

Topical Drug Delivery for Posterior Segment Disease

Novel formulations offer possibilities for efficacious therapies through topical routes.

BY DANIEL F. KIERNAN, MD; AND JENNIFER I. LIM, MD

Posterior segment diseases, including age-related macular degeneration (AMD), diabetic retinopathy, diabetic macular edema (DME), retinal vein occlusion (RVO), uveitis, and endophthalmitis, are responsible for causing visual impairment and blindness worldwide. The use of topical, systemic, transscleral, and intravitreal administration of pharmaceutical agents for treating these conditions has been the subject of myriad laboratory and clinical trial investigations.

Until recently, and with a few notable exceptions,¹⁻⁴ there was limited evidence from large clinical trials that pharmacotherapy demonstrated a useful biological effect or comparable clinical outcome compared with laser, vitreoretinal surgery or other approaches for the primary treatment of posterior segment disease. Within the past decade this paradigm has shifted, and drug delivery to the posterior segment has become important for treating several major vision-threatening ocular conditions, with strong evidence demonstrating superior efficacy compared with previous gold standards for treating neovascular AMD and central RVO with intravitreal vascular endothelial growth factor (VEGF) inhibiting agents⁵⁻⁸ and corticosteroids⁹ respectively.

The use of intravitreal implants has also seen a recent increase, with several new corticosteroid-containing devices in or about to enter clinical practice for the treatment of a variety of posterior segment conditions. These may offer a longer duration of effective drug concentration, thereby potentially reducing the frequency of treatments.

Additionally, advances in nanotechnology have led to the experimental use of topical permeation-enhancing liposomes and emulsions and biodegradable microspheres that can contain ocular pharmacologic agents

and thereby provide improved intravitreal delivery of a variety of medications. These technologies may allow sustained-release drug therapy and improve the side-effect profiles of currently available clinical treatments.

ANATOMIC CHALLENGES OF POSTERIOR SEGMENT DRUG DELIVERY

High intravitreal drug concentrations are required in the treatment of posterior segment diseases; however, the anatomy, physiology, and biochemistry of the eye make the eye resistant to significant concentrations of foreign substances. An understanding of the characteristics of the blood-eye barrier is important in efforts to achieve drug delivery for ophthalmic diseases. This barrier, which compartmentalizes the eye, is maintained by tight junctions at the retinal vascular endothelium, the iris vascular epithelium, and the nonpigmented ciliary epithelium.¹⁰ It comprises two components: an outer component formed by junctional complexes of the retinal pigmented epithelium (RPE) and the pigment epithelial cells of the pars plana, and an inner component formed by tight junctions between endothelial cells in the retinal capillaries. The barrier blocks pathogens from reaching ocular tissues but also hinders systemic pharmacologic agents from reaching potential targets inside the eye.^{11,12} It also reduces convection of molecules because it has no cellular components and is selectively permeable to more lipophilic molecules.¹³ Because of this, many strategies developed to deliver treatment for posterior segment disease have failed to show clinical efficacy. Figure 1 demonstrates an overview of potential mechanisms for posterior segment drug delivery.

TOPICAL DRUG ADMINISTRATION

Topical drug application, the most common method of ocular drug delivery, is useful in the treatment of many anterior segment disorders.¹⁴ This noninvasive mode of drug delivery selectively targets the anterior chamber structures; however, the cornea represents a significant barrier for efficient drug delivery. The corneal epithelium is a lipophilic tissue and contributes to a major reduction in penetration by hydrophilic drugs; less than 5% of the total administered topical dose reaches the aqueous humor,¹⁵ and far less penetrates into the posterior segment.^{16,17} A major fraction of drug following topical administration is lost through lacrimation, tear dilution, nasolacrimal drainage, and tear turnover.¹⁸ Such pre-corneal losses result in very low ocular bioavailability.

There are, however, several approaches to altering the method and route of topically applied agents that may increase their posterior segment penetration. These include use of cyclodextrins, prodrug formulations, permeability enhancers, transcorneal diffusion, and transconjunctival or transscleral penetration directly through the pars plana.

Cyclodextrins—cylindrical oligonucleotides with a hydrophilic outer surface and a lipophilic inner surface that are capable of forming inclusion complexes with lipophilic drugs—have been combined with corticosteroids, chloramphenicol, diclofenac, cyclosporine, and sulfonamide carbonic anhydrase inhibitors to form complexes that demonstrate significant corneal penetration.^{19,20} One study determined that dexamethasone-cyclodextrin complexes delivered topically to rabbit eyes reached significant levels in the retina and vitreous.²¹ This approach may be useful in the treatment of vitreoretinal diseases requiring chronic drug delivery.

Prodrug strategies have been attempted for improving the therapeutic efficacy of many drug molecules. Prodrug formulations use pharmacologically inactive derivatives of drug molecules that are better able to penetrate the cornea than the standard formulation of the drug.^{22,23} Within the cornea or after corneal penetration the prodrug is metabolized to the active parent compound. Most prodrugs, including the antiviral prodrugs ganciclovir and acyclovir, are delivered conventionally by topical application.

