

Drug Delivery to the Posterior Segment: An Update

Many routes for sustained drug delivery to the retina are in use or being explored.

BY DAVID S. BOYER, MD

As pharmacotherapy for posterior segment diseases becomes increasingly promising and effective, drug delivery to this closed compartment in the eye is an ongoing challenge faced by our profession and the ophthalmic pharmaceutical industry. Intravitreal injection has transformed the practice of retina, particularly the management of neovascular age-related macular degeneration (AMD) and diabetic macular edema (DME), but the need for frequent injections places a burden on patients and practices and increases safety concerns. A longer-acting, safer delivery method that can achieve the same level of visual results as frequent intravitreal injections is a continuing unmet medical need.

There are limitations and drawbacks with any route of approach to posterior segment drug delivery. With periocular or intravitreal injections, there is an initial high local concentration of drug due to the bolus injection, followed by rapid clearance; therefore, frequent reinjections are required. Periocular delivery carries the risk of side effects including globe penetration or perforation, orbital fibrosis, ptosis, and diplopia. Potential side effects of intravitreal injection include retinal detachment, intraocular hemorrhage, pseudoendophthalmitis or endophthalmitis, and traumatic cataract. With topical administration, typically only 1% to 5% of an applied dose reaches the anterior chamber. Posterior movement of drug from the aqueous humor is then further impeded by the iridolenticular diaphragm.

An ideal therapy would reach therapeutic doses in the target tissue with infrequent administration and would have a positive safety profile. Many centers are currently involved in investigations of alternative methods of deliv-

ery to the posterior segment, and some of these methods are already in clinical use, such as enduring injectable systems for extended release of drugs (Figure 1). This article reviews the status of current research in this area.

TOPICAL DELIVERY

Despite the impediments to topical delivery described above, the topical route remains attractive because of the ease of access and application. Preclinical and clinical studies with numerous agents have shown that it is possible to achieve therapeutic effects in the posterior segment after topical application. The agents investigated for posterior segment effects after topical delivery include the nonsteroidal antiinflammatory drug (NSAID) nepafenac, the multitargeted kinase inhibitor prodrug TG100801, the nicotinic antagonist mecamlamine, the tyrosine kinase inhibitor pazopanib, the aminosterol compound squalamine, and the antisense oligonucleotide aganirsen.¹⁻⁶

A phase 2 trial of squalamine in patients with wet AMD has achieved 50% of planned enrollment, with 60 patients enrolled, and results should be available in the first half of next year.⁵ A phase 2 clinical study of pazopanib in patients with neovascular AMD has been terminated due to lack of efficacy in a preliminary analysis.⁷

Prodrugs are biologically inactive compounds that are metabolized in the body to produce a drug. A prodrug approach has been used in the development and evaluation of topical administration of several agents for posterior segment therapeutic applications.

Such an approach was used with the multitargeted kinase inhibitor TG100572. In a murine model of laser-induced choroidal neovascularization (CNV), systemic

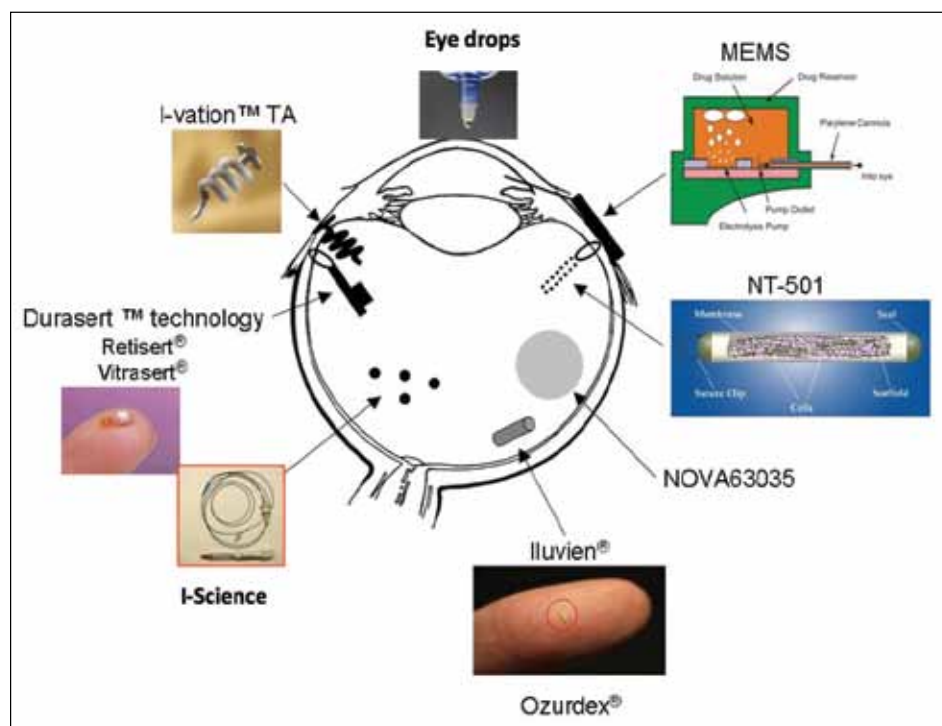


Figure 1. Numerous routes for posterior segment delivery have been or are being developed. Those pictured include topical administration, nonbiodegradable implants, biodegradable implants, suprachoroidal delivery via microcatheter, encapsulated cell technology, and micro-electromechanical systems.

