

Drug Delivery to the Posterior Segment

A review of methods and technologies available and those on the horizon.

BY DANIEL D. ESMAILI, MD; AND DAVID S. BOYER, MD

Drug delivery to the posterior segment of the eye is an area of intense investigation and immense potential. Despite the emergence of effective drugs to treat a variety of retinal diseases, surgeons still grapple with how best to administer these sight-saving medications. An ideal route of administration would deliver therapeutic levels of drug to targeted tissues in an exceedingly safe fashion while providing minimal disruption to the quality of life of the patient. This review touches on the present state of drug delivery technology and provides a glimpse of technologies in the pipeline.

DRUG DELIVERY TECHNOLOGIES: A REVIEW Intravitreal Injection

The current delivery method of choice is intravitreal injection, which has a positive safety and efficacy profile. Dosing by this route provides a large initial bolus of drug beyond therapeutic levels, which then clears rapidly. Intravitreal injections typically require frequent visits by patients who may be of advanced age or in poor health, and there is associated discomfort.

At a Glance

- Intravitreal injection is the current drug delivery method of choice.
- Topical drug delivery offers easy administration, but ocular bioavailability is limited; less than 5% of the dose reaches deeper ocular tissues.
- Emerging technologies, including nanotechnology-based intravitreal approaches, scleral-fixated slow-release implants, and suprachoroidal delivery strategies, may provide targeted drug delivery with superior durability.

The expansion of treatment indications and an aging population have deepened the treatment burden both for patients undergoing frequent injections and for the providers trying to accommodate such treatments. Currently available intravitreal therapeutics have demonstrated impressive efficacy and safety with modest durability. Research efforts have been aimed at manipulating the vehicle for delivery of these agents, in order to create a drug delivery platform that optimizes efficacy and increases durability.

Intraocular Implants

Other approaches to drug delivery involve implanting a device to provide slow release of drug over an extended period of time.

Currently Available

Several drug delivery implants are available for the treatment of uveitis, retinal vein occlusion (RVO), and diabetic macular edema (DME). The first nonbiodegradable intraocular implant developed for long-term drug delivery was Vitrasert (Bausch + Lomb), a scleral-fixated device based on the Durasert technology developed by pSivida Corp for glaucoma. Vitrasert delivered ganciclovir for up to 6 months in patients with cytomegalovirus retinitis. The fluocinolone acetonide intravitreal implant 0.59 mg (Retisert, Bausch + Lomb), also a scleral-fixated implant based on the Durasert technology, delivers fluocinolone acetonide for up to 3 years in patients with uveitis.¹

Two other devices have been approved more recently: the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan), a biodegradable, intravitreal implant that provides sustained release of dexamethasone for patients with uveitis, DME, and RVO-associated macular edema; and the fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera Sciences), an intravitreal implant designed for

sustained release of fluocinolone acetonide in patients with long-standing DME.^{2,3}

In the Pipeline

Several novel approaches have been undertaken in this arena. An encapsulated cell technology platform, NT-501 (Renexus, Neurotech), contains genetically engineered retinal pigment epithelium (RPE) cells from a human cell line that are capable of producing a therapeutic factor. The immunologically isolated cells are housed within a semipermeable polymer capsule that is sutured to the sclera and allowed to secrete the therapeutic factor in a continuous fashion over an extended period of time. The NT-501 implant secretes recombinant ciliary neurotrophic factor. A phase 2 study in patients with geographic atrophy did not reveal any safety concerns.⁴ With a similar strategy, Neurotech's NT-503 uses engineered RPE cells capable of producing a VEGF receptor Fc-fusion protein for the treatment of neovascular AMD, and the company's NT-503/506 targets both VEGF and platelet-derived growth factor (PDGF) receptors for neovascular AMD.

The ODTx device (On Demand Therapeutics) is a biocompatible, nonresorbable, injectable implant that contains multiple discrete reservoirs to store and protect small- or large-molecule drugs. The device is activated by a standard laser, which can be used to create an opening in an individual reservoir to release the drug.

