Drug Delivery to the Posterior Pole

BY MARK R. WIELAND, MD; AND ANNE E. FUNG, MD

In recent years, the use of intravitreal injections for the treatment of posterior segment diseases has skyrocketed as new therapeutic modalities have become available. Regular monthly injections of a vascular endothelial growth factor (VEGF) inhibitor have been shown to reduce and reverse vision loss in patients with exudative age-related macular degeneration.[1,2] At the same time, use of off-label injections of steroids and anti-VEGF agents for the treatment of diabetic macular edema (DME), edema related to retinal vascular occlusions, and other conditions, has also increased.[3-6]

All of these injections have limited duration of efficacy, and in most cases they are repeated as needed based on regular monitoring of edema with optical coherence tomography. As a result, there is strain on the patient, the physician, and the health care system due to the need for regular office visits, as well as increased risk of the complications of intravitreal injections, including endophthalmitis, retinal detachment, and, with steroid injections, the development of cataract and/or glaucoma.

Many retina practitioners would like to be able to more precisely tailor their therapies to the patient's needs and eliminate the inconvenience and risks associated with intravitreal injections. A number of approaches designed to provide extended delivery of drugs to the posterior pole are currently in use or in various stages of investigation. These approaches, outlined in Table 1, include drug delivery devices, polymer depots, encapsulated cell technology, pumps, and iontophoresis. This article reviews the status of some posterior-segment drug-delivery technologies and highly experimental approaches (not all approaches listed in Table 1 are discussed) currently in use or under investigation.

TABLE 1. CURRENT APPROACHES

- Drug Delivery Device (Vitrasert, Retisert, I-Vation)
- Polymer Depot (Ozurdex, Iluvien)
- Encapsulated Cells (Neurotech)
- Pumps (Replenish, Iveena)
- Iontophoresis (Eyegate Pharma)

THE IDEAL DEVICE

The ideal device for extended delivery of drugs to the posterior segment would combine the following important considerations: an appropriate anatomic location, for example, in the vitreous cavity or the subretinal or suprachoroidal space; an ability to deliver multiple drugs for combination therapies; controlled release to allow the drug to reach the target tissue in a timely manner, in sufficient concentration, and to remain there long enough to have a therapeutic effect; and minimal side effects. A refillable reservoir would be an ideal attribute, although clearly this would be difficult to develop technologically. Given the volume of patients for which such a device might be a viable treatment option, the ability to deliver it in an in-office procedure would clearly be preferable over an OR-based procedure.

The use of therapeutic proteins to treat retinal diseases is rapidly growing. Although effective drug-delivery systems have been developed for steroids, protein delivery has proved to be more challenging. Some have expressed concern about the stability of proteins in a sustained-delivery setting at body temperature, but although hotter temperatures can accelerate protein degradation, this does not appear to be the most important aspect. A more significant issue for extended protein delivery is hydrolysis. Proteins require dry formulation for stability, so a protein-delivery device must provide a barrier to hydrolysis. At the same time, however, bioerodable polymer systems and pumps require hydrolysis and are therefore problematic for protein delivery.

TABLE 2. CURRENT DRUG DELIVERY DEVICES

Device	Active agent	Molecular weight	Type	Duration	Disease
Ozurdex	Dexamethasone	392	Free floating biodegradable implant	3-6 months	ME associated with BVO,CVO,DME, Uveitis
Vitrasert	Ganciclovir	255	Scleral fixated non-biodegradable reservoir	6 months	CMV retinitis
I-Vation (Phase 2)	Triamcinalone	434	Scleral screw helical implant	18-36 mo	DME
Retisert	Fluocinolone	452	Scleral fixated nonbiodegradable reservoir	2-3 years	Uveitis
Iluvien (Pending Approval)	Fluocinolone	452	Free floating non-biodegradable implant	3 years	DME

DRUG DELIVERY DEVICES AND DEPOTS

Typically, drug delivery devices (Table 2) are tethered to the sclera, requiring an operating room procedure for implantation. Depots are free-floating devices placed in the vitreous cavity in an in-office procedure. Most of these devices currently are used to deliver steroids or other small-molecule drugs with low molecular weights.