delivery of TG100572 showed anti-CNV activity, but suggestions of systemic toxicity were also seen. An inactive prodrug was developed, TG100801, which converts in the eye to TG100572 by de-esterification. Topical administration of TG100801 suppressed CNV activity and reduced fluorescein leakage from the vasculature after topical delivery in rodent models.²

Topical nepafenac, also known as amfenac amide, is a prodrug that readily crosses the cornea and is converted in the eye to amfenac, a potent cyclooxygenase-1 and -2 inhibitor. A topical ophthalmic formulation of nepafenac was found to effectively penetrate into corneal tissue and reach the posterior segment in mice. In animal models this compound was found to inhibit CNV and ischemia-induced retinal neovascularization by decreasing production of VEGF.¹

TRANSSCLERAL DELIVERY

Transscleral diffusion is an appealing approach to posterior segment drug delivery because it positions the agent directly adjacent to the choroid and retinal pigment epithelium (RPE). Although periocular injection is in general safer than intraocular injection, there are numerous barriers to absorption through this route, as the drug must pass

through the episclera, sclera, choroid, Bruch membrane, and RPE. As a result, the highest drug concentrations develop in the sclera, the lowest in the vitreous, and the second lowest in the retina. In addition, subconjunctival clearance mechanisms can affect the duration of time that a depot of drug is available for absorption. Nevertheless, through the development of formulation modifications and drug delivery devices, this route can be a viable competitor to intravitreal injection.⁸

An episcleral drug reservoir has been described by Pontes de Carvalho et al.⁹ This impermeable silicone explant is attached to the sclera, and drugs placed inside have limited exposure to washout by the

conjunctival vessels. The device enhances transscleral drug delivery to the retina and vitreous compared with periocular injection. In animal models, this episcleral drug reservoir increased intravitreal bioavailability by 30- to 40-fold and the duration of action by 21-fold compared with standard sub-Tenon injection. Effective transscleral delivery of biopeptides as large as bevacizumab (160 kDa) can be accomplished using this system.^{8,9}

Another approach to transscleral delivery is a silicone holding device placed in the sub-Tenon space under the macula. With betamethasone inserted in a cavity in the device in rabbits, therapeutic levels of the agent were maintained for 4 weeks in the choroid under the macula.¹⁰

Placement of bevacizumab, formulated as a solid tablet, into the subconjunctival space has been described. The episcleral depot created in this manner resulted in increasing the duration of action of the VEGF inhibitor from 2 hours to 6 days.¹¹

INTRAOCULAR IMPLANTS

A number of intraocular implants for long-term delivery to the posterior segment have been developed, including several that have been on the market for some time. There are obvious advantages to delivery via an intraocular

implant: Barriers to bioavailability are removed, and dosing can be accomplished in known and predictable concentrations with minimal or no transient peaks. On the other hand, surgical implantation is invasive and presents iatrogenic risks, and a potent drug is required to assure a long-term therapeutic effect. The aims of implanted devices are to increase the duration of action of a given drug, reduce the effects of pulsed dosing, and improve the flexibility of drug-delivery regimens.

Both bioerodible and nonbioerodible devices have been developed. Some devices require surgical implantation, and others can be inserted in office-based procedures.

Among the nonbioerodible devices, the first 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. Vitrasert dispensed ganciclovir for up to 6 months in patients with cytomegalovirus retinitis. Retisert (fluocinolone acetonide; Bausch + Lomb), also a scleral-fixated implant based on the Durasert technology, was shown to deliver drug for up to 3 years in patients with uveitis; however, a very high percentage of patients develop cataract, and approximately 40% require surgery for glaucoma.¹²

Another surgically implanted device, using so-called encapsulated cell technology, is being developed by Neurotech. Surgically implanted in the vitreous through a scleral incision and anchored by a single suture, the device contains human RPE cells genetically modified to secrete a drug. A semi-permeable membrane allows the outward diffusion of drug and other cellular metabolites and inward diffusion of nutrients for cell survival but protects the contents from immunologic attack. One version of the Neurotech device, dubbed NT-501, secreting ciliary neurotrophic factor (CNTF), has been evaluated in a phase 2 trial for the treatment of geographic atrophy in dry AMD. A dose-dependent increase in retinal thickness was seen in that trial, along with visual acuity benefits in treated patients.¹³ Another version, NT-503, secretes a VEGF receptor Fc fusion protein that is reportedly 20-fold more efficient in neutralizing VEGF than ranibizumab. Release of this molecule for up to 1 year has been shown in rabbits. A phase 1 clinical trial of NT-503 in patients with neovascular AMD is ongoing outside the United States.¹⁴

