

Recent Advances in Back of the Eye Drug Delivery

An overview of what is new in research and development.

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INTRODUCTION

Once the active treatment agent is determined, the next biggest issue in drug development to treat diseases of the retina and vitreous are the obstacles inherent to back of the eye drug delivery. Generally, when it comes to patient safety, comfort, affordability, and ease of use, eye drops are superior to other forms of ocular drug delivery. But of all the routes (topical, systemic, intraocular, and periocular), topical is the least effective at delivering therapeutic concentrations to the retina.¹ Although a few new topical medications for retinal diseases are in clinical development, the majority of the development effort in retina therapeutics is focused on novel non-topical delivery.

Commercially available methods for intraocular drug delivery, which currently consist of only intravitreal injections and implantation, have several drawbacks. Intravitreal injections for chronic conditions, such as age-related macular degeneration (AMD), require frequent (monthly or bi-monthly) out-patient visits and can carry the risk of serious complications, including vitreous hemorrhage, retinal detachment, and endophthalmitis.² Intraocular implants require an inpatient, surgical environment and may require explantation in the case of an adverse event or if they are nonbiodegradable.

In the past few years, however, researchers have made strides toward the development of intraocular devices with fewer complications and relatively safe, sustained, and effective localized administration. Particulate polymeric drug delivery systems, known as microparticles

and nanoparticles, as well as phospholipid bilayer encapsulated drug delivery systems called liposomes, are being investigated as possible ways to lengthen drug bioavailability compared with standard solution injections. Iontophoresis, in which an electronic current is used to drive ionized drugs into tissues, is another promising new delivery technique for reaching the posterior segment and retina. In this article, we summarize some of the recent progress in ophthalmic drug delivery to the posterior segment.

INTRAVITREAL INJECTION

Since their first use in patients in 1945,³ intravitreal injections have proven to provide superior drug bioavailability in the posterior segment compared to topical and systemically delivered agents. In the past 5 years, their use has increased dramatically due to the effectiveness of anti-VEGF therapeutics, like ranibizumab (Lucentis, Genentech, Inc.) and bevacizumab (Avastin, Genentech, Inc.) for the treatment of wet AMD.^{4,5}

Unfortunately, present formulations of ranibizumab or bevacizumab typically need to be re-injected every 4 to 6 weeks. One of the ways to increase the interval between the injections could be the use of hydrogels. From the results of a recently published study in rabbits, it appears possible that thermoresponsive polymers could eventually be used to achieve sustained release of anti-VEGF proteins, such as ranibizumab and bevacizumab, lasting 3 to 6 months.⁶ At room temperature these hydrogels are in a liquid gel-like phase, but once

SUPRACHOROIDAL DRUG ADMINISTRATION FOR TREATMENT OF RETINAL DISEASE

The suprachoroidal space (SCS) is a potential space in the eye, which lies between the sclera and the choroid. A small microcatheter (iTrack-400, iScience Interventional Corporation, Menlo Park, CA) approximately 300 μm in diameter has been shown to be able to access the suprachoroidal space from a small anterior incision at the pars plana (Figure 1). The microcatheter can be atraumatically advanced to the macular region while visualizing the illuminated beacon tip of the microcatheter, both transscleral and through the retina and pupillary aperture (Figure 2). The microcatheter is US Food and Drug Administration-approved and Conformité Européenne-marked for fluid infusion and aspiration during ophthalmic surgery.

A study to evaluate the safety and pharmacokinetics of SCS drug administration to the posterior segment has been performed by Timothy Olsen, MD.¹ The study utilized a simple surgical protocol, making a small pars plana incision to access the SCS, placing and advancing the microcatheter to the posterior pole (macular region or optic nerve periphery), then delivering triamcinolone acetonide (TA). A study with 75 juvenile pigs was focused on pharmacokinetics and dose ranging using the microcatheter to deliver the drug. The study evaluated histopathology and pharmacokinetics of systemic (serum) concentrations and of ocular tissues, at time points from 12 hours to 120 days.