Ozurdex (Allergan) is a free-floating biodegradable implant that dispenses dexamethasone. It is approved for the treatment of uveitis, DME, and macular edema secondary to venous occlusion. It is associated with a low rate of cataract formation (5%) and a low rate of glaucoma requiring surgery (1%) at 6 months.[7] It is injected with a 23-gauge device in an office-based procedure and appears to last 3 to 6 months.

Vitrasert (Bausch + Lomb) was the prototype posterior segment drug-delivery device, developed to deliver ganciclovir for the treatment of cytomegalovirus retinitis. After implantation in a rather invasive OR-based procedure, the scleral-fixated nonbiodegradable reservoir effectively releases ganciclovir for 6 months.

I-vation (SurModics) is a non-ferrous, nonbiodegradable metal implant inserted in an OR-based procedure with a 25-gauge device to deliver triamcinolone for 18 to 36 months.[8] The helix-shaped device, which can be screwed in and removed as needed, is currently in phase 2 clinical trials.

Retisert (Bausch + Lomb) is a scleral-fixated implant that delivers fluocinolone acetonide for the treatment of refractory uveitis for up to 3 years. Almost 100% of recipients develop cataract by 2 to 3 years after implantation, and approximately 40% require surgery for steroid-induced glaucoma.[9]

Iluvien (Alimera Sciences) is a free-floating, nonbiodegradable implant, inserted with a 25-gauge needle in an office-based procedure, which delivers fluocinolone for up to 3 years.[10] The rate of cataract formation is less than with Retisert, but still 75 to 80%, and the rate of steroid-induced glaucoma requiring surgery is about 5% or less at the 36 month readout. The device is pending regulatory approval for treatment of DME.

NEW APPROACHES

Novel approaches to posterior segment drug delivery are also in development.

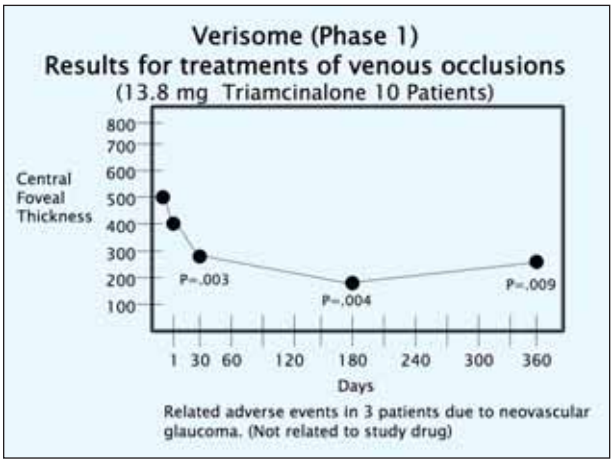

Figure 1. A decrease in central foveal thickness was achieved by 30 days after injection and maintained for 1 year.

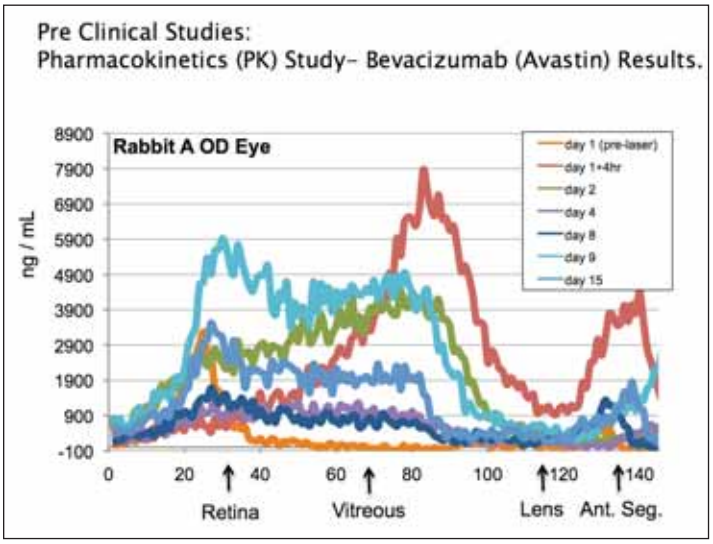

Figure 2. The release of bevacizumab in rabbit eyes with significant concentrations in the vitreous early, and concentrations in the retina by 3 to 4 days after implantation.