Iluvien (fluocinolone acetonide, Alimera Sciences) is also a nonbioerodible device, but it is not affixed to the sclera and does not require surgical implantation. The device is small enough to be injected in an office setting using an inserter with a 25-gauge needle, and it provides sustained delivery of fluocinolone to the back of the eye for up to 3 years. In the randomized phase 3 FAME studies, at 36-month follow-up, incidence of cataract surgery in patients who were phakic at baseline was 80%, and 4.8% of

patients required surgery to reduce intraocular pressure.¹⁵

I-Vation, a titanium helical implant coated with drug-eluting polymer, was reported to deliver triamcinolone acetonide for 18 to 36 months in a phase 1 trial in patients with DME.¹⁶ A phase 2b trial of the device sponsored by Merck, begun in 2008, was terminated that same year.¹⁷

Ozurdex (dexamethasone, Allergan) is a bioerodible implant with a duration of action of 6 months; it is injected in an in-office procedure using a 23-gauge inserter. The device, with US regulatory approvals for the treatment of uveitis, DME, and macular edema secondary to venous occlusion, is associated with a low rate of cataract formation (5%) and a low rate of glaucoma requiring surgery (1%) at 6 months.¹⁸

A micro-electromechanical systems (MEMS) device has also been investigated for intraocular drug delivery. The MEMS device, containing a drug reservoir with a refill port, a battery, and electronics, is implanted in the subconjunctival space, and a flexible cannula from the device is inserted through an incision into the posterior segment to deliver the drug. The device uses electrolysis to convey the desired dosage volume, and it can be refilled with drug, allowing long-term therapy without repeated surgeries.¹⁹

The Port Delivery System (PDS) is another a refillable device for long-term delivery, placed surgically through a 3.2 mm scleral incision and then refillable in the office. It is tunable to accommodate large or small molecules. A phase 1 study to determine the safety and preliminary efficacy of the PDS has been completed. In this 12 month study, 20 patients with wet AMD received ranibizumab, and implant refill eligibility was determined monthly based upon predetermined criteria. Investigators reported improvement in best corrected visual acuity, reduction in macular thickness, and reduction in CNV leakage area. A longer phase 2 trial is planned for the device, which is being developed by Forsight Vision.²⁰

OTHER APPROACHES

Iontophoresis is a noninvasive technique that uses an electrical current to drive drugs in the form of ions through a tissue or membrane. A weak direct current drives charged molecules across the sclera and into the choroid, retina, and vitreous. The drug itself serves as the conductor. Iontophoresis reportedly does not affect the structure or function of the eye. Ocular iontophoresis can be used to create a drug depot in the sclera for subsequent sustained release, reducing the number and frequency of treatments.²¹ A company called Aciont is developing this technology.²²

Microneedles, with lengths of 800 μm to 1000 μm , have been used to inject micro- and nanoparticles into the suprachoroidal space without surgery in rabbit, pig,

and human ex vivo eyes. Suprachoroidal injection with microneedles targets the chorioretinal tissues better than an intravitreal injection, according to investigators. The needles puncture into the suprachoroidal space, allowing drug delivery to that space in a safe manner, and reducing systemic and local exposure.²³

The suprachoroidal space has also been investigated as a site for drug deposition for long-term delivery to the posterior segment. A decade ago, Einmahl and colleagues described injection of a bioerodible polymer gel into this space in rabbits, with echographic evidence of persistence for up to 3 weeks.²⁴ Following this, Olsen and colleagues demonstrated the principle of delivery to the posterior pole via cannulation into the suprachoroidal space in animal eyes.²⁵

A device that can be used for suprachoroidal drug delivery, the iTrack microcatheter (iScience Interventional), has been introduced commercially. The microcannula includes an optical fiber that allows transmission of light to the tip to guide surgical insertion. Tetz et al recently reported the European experience with this device in a retrospective analysis.²⁶ In 21 eyes with wet AMD unresponsive to conventional therapies the microcatheter was used to deliver a combination of 4 mg bevacizumab and 4 mg triamcinolone to the submacular suprachoroidal space. The drug was delivered successfully and atraumatically in all cases, with no serious intraoperative or postoperative complications.

Gene therapy, causing the body's own cells to produce therapeutic proteins on an ongoing basis, is a potentially exciting area for development, and a number of companies and centers are exploring these possibilities. One such company, Avalanche, is exploring the use of adeno-associated viral vectors to deliver a gene to express a therapeutic molecule in patients with AMD. A phase 1/2 clinical trial, in which 2 different doses of the biologic (called rAAV.sFlt-1), delivered via subretinal injection, will be compared with ranibizumab-only therapy, has begun in Australia.²⁷

Gene delivery is an area that is rapidly changing and growing, and a comprehensive review of efforts in this space is beyond the scope of this article.

CONCLUSIONS

The effects of chronic anti-VEGF therapy are not known. Significant barriers exist to safe and effective long-term drug delivery to the retina. Topical and episcleral drug delivery routes offer promise as alternatives, but each carries some disadvantages. For the foreseeable future, bioerodible and nonbioerodible intravitreal drug delivery systems may provide the best methods of disposition into the posterior segment. Gene therapy is a promising area that is only now in its infancy. ■

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