The results of the animal studies have not shown any significant adverse effects due to microcatheter access or the drug delivered to the SCS. Evaluation of retinal and choroidal blood flow using indocyanine green and fluorescein angiography was performed on study animals with no significant changes noted. Pharmacokinetics with TA showed significant concentrations in the ocular tissues, including the choroid and retina, for an extended period of time, up to the longest postoperative examination at 120 days. The choroid, in particular,

demonstrated a tenfold increase in drug concentration as compared to the retina over 120 days. Systemic levels of triamcinolone were also evaluated from blood samples and the results demonstrated very low levels, indicating a localized delivery to the ocular tissues from the SCS.

Currently, a European study is investigating the administration of a combination of bevacizumab and triamcinolone in the treatment of advanced age-related macular degeneration. Additional clinical studies are under assessment. To date, approximately 40 patients have received drug injections into the posterior region of the suprachoroidal space. The surgical method appears uncomplicated and no adverse events have been observed to date. An additional study is being performed to elucidate the safety and efficacy of SCS drug administration in macular degeneration patients.

1. Olsen TW, Feng X, Wabner K, et al. Cannulation of the suprachoroidal space: a novel drug delivery methodology to the posterior segment. *Am J Ophthalmol.* 2006;142(5):777-787.

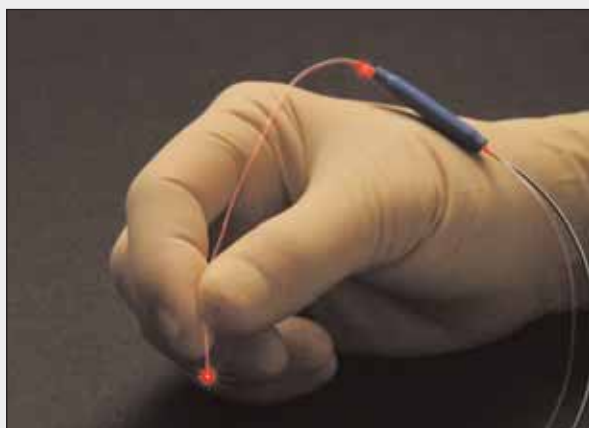


Figure 1. The ophthalmic microcatheter.

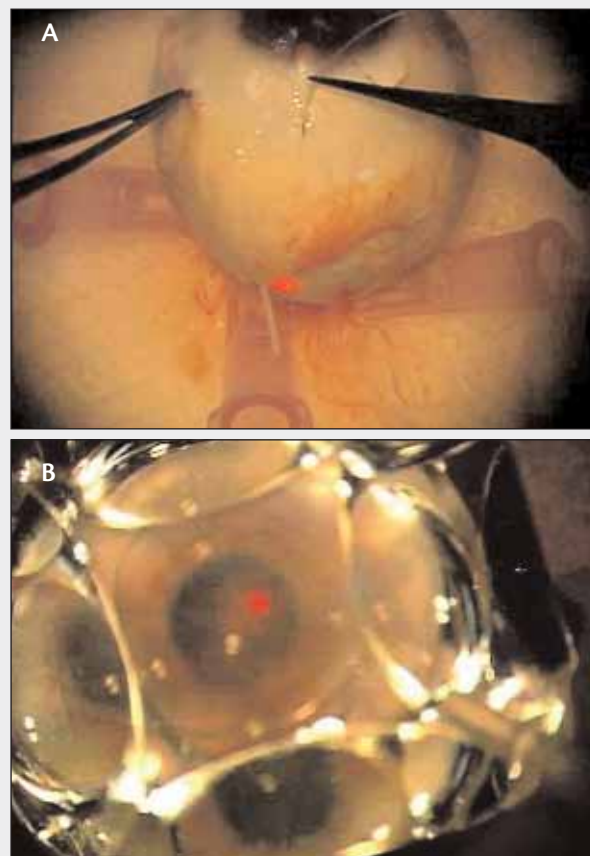


Figure 2. Views of microcatheter beacon tip in suprachoroidal space of human cadaver eye. Beacon viewed transsclerally (A). Beacon viewed transretinally through the pupillary aperture (B).

