

Corticosteroids in Uveitis

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Uveitis predominantly affects people of working age and can be a devastating sight-threatening condition. It has a worldwide prevalence ranging from 38 to 730 per 100 000, with a prevalence of 200 per 100 000 in the United States. Approximately 5 to 20% of legal blindness in developed countries is due to uveitis, and it has been estimated that uveitis accounts for 10 to 15% of all cases of total blindness in the United States.¹ The frequency of visual loss varies with the type of uveitis; posterior segment uveitis accounts for approximately 10 to 15% of blindness in the United States.²

The goals of therapy for uveitis are to reduce inflammation, prevent damage to ocular structures, and prevent long-term visual loss. Corticosteroids have been the mainstay of treatment for posterior segment uveitis and are commonly administered systemically or through periocular injections. The topical route is usually not used because the drug does not reach therapeutic levels in the posterior segment of the eye.³

Corticosteroids are potent antiinflammatory and immunosuppressive agents. They inhibit phospholipase A2 and the production of prostaglandins and leukotrienes. Several cytokine and adhesion signaling pathways associated with inflammation, vascular permeability and leukostasis are also inhibited. Corticosteroids also stabilize the blood-retina barrier by affecting the expression of certain molecules involved in ion and water flux, as well as enhancing tight junction integrity, making them good agents for reducing macular edema.

ROUTES OF CORTICOSTEROID DELIVERY

Systemic corticosteroids. Systemic corticosteroids, although efficient at controlling inflammation, are associated with numerous side effects such as Cushing syndrome, adrenal suppression, and osteoporosis, thus making them a poor choice for long-term use. The use of immunosuppressive agents other than corticosteroids (eg, antimetabolites, calcineurin inhibitors, alkylating agents and biologics) must be monitored closely as they are also associated with systemic toxicity.^{2,3}



Figure 1. Release of dexamethasone from the Ozurdex intra-vitreal implant.

Periocular corticosteroids. Patients with chronic refractory or recurrent inflammation who do not tolerate systemic therapy may require targeted ocular therapy. Periocular corticosteroid injections through the sub-Tenon or transeptal route are commonly used and are less invasive than intravitreal injections; however, these injections often have to be repeated at 2 to 4-month intervals to maintain adequate control. They also have the potential risk of globe perforation, orbital fibrosis, orbital fat prolapse, and ptosis.^{2,3}

Intravitreal corticosteroids. Intravitreal injection is another popular modality of intraocular corticosteroid delivery. Triamcinolone acetonide injections have also been employed to treat cystoid macular edema associated with uveitis but the effect is transient and carries with it the risks common to intravitreal surgery, such as vitreous hemorrhage, retinal detachment, and endophthalmitis. Triamcinolone acetonide is a synthetic, water-insoluble corticosteroid that is 5 times more potent than equivalent doses of prednisone. It has been shown to have profound antiangiogenic effects. Its relatively small particles can be injected in and around the eye, and its duration of action is several months.⁴ Studies have shown that measurable concentrations of a 4-mg intravitreal dose in a nonvitrectomized eye



Figure 2. The Retisert implant, shown relative to the tip of a pencil.

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is maintained for approximately 3 months.⁵ Several formulations are available for intraocular injection. Triesence (Alcon Laboratories Inc.) is a commercially available preservative-free preparation of triamcinolone acetonide that is US Food and Drug Administration-approved for intraocular use. The concentration of triamcinolone acetonide is 40 mg/mL, and recommended dosing is 1 to 4 mg (25–100 µL). Trivaris (Allergan Inc.) is another commercially available preservative-free triamcinolone acetonide preparation available as a single-use syringe for intravitreal injection. It is a gel preparation and has a concentration of 80 mg/mL. Kenalog (Bristol-Myers Squibb) is available for off-label use. It can be used in its provided form, but the preservative can be removed by a compounding pharmacy prior to administration.⁴

Several studies have advocated the use of intravitreal triamcinolone acetonide in the treatment of patients with Behcet disease with note of resolution of inflammation and improvement in visual acuity.^{4,6} Several case reports also illustrate favorable results with the use of intravitreal triamcinolone acetonide as treatment for both acute and chronic sympathetic ophthalmia and Vogt-Koyanagi-Harada disease.⁴

Although intravitreal injections of triamcinolone acetonide seem to be effective in treating various forms of uveitis, this still requires frequent injections as the drug lasts only for approximately 3 months. Hence, the patient is subject to an increased risk of complications common to intravitreal surgery, such as vitreous hemorrhage, retinal detachment, and endophthalmitis.

