Implantable Posterior Segment Drug Delivery Devices; Novel Alternatives to Currently Available Treatments

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The efficacy of drug delivery to the posterior segment by systemic, local or topical routes is hindered by the blood-retinal barrier, tight intercellular junctions and scantly vascularized spaces. Although intravitreal injection has proved effective for delivery of therapeutic agents into the vitreous cavity and retina, it is impractical for frequent or sustained dosing. Intravitreal sustained release implants offer long-term pharmacotherapeutic exposure to the posterior segment. This novel method bypasses ocular barriers, avoids systemic complications and improves compliance.

VITRASERT

The pioneer of intravitreal implants is Vitrasert (Bausch & Lomb, Rochester, USA) which has been available for more than 10 years. It is a sustained release implant for delivery of ganciclovir for treatment of cytomegalovirus (CMV) retinitis. Conventional treatment for AIDS associated cytomegalovirus retinitis is intravenous and intravitreal injection of antiviral agents. However, the ganciclovir implant has become the preferred method of administration because it provides a long duration of remission and has a favorable side effect profile, especially in isolated ocular CMV infections. In a phase III clinical trial on 188 AIDS patients with newly diagnosed CMV retinitis, the time to disease progression was significantly longer in patients who received Vitrasert (216 days) than those who received intravenous ganciclovir (106 days). This implant delivers medication for five to eight months and can be replaced or removed thereafter.

RETISERT

The only FDA-approved steroid implant, Retisert (Bausch & Lomb, Rochester, USA), incorporates a small reservoir containing only 0.59 mg of fluocinolone acetonide (FA) and continuously delivers low levels of the drug (approximately 0.6 μg/day) into the vitreous cavity for up to 3 years. During different clinical trials, inflammation was well controlled in all eyes and the rate of uveitis recurrence was decreased from 40-54% to 6-14%. Interestingly, Retisert also stabilized or improved visual acuity in 80% of patients and reduced the need for systemic or topical adjunctive therapy.

Several studies have been conducted to evaluate the safety and efficacy of Retisert for treatment of macular edema associated with diabetic retinopathy and retinal vein occlusion (RVO). Preliminary results showed that the implant was effective in reducing edema and improving visual acuity in a significant proportion of eyes. More recently, promising results have also been reported for combined phacoemulsification and intravitreal Retisert implantation for treatment of cataract associated with chronic uveitis.

The major drawback to this implant is its side effect profile; within 34 weeks of implantation, 60% of patients required intraocular pressure (IOP) lowering medications. At an average post-implant period of 2 years, 32% of patients required glaucoma filtering procedures and nearly all phakic eyes developed visually significant cataracts. Following any type of intravitreal implantation, surgical complications may occur in a small number of patients

and include choroidal detachment, endophthalmitis, hypotony, retinal detachment, vitreous hemorrhage, vitreous loss, exacerbation of intraocular inflammation and wound dehiscence.

ILUVIEN

Iluvien (Alimera Sciences, Alpharetta, USA), previously known as Medidur FA, is a non-erodible insert in phase III trials for extended delivery of FA in patients with diabetic macular edema (DME). It measures 3.5 mm in length and 0.37 mm in diameter. A #25 gauge insertion system facilitates intravitreal implantation of Iluvien in an office-based setting. Once in the vitreous cavity, the device has an initial daily release rate of either 0.23 or 0.45 µg of FA, the lowest doses of the drug currently under study for sustained delivery. Its therapeutic effect is expected to last up to 36 months. When the active agent is depleted, the inert Iluvien insert may be retained in the eye. In a phase II study 20 patients were treated with low dose (0.23 µg per day) and 17 patients received high dose (0.45 µg per day) FA for 12 months. No adverse events related to IOP were observed in the low-dose group but 23.5% of eyes in the high-dose group experienced IOP of 30 mmHg or more at some time point. Visual acuity improved by 15 letters or more in both groups (23.1% and 27.3% in the low and high dose groups respectively).

