG experienced elevations in IOP of greater than 6 mm Hg after a 4-week course of topical dexamethasone 0.1%.[5] Similar results were reported around the same time in a study involving topical betamethasone 0.1% used for 2 to 4 weeks.[7] This study attributed the rise in IOP to a decreased outflow of aqueous humor. In addition, the investigators reported a normalization of pressure approximately 1 week after patients discontinued the steroid medication.

The study by Armaly demonstrated that older adult patients were at higher risk for increases in IOP than younger adult patients.[5] In a recent study of the effects of topical dexamethasone 0.1% on young children, Lam and colleagues showed that a majority of children receiving this drug two or four times a day experienced elevations in IOP of at least 21 mm Hg.[8] Between one-quarter and one-third of recipients experienced rises in IOP of greater than 30 mm Hg. Lam et al showed peak IOP to be both dose dependent and more quickly achieved in children aged 6 and under. The reason behind this bimodal distribution in steroid responsiveness according to age remains a mystery.

In 1964, Becker and Hahn were the first to report an

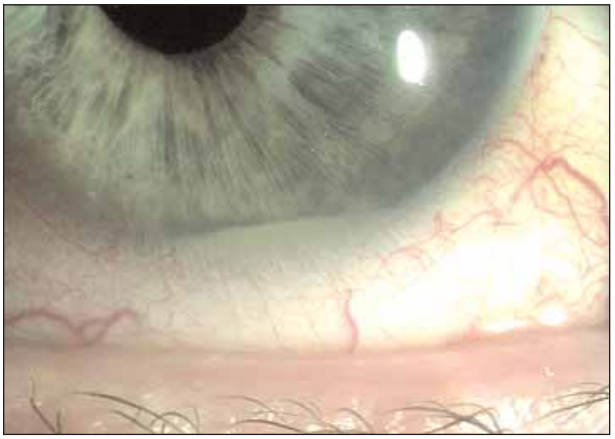

Figure 1. There is a hypopyon-like appearance of layered triamcinolone in the anterior chamber 2 days after injection. Note that no conjunctival injection is evident, as one would find in endophthalmitis.

association between steroid response and family history.[6] Specifically, patients included in their study who had a first-degree relative who had already been diagnosed with POAG were at significantly greater risk of experiencing increased IOP in response to the administration of topical corticosteroids. This finding suggested the presence of a hereditary, not stochastic, mechanism for steroid responsiveness that is still being studied today.

"Evidence supports three independent potential mechanisms of increased resistance to the outflow of aqueous humor that can act synergistically to produce corticosteroid-induced ocular hypertension."

More recently, the intravitreal administration of corticosteroids, in particular triamcinolone acetonide, has been used to treat numerous vision-threatening intraocular neovascular, edematous, and inflammatory diseases, including exudative AMD, proliferative diabetic retinopathy, macular edema, and chronic intraocular inflammation. Triamcinolone acetonide is known to have 35 times the glucocorticoid receptor binding potency of cortisol. Concerns have arisen regarding the risk of increases in IOP in response to the local administration of concentrated, potent corticosteroids.

In 2003, Jonas and colleagues reported the results of a study of 75 eyes in 71 patients with exudative AMD or diffuse diabetic macular edema who had received an intravitreal injection of 25 mg of triamcinolone acetonide.[9] The researchers showed a significant mean increase in IOP of 8 mm Hg approximately 2 months after the injection of the drug. Fifty-two percent of the eyes studied had maximum IOPs of greater than 21 mm Hg. Topical medications normalized the IOP in all eyes, with no evidence of damage to the optic nerve noted in all but one eye. Perhaps most interestingly, the IOP increased after repeat injections of triamcinolone acetonide only in eyes that had experienced a rise in pressure after the first injection. This evidence suggests that some eyes are predisposed to experiencing elevations in IOP in response to corticosteroids, whereas others are not. These findings were confirmed by the same researchers in a meta-analysis of similar cases, published in 2005,[10] as well as by a different group that reported its findings in 2004.[11]

Singh and colleagues recently reported three cases in which the IOP rose rapidly to between 39 and 49 mm Hg in less than 1 week after the intravitreal injection of 4 mg triamcinolone acetonide for the treatment of refractory macular edema.[12] All three patients required surgical management of their IOP. This report illustrates the importance of closely monitoring the IOP of patients who receive intravitreal corticosteroid injections. Because the concentration of intraocular steroid implants, such as those containing dexamethasone or fluocinolone, remains high in the eye for months to years, an extended follow-up of at least once every 6 months is required (although it is likely that the patient's primary ocular disease will necessitate examinations at least as often).[2] It is possible that some cases of elevated IOP after the intravitreal injection of corticosteroids could be related to the deposition of triamcinolone within the anterior chamber (Figure 1).