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SUSTAINED-RELEASE INTRAVITREAL IMPLANTS

The quest for a delivery system or route of drug administration that will bring high levels of drug directly to the posterior segment while minimizing systemic absorption and thus causing less toxicity, as well as reducing the need for frequent intraocular injections and decreasing the rates of ocular complications, led to the development of sustained-release intravitreal corticosteroid implants.

Fluocinolone acetonide is a corticosteroid with 1/24 the solubility of dexamethasone in aqueous solution, allowing steroid release over a much longer time period.⁷ This led to the study and development of the fluocinolone acetonide intravitreal implant. It achieves high concentrations in the posterior segment, with urine and plasma levels below threshold of detection, indicating very low systemic absorption.⁸ Retisert (Bausch + Lomb) is a nonbiodegradable, 0.59-mg sustained-release fluocinolone acetonide intravitreal implant, designed to continuously release the drug in a linear fashion over a period of approximately 2.5 years. It is FDA approved for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

Thirty-four-week³ and 3-year⁹ results of a pivotal phase 2b/3 study of 0.59-mg and 2.1-mg fluocinolone acetonide intravitreal implants demonstrated a significant reduction in recurrence of uveitis in implanted eyes. A phase 2b/3 trial¹⁰ comparing the intravitreal fluocinolone acetonide implant with standard therapy (systemic corticosteroid alone or in combination with other immunosuppressive agents) showed that the fluocinolone acetonide implant was associated with delayed onset of observed recurrence of uveitis and a lower rate of recurrence of uveitis.

Dexamethasone is 5 times more potent than triamcinolone acetonide, and more hydrophilic, allowing higher vitreous concentrations.¹¹ Because of the short half-life of dexamethasone in the vitreous cavity, a sustained-release intravitreal implant was developed.

The Ozurdex (Allergan Inc.) dexamethasone intravitreal implant is an injectable, biodegradable implant that contains 0.7 mg preservative-free dexamethasone. The FDA approved it for the treatment of macular edema associated with retinal vein occlusion and for noninfectious posterior uveitis. It releases the drug by diffusion in a biphasic fashion, with higher doses up to 60 days, followed by a rapid decline between days 60 and 90, then it achieves lower steady levels up to 6 months.¹¹ Each implant is supplied in a preloaded, single-use applicator, allowing administration as an in-office procedure.

Williams et al¹² found that more than 50% of patients with the dexamethasone implant achieved a gain in best-corrected visual acuity (BCVA) of 10-15 letters compared with observation alone. A 26-week, sham-controlled phase 3 trial¹³ demonstrated that 4 times more eyes treated with the 700 mg implant had complete resolution of vitreous haze compared with sham treatment by 8 weeks, which was reflected in improvement in BCVA.

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A retrospective comparative case series to compare the safety and efficacy of the fluocinolone acetonide implant and the dexamethasone implant in patients with noninfectious uveitis was done at the Massachusetts Eye Research and Surgery Institution (MERSI) (submitted for publication). Twenty-seven eyes received either the fluocinolone acetonide (n=16) or dexamethasone (n=11) implant. The main outcome measure was recurrence rate of uveitis after implantation. No statistically significant differences were found in the recurrence rates or in improvement in BCVA and inflammation. However, there were higher rates of cataract progression and need for glaucoma medications, laser and surgery with the fluocinolone implant.

SUMMARY

Before the introduction of sustained-release intravitreal corticosteroid implants, repeated intravitreal injections

of triamcinolone acetonide were used to treat a variety of retinal and uveitic disorders. These implants have addressed the need for achieving high concentrations of corticosteroid to the posterior segment of the eye and the concern of systemic toxicity and ocular complications associated with repeated injections. They have brought numerous eyes with recurrent or refractory ocular inflammation into durable remission. In addition to the 2.1-mg fluocinolone acetonide implant, we now have the dexamethasone intravitreal implant as a new addition to the armamentarium in the management of uveitis. ■

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