Two phase III registration trials for Iluvien, in a program called FAME (Fluocinolone Acetonide in Diabetic Macular Edema), completed enrollment of 956 patients in October 2007. The studies include patients from North America, Europe, and Asia. The efficacy analysis will be completed in late 2009 after 24 months of follow-up and final analysis is planned at the end of 36 months.

POSURDEX

Posurdex (Allergan, Irvine, USA) is a polymer pellet that releases dexamethasone as it biodegrades. It has reached phase III evaluation for treatment of DME and RVO. The pellet completely dissolves in about 37 days, however initial studies suggest that the effect of the drug may persist for 2 or more months after dissolution. Although Posurdex was initially implanted surgically, phase III studies evaluating patients with DME are being conducted with a #22 gauge applicator that permits treatment as an office-based procedure.

In a phase II dexamethasone study with Posurdex, 306 patients were randomized to a 350-µg implant, a 700-µg implant, or observation. Although the majority of patients in this study had DME, 102 patients had RVO, 25 subjects had Irvine-Gass syndrome, and 14 cases had uveitis. At six months, 36% of subjects in the 700-µg group and 27% of those in the 350-µg group versus 19% of the observation group had at least 2 lines of improvement in visual acuity. A 3-line or better improvement was achieved in 19% of those on the highest dose of dexamethasone versus 8% of the observation group. The most common adverse event was an increase in IOP. A 10 mmHg or greater increase in IOP was observed in 17% of the 700-µg group, 12% of the 350-µg group and 3% of the observation group.

Like Iluvien, the Posurdex platform has the potential for a variety of applications outside the current initiative to deliver steroids for the treatment of DME and RVO. For example, studies have already been initiated to evaluate combination therapy with ranibizumab to treat exudative age-related macular degeneration (AMD).

I-VATION

I-Vation (SurModics, Eden Prairie, USA) has been evaluated in a 30-patient phase I study, testing the delivery of triamcinolone acetonide in patients with DME. Although phase I studies are primarily safety evaluations, favorable changes in visual acuity were reported along with acceptable tolerability. I-Vation, which can be made with a variety of polymer matrix formulations, is expected to be compatible with a broad array of active agents. Unlike Iluvien and Posurdex, I-Vation requires the implant to be surgically fixed at the pars plana. The implant's small diameter enables implantation through a small (less than 0.5 mm) pars plana sclerotomy, the thin cup of the implant is designed to reside under the conjunctiva, faci-

litating retrieval if necessary. In comparison to Iluvien or Posurdex, the compatibility of the I-Vation platform with different polymers increases its versatility for developing dosing characteristics specific to different types of retinal therapies.

BRIMONIDINE IMPLANT

Brimonidine is an alpha-2-selective adrenergic receptor agonist used for treatment of glaucoma which reduces IOP by decreasing aqueous humor production and increasing uveoscleral outflow. Recent studies have suggested that brimonidine can promote survival of injured retinal ganglion nerve cells by activation of the alpha-2-adrenoceptor in the retina and/or optic nerve. Two phase II clinical trials are now recruiting patients with retinitis pigmentosa and geographic atrophy due to AMD to evaluate the safety and efficacy of a brimonidine intravitreal implant (Allergan, Irvine, USA). The results are expected to be available in 2 years.

Other injectable intravitreal devices are in development. Although the majority of clinical studies have so far concentrated on treatment of DME, uveitis, and retinitis; the potential role of these devices for neovascular retinal disorders, particularly AMD, are considerable. Single intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) antibodies have been associated with significant clinical benefits, including improvement in visual acuity. Sustained VEGF inhibition may increase the efficacy of such treatment. It is unclear whether any currently developing concepts has the potential to eventually dominate most indications of sustained intravitreal drug delivery or if differences in design and characteristics may offer relative advantages for a given device for different indications.

SUGGESTED READINGS

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