The Port Delivery System, developed by ForSight Vision⁴, has been licensed by Genentech/Roche for delivery of ranibizumab (Lucentis, Genentech). It is a scleral-fixated, nonbiodegradable drug delivery implant designed to provide sustained release of drug into the vitreous over a period of months. One of its appealing features is its ability to be refilled via transconjunctival injection. Following completion of a phase 1 trial for treatment of neovascular AMD, the Long-Acting Delivery of Ranibizumab (LADDER) study will further evaluate this technology.

The Replenish MicroPump (Replenish) is an implantable device based on microelectromechanical systems engineering, containing a drug reservoir with a refillable port, battery, and electronics. It is implanted in the subconjunctival space, and a flexible cannula is inserted through an incision into the posterior segment to release nanoliter doses of drug at a programmed interval.

Topical Administration

The topical route of drug delivery is attractive because of its ease of access and administration. Unfortunately, numerous anatomic and physiologic constraints limit ocular bioavailability, and less than 5% of a topically applied dose reaches the deeper ocular tissues.⁵ To

improve efficiency, strategies such as the use of prodrugs and permeation-enhancing nanoparticles have been developed to optimize penetration. The use of viscosity enhancers can increase drug contact time on the cornea and hence drug release to the posterior segment.

Squalamine is a small molecule that counteracts multiple growth factors including VEGF, PDGF, and basic fibroblast growth factor. A phase 2 clinical trial of topically applied squalamine eye drops (OHR-102, Ohr Pharmaceutical) for the treatment of AMD compared a combination of topical squalamine plus intravitreal ranibizumab with intravitreal ranibizumab monotherapy. The primary endpoint of the study was the mean number of injections in each treatment arm, and no significant difference was seen. In a subgroup analysis, 42% of patients with a classic component of choroidal neovascularization showed a 3-line vision gain in the squalamine group compared with 28% in the ranibizumab monotherapy group.⁶

Several other molecules for topical delivery have been developed to inhibit VEGF activity. Regorafenib (Stivarga, Bayer HealthCare) is a multikinase inhibitor packaged in an oily suspension formulation for improved delivery. After a successful phase 1 trial to determine tolerability, a phase 2 study is under way. PanOptica is testing PAN-90806, a small-molecule selective VEGF receptor antagonist, as a topical treatment for neovascular AMD in a phase 1 trial.

Aganirsen (GS-101, Gene Signal) is an antisense oligonucleotide that inhibits insulin receptor substrate-1 expression. In the I-CAN phase 3 trial, topical aganirsen reduced the relative area of corneal neovascularization in patients with keratitis.⁷ The compound is being prepared for phase 2 trials in patients with AMD and DME.

Iontophoresis

Iontophoresis is a noninvasive method designed to improve the penetration of a charged compound across membranes. For ocular drug delivery, an electrical current is applied across the eye to facilitate drug penetration. Iontophoresis has been combined with nanoparticle delivery systems to improve penetration.⁸ Several systems are available for iontophoresis, including the Eyegate II (EyeGate Pharma), OcuPhor (Iomed), and Visulex (Aciont) delivery systems.

Periocular Drug Delivery

Periocular drug delivery via the transscleral pathway is a safe means of achieving therapeutic drug levels, but it is limited by a steep drug concentration gradient, with high concentrations in the sclera and lower concentrations in the retina. Pontes de Carvalho et al have described an episcleral drug reservoir to allow transscleral delivery.⁹

They juxtaposed a silicone explant to the sclera that provided an avenue for transscleral delivery while limiting exposure to washout by the conjunctival vessels. This delivery system is being evaluated for the treatment of posterior segment diseases and glaucoma.

Suprachoroidal Delivery

The suprachoroidal space is an intriguing target for drug delivery. Administration of drugs into this space can potentially enable their access to the choroid and retina while limiting exposure to the anterior segment.

In 2002, Einmahl et al described an injection of a biodegradable polymer gel into the suprachoroidal space in rabbits.¹⁰ Olsen et al described a novel surgical technique for delivering triamcinolone to the posterior pole via cannulation of the suprachoroidal space.¹¹ In porcine and primate models, they noted successful delivery of triamcinolone to adjacent tissues that lasted 120 days.

