

Glaucoma and Intravitreal Steroids

Lee M. Jampol, MD - *Chicago, Illinois*

Lawrence A. Yannuzzi, MD - *New York, New York*

Robert N. Weinreb, MD - *La Jolla, California*

In what seems to be an extraordinary advance in our field, the use of an intraocular steroid may have a beneficial effect (at least temporarily and, perhaps, long-term) on visual outcome in patients with diabetic macular edema, vein occlusions, leakage from neovascularization from age-related macular degeneration, and, possibly, other conditions.

Determination of the long-term efficacy of intravitreal injections or implants of steroids requires randomized clinical trials. However, because of the absence of highly effective treatments for these diseases, many patients are being treated with intraocular steroids. There has been a clear increase in the off-label utilization of intravitreal and periocular triamcinolone acetonide (Kenalog), and new implantable delivery devices are under study. Concomitant with the use of these steroids, however, is the specter of the development of glaucoma.

After their introduction as antiinflammatory agents, it was recognized that use of topical, systemic, and periocular steroids could cause an increase in intraocular pressure (IOP). The steroid-related rise in IOP is dose dependent, and there is variability in steroid responsiveness among individuals.¹ The mechanism for the rise in IOP is not known; however, it has been suggested that it is related to a biological effect mediated by activation of steroid receptors on the trabecular meshwork cells² and the resulting deposition of extracellular material, including myocilin and collagen.³ Although the mechanism for the increased IOP with intravitreal steroids is most likely similar to that after topical application—namely, trabecular meshwork cell dysfunction—it also has been suggested that gonioscopically observable particulate matter from the injected material may obstruct the trabecular meshwork.⁴ With the fluocinolone implant, no such particles are released, yet glaucoma is very common, suggesting that pharmacologic effects (rather than mechanical obstruction) are occurring. Some individuals, including those with preexisting glaucoma or a family history of glaucoma, are particularly sensitive and may respond with a moderate or marked rise in IOP within just a few weeks of infrequent glucocorticoid dosing. Others are relatively insensitive and only have a rise in IOP with frequent dosing of a potent steroid for several weeks or more.

Most of our existing knowledge about IOP elevation from steroids relates to topical therapy. After the topical administration of a potent glucocorticoid for 6 weeks,¹ IOP is increased by >5 mmHg in 20% of the general population,

and in one quarter of these, the increase can be substantial. If the steroid is discontinued, then the IOP usually reverts to its baseline level. However, some patients, particularly those who have received treatment for several months, continue to have high IOP even after the steroid is withdrawn. Loss of optic nerve fibers with concomitant loss of visual field may occur.⁵ It should be noted that some antiangiogenic steroids do not have glucocorticoid effects (e.g., anecortave acetate⁶) and do not raise IOP. This also seems to be true for drugs that block vascular endothelial growth factor,⁷ such as pegaptanib and ranibizumab.

Given the potential risks associated with an intraocular steroid injection, it is recommended that patients should have a baseline examination of the IOP, optic disc, and retinal nerve fiber layer (RNFL) to exclude the possibility of preexisting glaucoma. Preexisting glaucoma should not be considered an absolute contraindication to intraocular steroid injection, but rather should alert a clinician to the particular need for careful follow-up examinations and treatment, if indicated. After use of intraocular steroids, clinicians are interested in knowing how best to observe a patient to detect steroid glaucoma and how it should be treated if detected. Certainly it is essential to monitor IOP regularly. A rise in IOP can occur rapidly, and IOP should be measured at least once during the first poststeroid month. A rise in IOP also can occur only after several months. Therefore, it is important to continue to monitor IOP monthly for several poststeroid months.

The functional status of the optic nerve is usually followed with standard automated perimetry or the more sensitive selective perimetry.⁸ However, most patients requiring intraocular steroids already have impaired retinal function from their underlying disease, and any type of perimetric testing to detect glaucomatous optic nerve damage may be obfuscated by an artifact. Therefore, structural assessment of the optic disc and parapapillary RNFL are particularly important. This can be done with careful clinical observation using a handheld lens and the slit-lamp biomicroscope, or by imaging and quantitatively assessing the RNFL or optic disc topography.

