Steroid Therapy and IOP

Along with the benefits of intravitreal injections and sustained-release implants comes the risk of steroid-induced ocular hypertension.

**BY BRADLEY P. ROTH, MS, AND BARBARA SMIT, MD, PhD**

Intravitreal steroid therapy is used to treat numerous posterior segment diseases, including noninfectious uveitis and macular edema associated with diabetes or retinal vein occlusion. These diseases respond well to long-acting steroid therapy but may require treatment for months to years. Current steroid therapies include intravitreal injections and sustained-release implants that are injected or surgically inserted. As a result of extended treatment, the incidence of steroid-induced ocular hypertension (OHT) is on the rise. Long-term delivery systems and repeated dosing make the management of elevated IOP after intravitreal steroid therapy a significant concern for clinicians. Steroid-induced OHT has been extensively documented for both intravitreal injections and sustained-release implants.

**BACKGROUND**

Steroid-induced OHT was first identified in 1950 and has since been well documented. Studies have demonstrated that about one-third of the population has a moderate response to topical steroid therapy, with IOP increases of 6 to 15 mm Hg or an IOP between 20 and 31 mm Hg. A smaller proportion of the population—approximately 4% to 6%—are high responders, with IOP increases of more than 15 mm Hg or an IOP greater than 31 mm Hg. The remaining two-thirds of the population are considered nonresponders, with increases of less than 6 mm Hg and an IOP lower than 20 mm Hg. The incidence of steroid-induced OHT appears to be higher after intraocular injections of the agents than after topical administration, and it varies with the drug and mode of delivery.

Other risk factors for developing steroid-induced OHT include a diagnosis of primary open-angle glaucoma (POAG) and having a first-degree relative with POAG. The proportion of these adults who are steroid responders increases to 90% and 60%, respectively. Other notable risk factors include high myopia, connective tissue disease, and type 1 diabetes. Patients with these risk factors may require more frequent follow-up after treatment with intravitreal steroids. Additionally, both children and elderly patients have an increased frequency of steroid-induced OHT and should be monitored accordingly.

**MECHANISM OF THE STEROID RESPONSE**

Although the steroid response has been well documented, the specific mechanism is incompletely understood. Elevated IOP is attributed to increased resistance to aqueous outflow through the trabecular meshwork caused by one of three mechanisms: mechanical occlusion, changes in the microstructure, and inhibition of enzymatic activity. Physical obstruction of the trabecular meshwork by triamcinolone acetonide (TA) crystals may also lead to OHT after an intravitreal injection of triamcinolone acetonide (IVTA [Kenalog; Bristol-Myers Squibb]). The deposition of crystals in the anterior chamber angle forms a pseudohypopyon in only 0.2% to 2% of eyes that receive IVTA. Previous vitrectomy, pseudophakia, or aphakia may increase this likelihood. Exposure to corticosteroids increases outflow resistance through the trabecular meshwork. One hypothesis is that steroid exposure decreases the rate at which the extracellular matrix degrades, leading to an accumulation of these molecules, which reduces the available space for aqueous to exit through the angle. A second hypothesis is that steroid treatment reduces the phagocytic activity of trabecular meshwork cells, resulting in a buildup of debris that blocks the angle. The use of steroids induces extensive cross-linking and reorganization in the cytoskeletal elements of the trabecular meshwork and may contribute to the increase in outflow resistance. These changes are reversible upon the discontinuation of steroid therapy.

Changes in cellular adhesion molecules may also increase tight junction proteins in endothelial cells, thus decreasing transcellular flow and raising outflow resistance. Finally, exposure to steroids stabilizes lysosomal membranes, causing an increase in polysaccharides. These changes, along with alterations of the nucleus, golgi apparatus, and endoplasmic reticulum, cause the cells of the trabecular meshwork to enlarge, which may further increase resistance to aqueous flow.
MODES OF DELIVERY

Intravitreal Triamcinolone Acetonide

TA is minimally soluble in aqueous solution. White crystals are visible in the inferior vitreous after an injection. The low solubility of IVTA facilitates a longer duration of action, as the crystals dissolve slowly into the vitreous. The most common dosing is 4 mg in the United States and up to 25 mg in Europe. Previous vitrectomy reduces the half-life of IVTA substantially, from greater than 15 days in nonvitrectomized eyes to about 3 days in vitrectomized eyes.

The time frame for an increase in IOP after IVTA varies widely. A recent meta-analysis of 115 IVTA studies reported that the onset of OHT after 4 mg IVTA may be as early as 1 week after injection, and the effects may last up to 9 months. The study also determined that 32.1% of patients treated with IVTA will develop OHT and have an IOP of 21 mm Hg or greater. Patients’ risk of developing steroid-induced OHT is 45.9% with the 25-mg dose and 32.1% with the 4-mg dose.

Dexamethasone Intravitreal Implant

The extended-release dexamethasone intravitreal implant 0.7 mg (Ozurdex; Allergan) steadily dispenses the drug over 3 to 6 months and is fully biodegradable. The cylindrically shaped implant is approximately 6 mm long and 0.5 mm in diameter. It is administered via a 22-gauge needle through the pars plana and may be visible in the inferior vitreous. Increases in IOP of 10 mm Hg or more or an IOP greater than 25 mm Hg occurred in 15.3% of 746 studied eyes. Peak IOP was found to occur approximately 6 weeks after placement of the implant and returned to normal 6 months after implantation.

