INSIDE THE UVEITIS TOOLBOX

An examination of the delivery methods available for releasing steroids into the posterior segment.

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Uveitis is a leading cause of blindness and visual morbidity in the developed world, and it accounts for 15% to 20% of all cases of legal blindness in the United States.[1-3] Macular edema is the most common cause of visual acuity loss in patients with uveitis. Other potential complications include cataract and glaucoma.[4-8] Early diagnosis and treatment of uveitis are important for the prevention of visual acuity loss and associated complications.

Local and systemic corticosteroids, in combination with immunomodulatory therapies, are the standard of care for noninfectious uveitis. Steroids suppress inflammation of the uveal tract by inhibiting the expression of various proinflammatory factors, and, although they are effective, they carry significant ocular and systemic side effects. Systemic corticosteroids are useful in posterior uveitis, particularly in cases in which inflammation is bilateral or associated with underlying systemic disease. However, this systemic therapy is associated with significant side effects including hypertension, diabetes mellitus, osteoporosis, infections, adrenal suppression, and Cushing syndrome. Owing to the risk of systemic side effects associated with oral steroids and steroid-sparing agents, local steroid therapy has become an increasingly attractive option for patients with uveitis, particularly when inflammation is unilateral and isolated to the eyes.[9]

There are now more local steroid drug delivery options than ever for patients with uveitis. This article reviews the available steroid drug delivery systems for the treatment of this condition.

SUPRACHOROIDAL CORTICOSTEROID INJECTION

Suprachoroidal injection of specially formulated triamcinolone acetonide is a drug delivery approach currently under development for the treatment of posterior uveitis. With this technique, the suprachoroidal space acts as a reservoir, permitting sustained drug delivery near the source of pathology with a single injection.

Clearside Biomedical is conducting a phase 1/2 open-label clinical trial to assess the safety and tolerability of suprachoroidal injections of its proprietary formula of triamcinolone acetonide, CLS-TA, with the Clearside SCS microinjector in patients with noninfectious uveitis. The 6-month data from the trial show excellent drug safety and promising efficacy outcomes. Upon completion, findings of this trial may direct the future use of suprachoroidal injections in patients with uveitis.[10] Most of the preclinical data available are promising. The drug remains in the ocular tissue for at least 120 days, with minimal levels in the systemic circulation.[11] The preclinical data also suggest lower dose requirements, allowing for a potential reduction in dose-dependent side effects.[12]

INTRAVITREAL CORTICOSTEROID IMPLANTS

Intraocular steroid implants were designed for sustained release of medication, reducing the need for frequent injections. They offer a favorable option for long-term suppression of ocular inflammation and, unlike chronic oral steroid therapy, have minimal risks of systemic side effects. Three sustained-release steroid implants have been approved by the US Food and Drug Administration (FDA)

AT A GLANCE

- Local steroid therapy has become a favorable option for patients with uveitis.
- Available and potential drug delivery methods include suprachoroidal injection and injected or anchored implants.
- Retina specialists should weigh the advantages and disadvantages of the different treatment options and get the patient's informed consent before initiating therapy.

for use in ocular diseases: the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan), the fluocinolone acetonide intravitreal implant 0.59 mg (Retisert, Bausch + Lomb), and the fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera Sciences).

Dexamethasone Intravitreal Implant

The dexamethasone intravitreal implant is a biodegradable copolymer of lactic and glycolic acid, implanted using a 22-gauge applicator, and releasing 0.7 mg of dexamethasone into the vitreous over approximately 6 months. It can be injected in an outpatient setting with good tolerability in most patients and meaningful improvement in intraocular inflammation and visual acuity.[11,13,14] In 2010, the FDA approved the implant for treatment of noninfectious uveitis involving the posterior segment. It is also used for management of diabetes and retinal vein occlusion.

In 2011, Lowder et al reported the results of a 26-week study comparing the safety and efficacy of two doses (0.35 mg and 0.7 mg) of the dexamethasone implant with sham procedure in 229 randomized patients. A much higher proportion of patients showed improvement in vitreous haze score at week 8 in the dexamethasone groups compared with sham (47% and 36% for 0.7-mg and 0.35-mg groups, respectively, vs. 12% for the sham group). Gains in BCVA from baseline were significantly greater for eyes in the dexamethasone groups as compared with sham ($P = .002$). There were no major safety concerns, although the dexamethasone groups reported higher incidences than the sham group of intraocular pressure (IOP) greater than 25 mm Hg (7.1% and 8.7% for 0.7-mg and 0.35-mg groups, respectively, vs. 4.2% for the sham group) and cataract (15% and 12% for 0.7-mg and 0.35-mg groups, respectively, vs. 7% for the sham group). However, these differences were not statistically significant.[11]