exposed to body temperature they solidify into a porous mass capable of steadily releasing protein for prolonged periods of time.⁶

In order to decrease the occurrence of complications associated with intravitreal injections, researchers are investigating new applicator systems that can provide safe, effective, and sutureless drug delivery. In initial clinical trials, a new intravitreal drug applicator known as the Dexamethasone Posterior Segment Drug Delivery System (dexamethasone DDS; Allergan, Inc.), developed for the treatment of macular edema, was well tolerated and improved visual acuity, and decreased macular thickness and fluorescein leakage in patients with persistent ME.⁷

MICROPARTICLES, NANOPARTICLES, AND LIPOSOMES

One problem that limits the effectiveness of intravitreal injections is the lack of homogeneity of the human vitreous caused by gradients. Many injected drugs do not spread uniformly throughout the vitreous and significant variability in drug concentration can exist at the target site. These issues have spurred researchers to develop new formulations which can spread more uniformly throughout the vitreous, increase the duration of action, and decrease peak concentration, through the use of micro- or nanoparticles.

Injectable nanoparticles (1 nm to 1000 nm in diameter) and microparticles (1 μ m to 1000 μ m in diameter) made of polymer encapsulated drug are relatively new delivery systems which aim to increase the duration of action to several weeks for small molecules and the penetration of an agent. Particulate systems can be in the form of a uniform polymer-drug combination, known as nanospheres and microspheres, in which the drug is dispersed homogeneously throughout a polymer matrix, or they can be in the form of nanocapsules and microcapsules, in which the drug is surrounded by spherical polymer capsule and released through its pores. The speed of release of a drug from both types of particulate systems is determined primarily by the speed of biodegradation of the polymer.⁸

Almost any drug can be encapsulated, avoiding the solubility issues inherent to liquid intravitreal injections. These delivery systems can aid in stabilizing the active form of a drug, increase half-life, increase drug absorption due to a slower elimination rate, and decrease peak concentrations reducing the risk of toxicity.⁹ One drawback is that nanoparticles and microparticles are heavier than the vitreous, so when injected they tend to sink to the bottom of the vitreous cavity, leading to an uneven drug distribution.

Particle size can also have profound effects on the drug bioavailability after injection, with larger particulate systems tending to maintain superior sustained drug release. In rabbits, polylactic acid microspheres can remain in the vitreous for 1.5 months.¹⁰ Nanoparticles diffuse more rapidly into ocular tissues possibly providing more evenly distributed bioavailability.

Presently, micro- or nanoparticles are at the stage of preclinical testing. They are being studied as ways to facilitate gene therapy for diseases of the retina. Gene-based drugs can express their protein products for prolonged periods and oligonucleotides, such as formivirsen (Vitravene, Novartis), which is currently available as an intravitreal injection for the treatment of CMV retinitis, may provide even longer lasting treatment if encapsulated. Additionally, a particular type of nanoparticles/polycation complex (PIC) micelles that can be laser-activated are in development and have successfully inserted DNA into rat retinas through a process called photochemical internalization, in which light induces the transfer of DNA directly into cells.¹¹ In a rat model of choroidal neovascularization, DNA inserted into a complex with cationic peptides and enveloped inside a photosensitizing compound was laser irradiated after subconjunctival injection to produce transgene expression of antiangiogenic factors.¹¹

In addition to polymer particulate systems, drugs can be encapsulated into liposomes, microscopic vesicles comprised of phospholipid bilayer. Liposomes can bind to a cell membrane and facilitate drug transfer across the membrane, but are less stable than particles made of polymer. Both hydrophobic and hydrophilic drugs can be encapsulated into liposomes, and research has shown that they can effectively carry genes to the rat retina following injection.¹²