The iTrack 250A microcatheter (iScience Interventional) is a device designed to facilitate this approach. It includes an optical fiber that permits transmission of light to the tip of the device, allowing visualization during surgical intervention. In a prospective study using this technique, Tetz et al delivered combination triamcinolone and bevacizumab (Avastin, Genentech) to six patients with refractory DME or RVO-associated macular edema with subfoveal hard exudates. They noted improvement in visual acuity of at least 2 lines in four eyes, with clinical improvement in subfoveal hard exudates and reduction in central thickness on optical coherence tomography (OCT).¹²

Hollow microneedles have been used to access the suprachoroidal space in the office setting. Patel et al reported a minimally invasive technique using a hollow microneedle to penetrate the sclera and terminate in the suprachoroidal space.¹³ Clearside Biomedical has initiated separate phase 2 clinical trials using their microinjector technology for patients with macular edema secondary to uveitis or RVO. In the RVO trial, patients receive aflibercept (Eylea, Regeneron) with or without suprachoroidal triamcinolone acetonide.

Nanotechnology

Nanotechnology, which refers to substances of nanometer scale, offers promising avenues for posterior segment drug delivery. Several nanotechnology approaches are being explored as methods to improve the penetration of drugs across membranes and to allow controlled release to tissues of interest with consequent improvement in duration. At the heart of this approach are nanosized carrier systems that can package drugs for sustained delivery to targeted tissues.

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These include nanospheres, nanocapsules, liposomes, nanomicelles, and dendrimers.¹⁴

Liposomes are colloidal spheres composed of a phospholipid bilayer that can encapsulate hydrophilic drugs within their aqueous core and hydrophobic drugs within the bilayer. Liposomal amphotericin B (AmBisome, Gilead Sciences) has been studied in fungal endophthalmitis in rhesus monkeys,¹⁵ and a liposomal preparation of bevacizumab has been studied in humans.¹⁶

Microparticles and nanoparticles are spherical preparations; microparticles range in diameter from 1 μm to several hundred microns, and nanoparticles are less than 1 μm in diameter. They are often composed of biodegradable polymers such as polylactic acid (PLA), polyglycolic acid (PGA), and poly (lactic-co-glycolic acid), or PLGA. Zhang et al investigated intravitreal injection of dexamethasone-loaded PLGA nanoparticles in rabbits. They found that dexamethasone levels were maintained in the vitreous over a period of 30 days as compared with only trace amounts seen on day 7 after injection of a standard dexamethasone solution.¹⁷

Ocular Therapeutix has used polyethylene glycol (PEG) to encapsulate drug-loaded microspheres that can be tailored to deliver sustained levels of drug at a therapeutic dose. The PEG bioresorbable hydrogel creates a tight meshwork that can trap anti-VEGF molecules. The PEG hydrogel and anti-VEGF molecules are injected, and as the hydrogel degrades via hydrolysis, the mesh size increases and anti-VEGF particles are gradually released.

Icon BioScience has developed the Verisome drug delivery platform for small molecules, proteins, and monoclonal antibodies. Once injected, the material coalesces to form a spherule in the inferior vitreous that can slowly degrade and release medication over an extended period of time. IBI-20089 is triamcinolone formulated via the Verisome technology. In a phase 1 study, Lim et al treated 10 patients with macular edema secondary to RVO with a single injection of either 6.9 mg (25 μL) or 13.8 mg (50 μL) triamcinolone and then followed them for 1 year. The

five patients who received 13.8 mg (50 μ L) experienced a significant and sustained reduction in mean central sub-field OCT thickness from 518 μ m at baseline to 289 μ m at day 30, 207 μ m at day 180, and 278 μ m at day 360. Three patients in the study had elevated intraocular pressure, of which two cases were due to neovascular glaucoma.¹⁸

CONCLUSION

The anatomic and physiologic defenses that preserve the integrity of the eye also create unique challenges for drug delivery. Through various approaches, numerous investigators are exploring more effective ways to deliver ocular therapeutics to the posterior segment. ■

Daniel D. Esmaili, MD, is a retina specialist in private practice at Retina Vitreous Associates Medical Group in Los Angeles, Calif. Dr. Esmaili may be reached at desmaili@laretina.com.



David S. Boyer, MD, is a clinical professor of ophthalmology at the University of Southern California Keck School of Medicine, Department of Ophthalmology, in Los Angeles, Calif. He is a member of the Retina Today Editorial Board. Dr. Boyer may be reached at +1-310-854-6201 or vitdoc@aol.com.



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