Drug Delivery Mechanisms for Treatment of Uveitis

Sustained-release formulations help ease burden of injections.

BY C. STEPHEN FOSTER, MD

Inflammation of the uvea, broadly speaking, can occur as a consequence of a number of factors. These include trauma, which is uncommon, cancer, which is relatively uncommon, autoimmunity, and infection. If the cause is infection, the proper therapy is to kill the responsible microbe with the appropriate pharmacotherapy: antibiotic, antiviral, antifungal, or antiparasitic drugs.

When no infectious microbes can be implicated, uveitis is said to be idiopathic or autoimmune, and the principal aim of therapy must be suppression of inflammation in order to save eyesight. Uveitis is estimated to be responsible for 10 to 15% of the blindness in the United States.[1]

STEROIDS: INJECTION, IMPLANTATION, INSERTION

By far the most common class of drugs called on to quench the inflammatory fire of uveitis is the corticosteroids, whether in the form of drops, shots, pills, or intravenous or intraocular administration.

Intraocular steroid administration is an effective way of treating vision-threatening chronic uveitis in selected cases. The first technique used for intraocular delivery of steroids was frank injection, originally with what was known as "washed" Kenalog (triamcinolone acetonide, Bristol-Myers Squibb), for which the alcohol and preservatives were washed out of the manufacturer's formulation of the drug. More recently, Triesence (triamcinolone acetonide injectable suspension 40 mg/mL, Alcon), an ophthalmic preparation of the drug that does not contain preservatives, has become the standard for injection of corticosteroids.

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The first sustained-release drug delivery device approved by the US Food and Drug Administration (FDA) for the treatment of chronic noninfectious uveitis was Retisert (fluocinolone acetonide intravitreal implant 0.59 mg, Bausch + Lomb). Retisert is an engineered delivery system, implanted in an operating room procedure, which elutes a fixed amount of steroid into the vitreous cavity at a steady state over a period of at least 2 years. It has been on the market for several years now and has been implanted in the eyes of many patients with noninfectious posterior uveitis.

The primary, almost unavoidable complication of Retisert is cataract development, which occurs in virtually all patients who receive Retisert.[2] In addition, within 3 years after implantation, approximately 77% of patients receiving Retisert will require intraocular pressure (IOP)-lowering medications, and approximately 37% of people will require incisional surgery to control IOP.[2]

More recently, another intravitreal implant with a different steroid and different delivery system has been added to our armamentarium: Ozurdex (dexamethasone

intravitreal implant, Allergan). One does not have to go to the operating room to implant this delivery system. It is injected through a 22-gauge needle in an in-office procedure, similar to the way one would insert a trocar for use in small-gauge sutureless vitrectomy surgery. The device delivers a pulse of dexamethasone, followed by a lower steady state delivery over a 6-month period.

Ozurdex was originally FDA-approved for the treatment of macular edema following branch or central retinal vein occlusion, but more recently, it received an additional indication for the treatment of noninfectious posterior uveitis.[3]

Both cataract development and IOP elevation appear to be considerably less frequent with Ozurdex than with Retisert. In the clinical trials for approval of the drug, IOP increase was seen in 25% of patients, and 1% required surgery for IOP management. Cataract development was seen in 5% of patients.[3]

It should be noted that these were the results of 6-month studies with a single Ozurdex implant in each eye. Following a second injection of Ozurdex in cases in which that was indicated, the overall incidence of cataract development was higher after 1 year.[3] As noted, the effect of Ozurdex lasts for about 6 months, as compared with at least 2 years for Retisert.

ROLE OF IMAGING

In following patients with posterior uveitis, the bulk of our observations are made by slit-lamp examination, looking at signs such as inflammatory cells, protein haze in the vitreous, and obscuration of fundus details. Other methods can be used, but the only validated monitor of posterior uveitis is vitreous haze.[4] Although there are standardized photographs to help determine the level of haze, the classification system remains subjective and very unsatisfying.

Macular edema has been used by some as a proxy marker of uveitis. It is less than ideal for this purpose, however, because while macular edema clearly can occur in some patients with posterior uveitis, it may not occur in others. Furthermore, in a patient whose uveitis is clearly in remission, macular edema may persist because of dysfunction of the retinal pigment epithelium and breakdown of tight junctions. Therefore, macular edema is not a good proxy marker for active inflammation, and optical coherence tomography (OCT) scanning of the macula, although it is a wonderful technology, is not a good tool to document active inflammation or inflammation in remission.

Fluorescein angiography (FA) may be a better monitor of active inflammation than other technologies, even though many clinicians have moved away from it in favor of OCT. FA can identify very subtle inflammation of the capillaries that cannot be picked up on examination, much less by OCT scanning. This capillaritis can often explain a persistent macular edema sometimes seen in patients who appear to be in remission from uveitis. FA can provide clear evidence of this active inflammation in the capillaries, suppression of which is associated with clearing of the macular edema.

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CONCLUSIONS

Management of chronic idiopathic uveitis will continue to be a challenge for clinicians. It is helpful to have the recently introduced options for sustained-release delivery of steroids in our treatment arsenal. Although many retina physicians have become comfortable performing intravitreal injections in recent years, these procedures are not without risk. The risk is low, but it is not zero, and it is multiplied with the growing volume of intravitreal injections. Every time one punctures the globe there is a risk of infection and retinal detachment. Recently introduced sustained-release delivery systems have the potential to help us reduce the numbers of injections required to manage idiopathic posterior uveitis and to care for our patients with less risk but equal or improved efficacy. ■

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