INTRAOCULAR IMPLANTS

Ocular implants are designed to provide drug release into the posterior chamber for a longer period of time (months or even years) compared to particles or solutions.¹³ The implant is usually placed intravitreally at the level of pars plana during a surgical procedure. Compared to injections, drugs released from implants deliver more consistent levels, avoid the side effects associated with frequent injections, minimize peak concentrations, and result in a smaller quantity of drug needed during treatment.¹⁹ Like solution and particle injections, implants can also result in unequal drug distribution due to vitreous heterogeneity and placement of the implant peripheral to the retina to avoid disruption of the visual field. Implants do, however, come

closer than solution injections to following zero-order kinetics, in which the level of administered drug remains constant throughout the delivery period.

Ocular implants can be either biodegradable or non-biodegradable. Biodegradable implants do not require surgical removal, but often show variability in release kinetics due to differing rates of vitreous turnover and have a final burst in their drug release profile. Non-biodegradable implants provide more controlled drug

delivery but require a second surgical procedure for their removal.

Two ocular implants, Vitrasert (ganciclovir 4.5 mg, Bausch & Lomb, Rochester, NY) and the recently approved Retisert (fluocinolone acetonide 0.59 mg, Bausch & Lomb), are commercially available for the treatment of AIDS-related cytomegalovirus (CMV) retinitis, and posterior uveitis, respectively. The nonbiodegradable Vitrasert implant releases ganciclovir for approximately 5

IONTOPHERESIS DRUG DELIVERY

Iontophoresis is a method of drug delivery by which an electrical field is activated to change the permeability of cells and allow for penetration and delivery of an ionized drug to a targeted area. The EyeGate II iontophoresis drug delivery system (EyeGate Pharma Waltham, MA; Figure 1) focuses on delivery through the sclera and is currently working on methods to penetrate to the anterior and posterior segments of the eye.

Iontophoresis is a noninvasive drug delivery technology. It uses a reusable battery-powered generator and a disposable applicator. The EyeGate II uses an inert electrode that can accommodate both positively and negatively charged drugs. The mechanism of action of the inert electrode is electropulsion of same-charged molecules, which creates high velocity to achieve flux to the targeted tissue.

The surface area is important to this technology, due to current density. By delivering the current to the sclera (Figure 2), the surface area is maximized and current density is lowered, increasing the safety profile of the device.

The EyeGate II device has shown efficacy in delivering proteins, siRNA molecules, corticosteroid, and nanoparticles in rabbit studies.¹⁻³ Safety of the device applied to human sclerae was shown using a buffer solution.⁴ In March, the company completed a phase 2 study of EGP-437, a corticos-

teroid delivered using the EyeGate II drug delivery system, for the treatment of patients with dry eye disease. The company expects to report top-line results from the trial in the coming weeks, and plans to complete a second Phase II study in patients with severe uveitis later this year.

Simultaneously, EyeGate is considering expanding the EGP-437 development program to include patients with corneal graft rejection, and is researching the delivery of a broad range of compounds, including biologics and nanoparticles for the potential treatment of glaucoma, age-related macular degeneration and other serious ocular diseases.

1. Blalock T, Gee R, Manzo M, Ruiz-Perez B, Rao R. Single-dose treatment with dexamethasone phosphate resolves concanavalin A-induced dry eye in rabbits. Poster presented at the annual meeting of the Association for Research in Vision and Ophthalmology meeting; April 27-May 1 2008; Fort Lauderdale, FL.
2. Ruiz-Perez B, Blalock T, Dowie T, et al. Transscleral delivery of a 12.4 kDa protein by ocular iontophoresis. Poster presented at the annual meeting of the Association for Research in Vision and Ophthalmology meeting; April 27-May 1 2008; Fort Lauderdale, FL.
3. Patane M, Ji Guo, Schubert W, Iandrosca J. Iontophoretic delivery of PRINT® (Particle Replication In Non-wetting Templates) Nanoparticles using the EyeGate® II device. Poster presented at the annual meeting of the Controlled Release Society; July 12-16, 2008; New York.
4. Reddy M, Thimmaiah R, Cohen A, et al. Clinical experience with the EyeGate II® delivery system: safety and tolerability in healthy male and female adult volunteers. Poster presented at the annual meeting of the Association for Research in Vision and Ophthalmology meeting; April 27-May 1 2008; Fort Lauderdale, FL.