Even in the absence of preexisting glaucoma, certain patients are at considerable risk of developing glaucoma. High-risk patients include those with particularly high IOP (e.g., >35 mmHg) or other glaucoma risk factors such as a family history or known steroid IOP responsiveness. With intravitreal injection of a suspension of triamcinolone, the development of very high IOP has been noted in perhaps 40% of patients.⁹ The time course of steroid-induced ocular hypertension after intravitreal steroid injection varies and depends on numerous factors, including the dose and vol-

Supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York; Northwestern University, Evanston, Illinois; University of California San Diego, San Diego, California; and the Macula Foundation, Inc., New York, New York.

ume of injected drug, rate of clearance from the eye, presence of aphakia or pseudophakia, and, perhaps, the presence of an intact anterior hyaloid. Pressure elevation may be seen within days or weeks of the injection or implant placement. After a 4-mg intravitreal injection of triamcinolone, the elimination half-life in a nonvitrectomized eye is ~19 days, and in a vitrectomized eye, it is 3.2 days.¹⁰ In a nonvitrectomized eye, therapeutic levels (and, perhaps, their ocular hypertensive effects) may be present for as long as 90 days. Triamcinolone particles may be seen in the vitreous for ≥ 90 days.¹¹ If a higher dose of triamcinolone is used, the steroid and the ocular hypertension would be expected to last longer, although the dose may not necessarily be linearly related to the time. When an intraocular steroid injection is repeated, it is reasonable to speculate that the ocular hypertensive effects and their duration may be cumulative. For the fluocinolone implant, the period of steroid release may be as long as 2 to 3 years and, for the dexamethasone implant, ~30 days. In most patients, the IOP elevation subsides shortly thereafter. In a few patients, the IOP elevation may last considerably longer or be permanent. If the IOP cannot be controlled medically, explantation of the steroid implant may be necessary, or a trabeculectomy or placement of a glaucoma drainage implant may be done. It is possible that the incidence and severity of the IOP elevation vary, depending on the underlying retinal disease.

To assist investigators and clinicians in evaluating steroid therapies, we propose a classification of the IOP rises. This system can be used in patient care or clinical trials. A rise of ≥ 15 mmHg from baseline or an IOP consistently higher than 32 mmHg would be classified as a *mild adverse event*, especially if the IOP returns to near baseline levels with topical IOP-lowering therapy and this IOP rise is no longer present within 3 months. In this latter situation, topical medications can be withdrawn gradually.

If the IOP elevation does not respond adequately to topical therapy or this pressure elevation persists beyond 3 months, this could be classified as a *moderate adverse event*. Such patients need to be observed carefully for evidence of progressive optic nerve damage with structural and functional testing, as appropriate. Should optic nerve damage be detected, surgical treatment (as indicated below) should be considered. A *severe adverse event* would be a rise in pressure to such a level that surgery is necessary. These patients are those who have progressive optic nerve

damage despite maximum tolerated medical therapy or who have the likelihood of having such damage (IOP elevation exceeding 20 mmHg from baseline or above 40 mmHg). Admittedly, this is an arbitrary classification. It is meant to complement Food and Drug Administration–mandated reporting and to allow comparison of studies from different pharmaceutical companies and different investigators. Our classification can help characterize the IOP responses of steroid treatment. While we await new studies of intraocular steroids, attention should be directed to these rises in IOP, and patients should be evaluated and treated to prevent the development of glaucomatous optic nerve damage.

References

1. Polansky JR, Weinreb RN. Steroids as anti-inflammatory agents. In: Sears ML, ed. *Pharmacology of the Eye*. Berlin: Springer-Verlag; 1984:460–538. *Handbook of Experimental Pharmacology*. Vol. 69.
2. Weinreb RN, Bloom E, Baxter JD, et al. Detection of glucocorticoid receptors in cultured human trabecular cells. *Invest Ophthalmol Vis Sci* 1981;21:403–7.
3. Wordinger RJ, Clark AF. Effects of glucocorticoids on the trabecular meshwork: towards a better understanding of glaucoma. *Prog Retin Eye Res* 1999;18:629–67.
4. Singh IP, Ahmad SI, Yeh D, et al. Early rapid rise in intraocular pressure after intravitreal triamcinolone acetonide injection. *Am J Ophthalmol* 2004;138:286–7.
5. Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet* 2004;363:1711–20.
6. Anecortave Acetate Clinical Study Group. Anecortave acetate as monotherapy for treatment of subfoveal neovascularization in age-related macular degeneration: twelve-month clinical outcomes. *Ophthalmology* 2003;110:2372–83, discussion 2384–5.
7. Eyetech Study Group. Anti-vascular endothelial growth factor therapy for subfoveal choroidal neovascularization secondary to age-related macular degeneration: phase II study results. *Ophthalmology* 2003;110:979–86.
8. Weinreb RN, Greve EL, eds. *Glaucoma Diagnosis. Structure and Function*. The Hague: Kugler Publications; 2004.
9. Smithen LM, Ober MD, Maranan L, Spaide RF. Intravitreal triamcinolone acetonide and intraocular pressure. *Am J Ophthalmol* 2004;138:740–3.
10. Beer PM, Bakri SJ, Singh RJ, et al. Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection. *Ophthalmology* 2003;110:681–6.
11. Mason JO III, Somaiya MD, Singh RJ. Intravitreal concentration and clearance of triamcinolone acetonide in nonvitrectomized human eyes. *Retina* 2004;24:900–4.