Neurotech (Lincoln, RI) is developing an intraocular implant that delivers ciliary neurotrophic factor (CNTF), a protein that has been investigated for the treatment of motor neuron disease, to the posterior segment. The technology, dubbed NT-501, contains human cells that have been genetically modified to secrete CNTF. Implanted in an OR-based procedure, NT-501 slowed the loss of vision in a phase 2 study in patients with geographic atrophy due to dry AMD. In that study, the technology stabilized best corrected visual acuity at 12 months, with 96.3% of treated patients losing fewer than 3 lines of vision compared with 75% of sham-treated patients. No serious adverse events were reported, and the implant was well tolerated.[11]

The Verisome (Icon Bioscience, Inc.) is an intravitreal liquid drug delivery system formulated to release triamcinolone for up to 1 year. A 30-gauge needle is used to deliver the drug as a liquid in an office-based procedure. The drug delivery system is denser than the vitreous and typically sinks down to the inferior retinal periphery where it can be visualized as it slowly dissolves. The biodegradable system releases drug with zero-order kinetics and theoretically can be formulated for larger or smaller biologic molecules.

In a phase 1 study in 10 patients with cystoid macular edema secondary to ischemic or nonischemic venous occlusions receiving the Verisome, a decrease in central foveal thickness was achieved by 30 days after injection and maintained for 1 year (Figure 1). Three patients developed neovascular glaucoma, which resolved and was deemed not related to the study drug but rather to the ischemic nature of the patients' vascular occlusions.[12]

On Demand Therapeutics (Menlo Park, CA) has developed a novel drug delivery system that allows the delivery of protein or small-molecule drugs to the posterior segment. The nonresorbable rod, placed into the vitreous, has multiple discrete reservoirs that can contain multiple drugs. The compartments are hermetically sealed to preserve protein stability for up to 1 year, avoiding hydrolysis, oxidation, and denaturation. The dry, solid formulation of the drug decreases irreversible aggregation and delamination that is seen with liquid formulations.

The device is activated by using a standard laser and a Goldmann three-mirror lens to open the reservoirs. The proteins are not altered by the heat of the laser burn because of the shortness of the pulse. A pharmacokinetic study in rabbit eyes demonstrated the release of bevacizumab with significant concentrations in the vitreous early, and concentrations in the retina by 3 to 4 days after implantation (Figure 2).[13]

The suprachoroidal space is a relatively unexplored area for drug delivery to the posterior segment. Delivery through the suprachoroidal space may avoid the anterior chamber side effects of glaucoma and cataract development. It may also avoid washout and increase the duration of drug activity. It may allow access to the submacular space, and it affords a large potential anatomic space for drug deposition. iScience (Menlo Park, CA) has developed the world's smallest microcatheter, which can be routed through the pars plana into the suprachoroidal space to access the subfoveal space in an OR-based procedure. Delivery of triamcinolone using this technique has been evaluated in animals.[14]

iScience has also developed the Smart Needle, which allows injection into the potential suprachoroidal space with a pneumatic device in an office-based procedure. Proteins or small-molecule drugs can then be injected into the suprachoroidal space, and the drug appears to migrate toward the subfoveal space. This extravascular potential space may be ideal for sustained high-dose drug delivery.

CONCLUSION

There are many intriguing approaches to delivering drugs to the posterior pole. Some of those described above must be further investigated in preclinical and clinical settings before they are ready for use in our offices and patients. While it is clear that we have yet to develop the ideal poste-

rior-segment drug-delivery system, it is certain that a reliable, safe, and efficient method to deliver drugs to the retina and vitreous over extended periods will be a boon to our patients and our practices. ■

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