Figure 1. The EyeGate II delivery system.

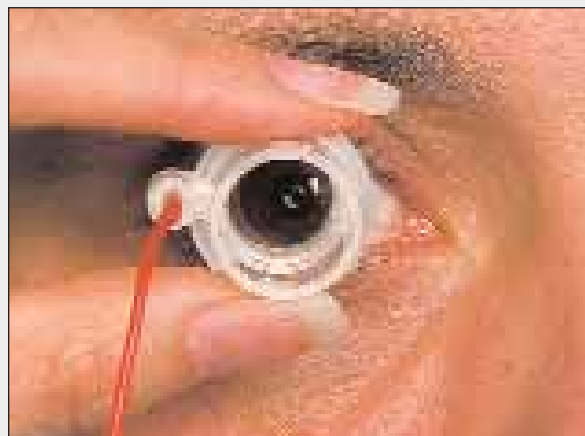


Figure 2. The applicator is placed directly upon the sclera.

to 8 months, while Retisert (also nonbiodegradable) can release fluocinolone for up to 30 months, and is currently the only approved treatment for noninfectious uveitis of the posterior segment.¹⁴

Recently, a novel doughnut shaped biodegradable implant has been investigated in vitro for delivery of ganciclovir and foscarnet. The central hole within the implant allows for easier suturing, and the implant does not ever need to be removed from the vitreous.¹⁵ Other intraocular implants in development include the biodegradable Posurdex (Allergan, Irvine, CA), a small pellet which delivers dexamethasone for the treatment of macular edema associated with retinal vein occlusion, and Iluvien (Alimera, Alpharetta, GA), a nonbiodegradable insert which releases the corticosteroid fluocinolone acetonide for the treatment of diabetic macular edema and is designed to sustain therapy for 24 to 36 months.¹⁶ Both implants are currently in phase 3 trials.

IONTOPHORESIS AND SUPRACHOROIDAL DRUG ADMINISTRATION

Iontophoresis (see "Iontophoresis Drug Delivery System" on page 49 for more information) is a method of drug delivery in which an electrical current drives charged drug molecules through either the cornea or sclera and into the vitreous and retina.¹⁷ It could offer a noninvasive alternative to intravitreal injections, particles, or implants. In a rabbit model, a drug loaded hydrogel iontophoresis system was able to produce high concentrations of dexamethasone in the retina following transcleral administration.¹⁸ The current leader in clinical ocular iontophoresis is EyeGate Pharma (Waltham, MA), which is currently investigating this technology for drug delivery.¹⁹

For patients with retinal tumors, iontophoresis is being researched as a potential noninvasive alternative to the use of systemic chemotherapy. In a mouse model, investigators found that iontophoresis could successfully transport carboplatin, a cytotoxic compound for treatment of retinoblastoma, to the retina.²⁰

Another delivery mechanism that is currently under study is suprachoroidal drug delivery. IScience Interventional Corporation (Menlo Park, CA) has developed a microcatheter system that shows the ability to access the suprachoroidal space (See "Suprachoroidal Drug Delivery" on page 47 for more information). Suprachoroidal drug delivery has been evaluated in animals in a safety and pharmacokinetic study with trimacinalone acetone.²¹ A study is underway in Europe to evaluate the delivery of combined bevacizumab (Avastin, Genentech, Inc.) and triamcinolone acetone for AMD and another study is planned for the United States later this year.

CONCLUSION

Several novel ophthalmic drug delivery systems are available or in development for the posterior segment eye diseases. The intensive efforts in this field offer hope for more effective, precise and safe treatment to patients with diseases of the retina and vitreous, the primary cause of blindness in the developed world. ■

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