Other studies have shown increases in IOP after inhaled and nasally[13] or subconjunctivally[14] administered corticosteroids. These findings suggest that, although the greatest elevations in IOP occur after the intravitreal and topical delivery of corticosteroids, the phenomenon is independent of the route of administration.

PATHOPHYSIOLOGY

Evidence supports three independent potential mechanisms of increased resistance to the outflow of aqueous humor that can act synergistically to produce corticosteroid-induced ocular hypertension: (1) structural changes of the trabecular meshwork; (2) a mechanical obstruction of the trabecular meshwork by steroid particles; and (3) the inhibition of phagocytosis by trabecular meshwork cells. One study suggested that dexamethasone prompts a glucocorticoid receptor-mediated cross-linking of actin-filament networks in trabecular meshwork cells that impedes the outflow of aqueous through this tissue.[15] Whether the steroid-induced expression of the protein myocilin decreases the outflow of aqueous through similar mechanisms to those of actin is the subject of controversy.[16]

In one of the cases of elevated IOP following the intravitreal injection of triamcinolone acetonide, a gonioscopic examination of the angle revealed the presence of whitish material that the case report's authors believed to be injected corticosteroid.[12] This case suggests that intraocular particles of a corticosteroid might be able to obstruct aqueous outflow directly. Recently published work by Zhang and colleagues has demonstrated that lower levels of glucocorticoid receptor beta in glaucomatous trabecular meshwork cells might alter the phagocytic ability of those cells, a situation possibly leading to a glucorticoid-mediated increase in resistance to aqueous outflow.[17]

MANAGEMENT

The management of corticosteroid-induced glaucoma should begin with

1. avoiding this class of drugs unless no better alternatives exist;
2. advising patients of their risks in advance of the drug's administration;
3. close and regular monitoring of the IOP of patients treated with corticosteroids (especially those with a personal or family history of POAG or steroid-induced glaucoma);
4. obtaining baseline visual fields and/or optic nerve photography or peripapillary retinal nerve fiber layer measurements, if appropriate.[2,3]

The frequency of IOP monitoring should match the patient's risk factors for steroid-induced spikes in pressure as well as the medication's potency, dosage, route of administration, and half-life and the duration of treatment. The authors suggest following infrequent recipients of topical steroids on a monthly basis.

In contrast, high-risk patients who receive intravitreal injections require examinations 1 day and 1 week after treatment and at least monthly follow-up examinations after the medication's cessation. In individuals with an IOP more than 20% above their baseline measurement, or in those for whom there is clinical or functional evidence of damage to their optic nerve during or after treatment with corticosteroids, the first prudent action is to discontinue or minimize the patients' exposure to the drug as soon as clinically feasible within the context of the underlying disease process. Of course, this step cannot be readily achieved with intravitreal corticosteroids. Topical pressure-lowering therapy should start immediately, with very close follow-up at regular intervals to measure the success of treatment. Most patients respond to topical IOP-lowering therapy. Physicians should perform gonioscopy on pseudophakic or postvitrectomy eyes to check for mechanical obstruction of the trabecular meshwork. Patients who do not respond to maximal topical therapy should be re-evaluated.

