Sustained-release Corticosteroid Delivery Systems

Implant technology offers promising solutions to the burden of repeated injections for retinal diseases.

BY SZILÁRD KISS, MD

Retina practices are becoming overwhelmed with the ever-increasing burdens of repeated intravitreal injections for the treatment of age-related macular degeneration (AMD) and macular edema associated with retinal vein occlusion (RVO) and diabetic retinopathy. The need for frequent intraocular injections and the potential side effects associated with those injections has focused attention on the development of alternative systems for the delivery of ophthalmic medications. A variety of methods have been proposed that achieve longer duration of pharmacologic effect with lower administration frequency and minimal side effects.

One nidus of activity in the development of sustained-release systems has been the delivery of corticosteroids to the posterior segment. Although intraocular corticosteroid injections have a limited duration of action and significant side effects including cataract and glaucoma, intraocular injections may be of benefit in certain ocular disorders. Corticosteroids suppress inflammation by inhibiting multiple inflammatory cytokines, resulting in decreased edema, fibrin deposition, capillary leakage, and migration of inflammatory cells. Moreover, corticosteroids may also have an inhibitory effect on the vascular endothelial growth factor (VEGF) pathway.[1]

Intravitreal triamcinolone acetonide (Kenalog 40, Bristol-Myers Squibb) has been used off-label for several years for treatment of macular edema in the setting of RVO, diabetes (diabetic macular edema [DME]), and uveitis. Triamcinolone acetonide has also been used as an adjunct in the treatment of AMD.

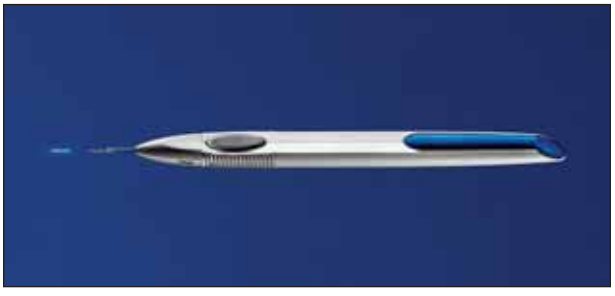

Figure 1. Ozurdex dexamethasone intravitreal implant.

Novel agents including preservative-free and sustained-release intravitreal implants are currently being evaluated for the treatment of RVO, DME, uveitis and AMD. Due to a potential for greater potency and more favorable side-effect profile, in addition to the corticosteroid triamcinolone acetonide, dexamethasone and fluocinolone acetonide are also being studied. These corticosteroids are placed into intravitreal implants that provide sustained-release of the drug at therapeutic levels for 6 months to 3 years.

DEXAMETHASONE INTRAVITREAL IMPLANT

The Ozurdex dexamethasone 0.7 mg intravitreal implant (Allergan, Inc.; Figure 1) received US Food and Drug Administration (FDA) approval in June 2009 for the treatment of macular edema following branch or central RVO. The implant is biodegradable and is administered via a 22-gauge applicator; it delivers dexamethasone to the vitreous cavity via Allergan's Novadur solid polymer delivery system. The Novadur system contains a poly D,L-

Figure 2. Iluvien sustained-release fluocinolone acetonide device next to a grain of rice.

lactide-co-glycolide (PLGA) polymer matrix. The PLGA matrix slowly degrades to lactic acid and glycolic acid, enabling extended release of dexamethasone over a 6-month period.[2]

The implant is administered in the office using a procedure similar to that of an intravitreal anti-VEGF injection. Given the 22-gauge needle size, however, a shelved injection technique is recommended to ensure a self-sealing wound. The implant is biodegradable, and at the end of the 6-month extended release period neither the drug nor the delivery system remains in the vitreous cavity.

FDA approval of the Ozurdex implant was based on two phase 3, multicenter, randomized, masked, sham-controlled, 6-month trials in patients with macular edema following RVO.[3] Patients were randomly assigned to receive either a single treatment with the implant or sham injection. Pooled data from the two studies showed that more patients in the implant group gained three lines of vision significantly faster compared with sham, with 20% to 30% of the implant-treated patients gaining three lines within 1 to 2 months compared with 7% to 12% of sham-treated patients. Improvement peaked at day 60, with 29.3% of patients in the implant group gaining three or more lines compared with 11.3% of patients in the sham group ($P<.001$). A significant difference was seen between the implant and sham groups through day 90 ($P<.001$).

Allergan, Inc., has completed a phase 3 trial of the Ozurdex implant for the treatment of ocular inflammation in the setting of posterior and intermediate uveitis. The drug is currently under FDA review for this indication. In addition, phase 3 trials of the implant are ongoing for the treatment of DME.