Fluocinolone Acetonide Implants

Retisert (Bausch + Lomb) is a sustained-release non-biodegradable fluocinolone acetonide (FA) implant that delivers 0.59 mg of the drug at a constant rate for 30 months. The implant is shaped like a baseball cap and is implanted surgically. The flat portion is sutured to the sclera, with the round portion left in the inferior vitreous. As reported across seven studies, 61.4% of treated eyes had an IOP greater than 30 mm Hg. Seventy-five percent of all eyes treated with the FA implant required IOP-lowering therapy, and 36.3% required IOP-lowering surgery.

The FDA approved Iluvien (Alimera Sciences), another sustained-release FA implant, in September 2014 for the treatment of diabetic macular edema. This implant is nonbiodegradable and releases FA 0.19 mg over 3 years. According to clinical trial data, 37.1% of treated eyes experienced an increase in IOP. Pressure-lowering topical medications were successful in most cases of elevated IOP; 4.8% of eyes required surgical intervention.

MANAGEMENT STRATEGIES

Medical Therapy

The medical management of steroid-induced OHT is nearly identical to that of POAG. Treatment is usually only necessary during the active period of the steroid treatment. In most cases, medical therapy is sufficient to control IOP and have an IOP of 21 mm Hg or greater. Patients’ risk of developing steroid-induced OHT is 45.9% with the 25-mg dose and 32.1% with the 4-mg dose.

β-Blockers, α2 agonists, and carbonic anhydrase inhibitors have all been shown to effectively control steroid-induced OHT. Prostaglandin analogues should be reserved as a last resort, because these drugs may induce uveitis or cystoid macular edema and are therefore contraindicated in patients who receive an intravitreal steroid for noninfectious ocular inflammation.

Laser Therapy

Few studies have examined the effectiveness of selective laser trabeculoplasty (SLT) for steroid-induced OHT. It has been suggested that SLT’s effectiveness at reducing the need for topical therapy is comparable to its effectiveness for POAG. In a retrospective study of seven patients with OHT after IVTA, IOP decreased from 38.4 to 23.9 mm Hg 3 months after the injection. SLT reduced the IOP in five eyes, and surgical intervention was required for the other two eyes. The IOP was maintained 6 months after the laser treatment in all five eyes, suggesting that SLT may be an effective option for patients who are intolerant of medical therapy or who are on maximum medical therapy.

Surgical Intervention

Although discontinuing steroid therapy has been shown to reliably reverse IOP increases after topical steroid therapy, there are multiple documented cases in which the IOP remained elevated even after the steroid implant was removed.
For cases of uncontrolled IOP after IVTA, vitrectomy was necessary in 8% of eyes injected with 0.4 mg TA that failed to respond to maximum medical therapy in 1 to 2 months after the injection. After TA was removed, the IOP returned to normal within 1 to 3 weeks. Filtering surgery may be necessary to maintain adequate IOP when vitreectomy is not sufficient or when continued steroid therapy is necessary. Trabeculectomy, viscocanalostomy, trabeculotomy, and tube shunts lower IOP to safe levels and reduce the need for medical therapy. Filtering surgery and shunts are particularly useful in patients who may need long-term intravitreal steroids, because the creation of an alternate drainage route reduces or eliminates the risk of developing steroid-induced OHT in the future.

RECOMMENDATIONS

Based on their systematic review of 129 articles, Kiddee et al proposes the following recommendations for IOP monitoring postintravitreal steroid injection/implantation. In patients receiving IVTA, IOP should be checked 1 week after IVTA, then at 2-week intervals for the first month, and then every month for 6 months. For patients receiving Ozurdex or Retisert, IOP should be monitored 2 weeks after implantation, then every 2 weeks for the first month, and then every month. Patients who receive Ozurdex or Retisert should be monitored for the first 6 months after implantation, and patients who receive Retisert should be checked regularly for 9 months after implantation.

CONCLUSION

Intravitreal steroid therapy is an effective tool for the long-term management of inflammatory and edematous retinal eye diseases. Intravitreal steroids pose a significant risk of OHT, however, especially in patients with POAG or a family history of glaucoma. The Ozurdex implant is associated with the lowest frequency of OHT and requires surgical intervention less often than IVTA or Retisert. The risk profile of TA is greater in eyes with prior vitrectomies or aphakia due to the risk of migration to the anterior chamber. Of the three steroid therapies available, Retisert is associated with the highest frequency of IOP spikes and the most frequent need for surgical interventions, but it also provides the longest duration of action. It is unclear if repeated dosing of IVTA, Ozurdex, or Iluvien would increase the rates of steroid-induced OHT to rates similar with Retisert. Some studies demonstrated higher rates of OHT with repeated injections, whereas others reported no difference in the rates with multiple injections.

All patients who receive intravitreal steroids should be monitored closely for OHT and treated accordingly to reduce or prevent glaucomatous damage.

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