In 2014, Zarranz-Ventura et al reported similar improvements in visual acuity and vitreous haze score outcomes in a retrospective cohort of 82 eyes of patients receiving a 0.7-mg dexamethasone implant.[13] These results of improved vision and resolution of macular edema are supported by several retrospective cohorts.[14-16] Arcinue et al compared the safety and efficacy of the 0.7-mg dexamethasone implant with that of the 0.59-mg fluocinolone acetonide implant in a comparative case series of 27 patients with noninfectious uveitis.[17] The dexamethasone implant was comparable in preventing disease recurrence and in improving inflammation and visual acuity. Eyes with the fluocinolone acetonide implant had 4.7 times greater risk of cataract progression and had a significantly greater need for glaucoma medications, laser treatment, and surgery compared with eyes in the dexamethasone group. However, the relatively low side effect profile of the dexamethasone implant must be weighed against higher retreatment rates, as eyes in the dexamethasone group were five times more likely to receive retreatment.[17]

Evidence suggests that the dexamethasone implant has a slightly better safety profile and longer-lasting effects than intravitreal triamcinolone acetonide injections.[11] It is a safe and effective option for the treatment of noninfectious uveitis and effectively suppresses ocular inflammation and improves visual acuity.

Fluocinolone Acetonide Implant 0.59 mg

The sustained-release fluocinolone acetonide 0.59 mg anchored implant delivers therapeutic drug levels for 30 months. The FDA approved it in 2005 for the treatment of chronic noninfectious posterior uveitis. Jaffe et al studied 36 eyes of patients with noninfectious posterior uveitis treated with this fluocinolone acetonide implant and reported significant improvement in visual acuity at 30 months (baseline BCVA = 20/250; BCVA at month 30 = 20/125; $P < .05$).[18] There was adequate suppression of inflammation, and no eyes experienced a recurrence in the first 2 years. There was also a significant reduction in systemic and local corticosteroid therapy use in the implanted eyes. The most significant side effects reported were an increase in IOP (56.1% of subjects were on IOP-lowering drops at the end of the study compared with 11.0% at baseline; $P = .005$) and cataract progression (eight patients underwent cataract extraction).[18]

In 2008, Callanan et al reported the findings of a 3-year multicenter trial that compared the safety and efficacy of 0.59-mg and 2.1-mg fluocinolone acetonide implants for the treatment of noninfectious posterior uveitis.[19] There was a significant reduction in recurrence rate ($P < .01$) and significant gains in visual acuity in the implanted eyes compared with nonimplanted eyes ($P < .01$), but the implanted eyes were also reported to have a higher incidence of IOP elevation, glaucoma surgery, and cataract progression.[19]

Pavesio et al reported better control of inflammation and significantly lower rates of recurrence in 66 patients treated with a 0.59-mg fluocinolone acetonide implant compared with 74 patients treated with systemic corticosteroid therapy.[20] The MUST trial research group reported similar improvements in vision favoring the implant group compared with systemic therapy among 255 randomized patients with noninfectious uveitis. However, the difference in visual gains was not significant between the groups (fluocinolone acetonide implant BCVA gain = 6 letters vs. systemic therapy BCVA gain = 3.2 letters, $P = .16$).[21] Both studies reported IOP elevation and cataract progression as the major adverse effects.[20,21] In 2015, the MUST trial research group reported similarly favorable visual outcomes and reduction in macular edema in 255 patients randomized to the fluocinolone

acetonide implant and systemic therapy group at the month 54 endpoint. However, the patients randomized to the implant group showed superior control of inflammation.[22]

In light of the evidence provided by the aforementioned clinical trials, the 0.59-mg fluocinolone acetonide implant demonstrates promise in the treatment of noninfectious posterior uveitis. It holds several advantages by providing long-term control of inflammation without systemic complications. The drawback lies in its high cost—both that associated with the price of the implant itself and the need for a surgical procedure for intraocular anchoring. The MUST trial research group presented the 3-year data on the cost and health utility of the fluocinolone acetonide implant compared with systemic corticosteroid therapy and reported the fluocinolone acetonide implant to be reasonably cost-effective in patients with unilateral intermediate, posterior, or panuveitis, but not with bilateral disease.[23] The rate of ocular adverse events including cataract formation and ocular hypertension are greater with the 0.59-mg fluocinolone acetonide implant than with the dexamethasone implant or intravitreal triamcinolone acetonide injections.[24,25]

Fluocinolone Acetonide Implant 0.19 mg

The injectable fluocinolone acetonide implant 0.19 mg is a nonbiodegradable cylindrical tube with a central drug-polymer matrix. The implant releases 0.19 mg of fluocinolone acetonide into the vitreous cavity over 3 years and can be inserted intravitreally via a 25-gauge needle in the office setting. The implant shows efficacy in reducing macular edema and improving visual acuity in patients with diabetic retinopathy, and it received FDA approval for this indication in 2014.[26,27] At present, no clinical data are available on the use of this implant in patients with noninfectious uveitis. Further studies assessing its long-term safety and efficacy in this patient population are warranted.

CONCLUSION

Corticosteroids are the preferred first-line agents in the treatment of noninfectious uveitis. There are few randomized control trials assessing and comparing the efficacy of local steroid therapies in the management of ocular inflammation. Most retrospective studies are limited by their small and heterogeneous nature, and no randomized controlled trials comparing these different options exist. These limitations require the clinician to carefully balance the advantages and disadvantages of each therapy while considering individual patient circumstances. Adequate counseling regarding the potential benefits and reported complications of each therapy can help the patient make an informed choice, which is imperative before initiating therapy. ■

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