FLUOCINOLONE ACETONIDE IMPLANT

The Iluvien sustained-release fluocinolone acetonide device (Alimera Sciences; Figure 2) is an injectable, non-biodegradable, intravitreal insert designed for sustained release of the corticosteroid fluocinolone acetonide for up to 36 months. The cylindrical device is 3.5 mm in length and 0.37 mm in diameter and is injected into the vitreous cavity with a proprietary 25-gauge needle in a manner similar to an intravitreal anti-VEGF injection. Unlike the Ozurdex implant 22-gauge injector, the 25-gauge Iluvien inserter needle allows a self-sealing wound without the need for a shelved injection technique.

Figure 3. I-vation intravitreal triamcinolone acetonide implant.

The insert drug delivery system is nonerodible and remains in the vitreous cavity even after the drug release has been exhausted. Therefore, patients requiring repeated injections may end up with multiple devices trapped in the vitreous base for an indefinite period of time.

Alimera recently announced positive results from the two phase 3 FAME trials (Fluocinolone Acetonide in Diabetic Macular Edema) involving 956 patients with DME who were randomized to either receive a high dose insert (0.45 µg/day), a low-dose insert (0.23 µg/day), or a sham insertion.[4] In Trial A, 26.8% of low dose patients and 26.2% of high dose patients gained 15 or more letters at 24 months compared with 14.7% of patients randomized to control ($P=.029$ and $P=.032$, respectively). In Trial B, 30.8% of low dose patients and 31.3% of high dose patients gained 15 or more letters compared with 17.8% of control patients ($P=.028$ and .026, respectively). Based on these results, Alimera plans to file a New Drug Application with the FDA in the second quarter of 2010 for the treatment of DME with the fluocinolone acetonide insert.[5]

In addition to DME, the Iluvien insert is in phase 2 trials for the treatment of wet AMD (in conjunction with ranibizumab [Lucentis, Genentech, Inc.]), dry AMD (in the setting of geographic atrophy), and macular edema secondary to RVO.

Figure 4. Verisome delivery system.

INTRAVITREAL TRIAMCINOLONE ACETONIDE IMPLANTS

The I-vation intravitreal triamcinolone acetonide implant (SurModics, Inc.; Figure 3) consists of three components: a non-ferrous metallic scaffold in the shape of a helix, a cap that is attached to the helix, and a drug-loaded polymer coating that encapsulates the helix. The helical shape maximizes the surface area available for drug coating and enables sutureless anchoring of the implant against the sclera. The thin cap is designed to reside under the conjunctival membrane. The insertion of the implant requires conjunctival cut-down and placement in an operating room through a 0.5-mm needlestick. The delivery system is non-biodegradable and remains in place even after the drug release is complete.

The implant utilizes the I-vation sustained drug delivery system for delivery of triamcinolone acetonide to the posterior segment of the eye. Although a phase 1 trial of 30 patients showed a reduction of DME at 24 months, a phase 2b clinical trial of I-vation was suspended in 2008.[6]

The Verisome delivery system (Icon Biosciences, Inc.; Figure 4) is a sustained-release drug delivery system that can be injected into the eye as a liquid via a standard 30-gauge needle. When injected into the vitreous, the liquid coalesces into a single spherule. The biodegradable vehicle provides controlled, extended drug release over a titratable period of up to 1 year. The drug delivery system degrades as the active agent is released over the intended time duration.

For its first clinical trial, the Verisome technology was formulated for injectable intraocular sustained-release delivery of triamcinolone acetonide (IBI-20089). The liquid-gel formulation was designed to deliver triamcinolone acetonide for up to 1 year via a single intravitreal injection. The phase 1/2 trial of IBI-20089 in patients with macular edema associated with RVO included two dosing levels, a 25-µL dose designed to last 6 months and a 50-µL dose designed to last 1 year. The results of the clinical trial confirmed the expected safety and efficacy characteristics and the controlled-release attributes of the technology.[7]

CORTICOSTEROID PRODRUG IMPLANT

The Cortiject implant (NOVA63035, Novagali Pharma) is a preservative- and solvent-free emulsion that contains a tissue-activated proprietary corticosteroid prodrug. Once released, the prodrug is activated at the level of the retina. A single intravitreal injection of the emulsion provides sustained release of the corticosteroid over a 6- to 9-month period. An open-label, phase 1, dose-escalation clinical study to assess the safety and tolerability of NOVA63035 in patients with DME is currently under way.[8]

SUMMARY

For several years, repeated intravitreal injections of non-FDA approved triamcinolone acetonide have been used to treat a variety of retinal diseases. Several sustained-release delivery systems are now in various stages of clinical testing (with Ozurdex already FDA approved) that balance the benefits of a variety of corticosteroids with the side-effect profile and the need for repeated injections. Sustained-release drug delivery systems have the potential to reduce the burdens of repeated intravitreal injections on patients and physicians and may ultimately lead to better care. ■

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