In the authors' experience, laser trabeculoplasty is not effective for steroid-induced ocular hypertension. Physicians should consider the baseline status of the patient's optic nerve and visual field, the degree and duration of the damage to the optic nerve, the possible duration of steroid therapy, and the available options. If the IOP is at alarming levels (> 50 mm Hg, even in the case of an optic nerve that appears healthy), surgical intervention with either a tube or a filter may be appropriate. These surgeries are required in fewer than 2% of patients receiving an intravitreal injection.[3] Surgeons should consider a vitrectomy or the explantation of the steroid implant for patients who have received intravitreal injections or intraocular implants of a corticosteroid.[2,18]

CONCLUSION

Despite the risks of ocular hypertension and glaucoma associated with the use of corticosteroids, these agents can safely treat most of the patients who need them without causing glaucomatous damage to their optic nerves. The key is to foster physicians' and patients' understanding of the risks associated with corticosteroids. In addition, clinicians must exercise caution in selecting, dosing, monitoring, and managing patients. ❑

Houman D. Hemmati, MD, PhD, is a second-year resident at the Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore. Dr. Hemmati may be reached at hhemmat2@jhmi.edu.

Alan L. Robin, MD, is Clinical Professor of Ophthalmology, the University of Maryland, and Associate Professor of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore. Dr. Robin may be reached at (410) 377-2422; arobin@glaucomaexpert.com.

1. Bernstein HN, Mills DW, Becker B. Steroid-induced elevation of intraocular pressure. *Arch Ophthalmol*. 1963;70:15-18.
2. Jampol LM, Yannuzzi LA, Weinreb RN. Glaucoma and intravitreal steroids. *Ophthalmology*. 2005;112(8):1325-1326.
3. Jones R 3rd, Rhee DJ. Corticosteroid-induced ocular hypertension and glaucoma: a brief review and update of the literature. *Curr Opin Ophthalmol*. 2006;17(2):163-167.
4. McLean JM, Gordon DM, Koteen H. Clinical experiences with ACTH and cortisone in ocular diseases. *Trans Am Acad Ophthalmol Otolaryngol*. 1951;55:565-572.
5. Armaly MF. Statistical attributes of the steroid hypertensive response in the clinically normal eye. I. The demonstration of three levels of response. *Invest Ophthalmol*. 1965;4:187-197.
6. Becker B, Hahn KA. Topical corticosteroids and heredity in primary open-angle glaucoma. *Am J Ophthalmol*. 1964;57:543-551.
7. Becker B. Intraocular pressure response to topical corticosteroids. *Invest Ophthalmol*. 1965;4:198-205.
8. Lam DS, Fan DS, Ng DS. et al. Ocular hypertensive and anti-inflammatory responses to different dosages of topical dexamethasone in children: a randomized trial. *Clin Experiment Ophthalmol*. 2005;33(3):252-258.
9. Jonas JB, Kreissig I, Degenring R. Intraocular pressure after intravitreal injection of triamcinolone acetonide. *Br J Ophthalmol*. 2003;87(1):24-27.
10. Jonas JB, Degenring RF, Kreissig I, et al. Intraocular pressure elevation after intravitreal triamcinolone acetonide injection. *Ophthalmology*. 2005;112:593-598.
11. Smithen LM, Ober MD, Maranan L, Spaide RF. Intravitreal triamcinolone acetonide and intraocular pressure. *Am J Ophthalmol*. 2004;138(5):740-743.
12. Singh IP, Ahmad SI, Yeh D, et al. Early rapid rise in intraocular pressure after intravitreal triamcinolone acetonide injection. *Am J Ophthalmol*. 2004;138(2):286-287.
13. Garbe E, LeLorier J, Boivin JF, Suissa S. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. *JAMA*. 1997;277(9):722-727.
14. Kalina RE. Increased intraocular pressure following subconjunctival corticosteroid administration. *Arch Ophthalmol*. 1969;81(6):788-790.
15. Clark AF, Wilson K, McCartney MD, et al. Glucocorticoid-induced formation of cross-linked actin networks in cultured human trabecular meshwork cells. *Invest Ophthalmol Vis Sci*. 1994;35(1): 281-294.
16. Alward WL. The genetics of open-angle glaucoma: the story of GLC1A and myocilin. *Eye*. 2000;14(pt 3B):429-436.
17. Zhang X, Ognibene CM, Clark AF, Yorio T. Dexamethasone inhibition of trabecular meshwork cell phagocytosis and its modulation by glucocorticoid receptor beta. *Exp Eye Res*. 2007;84(2):275-284.
18. Agrawal S, Agrawal J, Agrawal TP. Management of intractable glaucoma following intravitreal triamcinolone acetonide. *Am J Ophthalmol*. 2005;139(3):575-576; author reply 576.