Although straightforward application of topical antiviral agents is insufficient for effective posterior segment drug concentration, enhancement of drug absorption has been shown when these drugs are combined with liposome permeability enhancers.

TOPICAL ADMINISTRATION OF LIPOSOMES

Liposomes are composed of a membrane-like lipid bilayer formed from phospholipids and cholesterol surrounding an aqueous compartment, which allows encapsulation

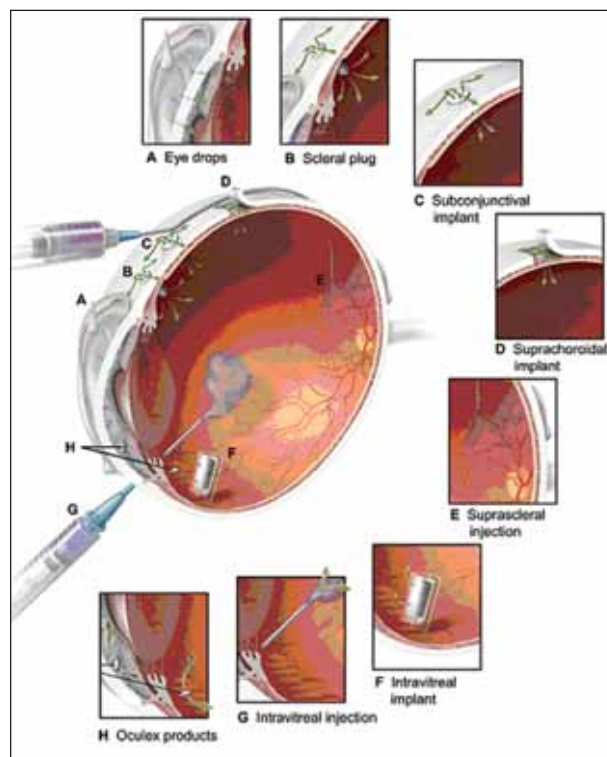


Figure 1. Sites and methods for ocular drug delivery to the eye. Various methods for delivery of drugs to the anterior and posterior chambers of the eye are illustrated, including sites for conventional drug delivery and newer routes. Reproduced by permission from Davis JL, Gilger BC, Robinson MR. *Curr Opin Mol Ther.* 2004;6(2):195-205. Copyright 2004 Thomson Corporation.

of a variety of drug molecules including proteins, nucleotides, and plasmids.²⁴ The liposome membranes are stable and can be deformed without disruption, potentially allowing injection through small-gauge needles. As a permeability enhancer, the liposome may facilitate slow drug release without alteration of the intrinsic characteristics of the encapsulated pharmaceutical agent. The binding affinity of liposomes to the cornea suggests that that uptake by the cornea is greatest for positively charged liposomes. In rabbit corneas, positively charged liposomes demonstrated enhanced transcorneal flux of penicillin G more than fourfold compared with controls.²⁵

Similarly, immunoliposomes of antiviral drugs, such as ganciclovir and iododeoxyuridine, using monoclonal antibodies to glycoprotein D of herpes simplex virus, have also been formulated and reported.²⁶ The permeability of ganciclovir solution was compared with a liposomal formulation containing ganciclovir. Transcorneal permeability and area under the curve were 3.9- and 1.7-fold higher than the solution, respectively. Ocular

tissue distribution was also higher in the sclera, cornea and vitreous humor with the liposomal formulation.²⁶ Another study reported that site-specific and sustained release immunoliposomes may act as improved vehicles for drug delivery in treatment of ocular herpes simplex virus infection. Antisense oligonucleotides that can be efficaciously used to treat ocular diseases such as cytomegalovirus retinitis can be encapsulated in liposomes and efficiently targeted to the retina.²⁸

In a rabbit model, a single injection of liposome-encapsulated 100 µg cidofovir prevented herpes simplex virus retinitis for more than 8 months.²⁹ Studies by Bochot et al showed that 37% of administered antiviral oligonucleotides were retained in the vitreous humor after 15 days.³⁰ Another group demonstrated that administration of liposome-encapsulated antiviral phosphodiester oligonucleotides resulted in sustained release into the vitreous and choroid, compared with release from a solution alone, and in a reduced distribution within the sclera and lens.³¹ Similar to microparticles and nanoparticles, liposomes can also impair vitreous clarity.³⁰ Furthermore, the long-term effects of liposomal injections in the eye are unknown.

Despite some advantages that make liposomes a potentially useful system for ocular drug delivery, the utility of liposomes may be limited by a short shelf life, limited drug-carrying capacity and difficulty associated with thorough sterilization. Additionally, using topical delivery, liposomes may not be able to release the entire payload of active drug relative to a free solution form.³¹ Liposomal formulations, however, can release active drug, especially oligonucleotides, in a sustained manner following intravitreal injection.²⁸ PEGylated liposomes containing oligonucleotides resulted in a higher percentage of active drug (30% of the total dose) after 2 weeks compared with release from solution. Some researchers have formulated liposomes coated with an envelope of inactivated hemagglutinating virus of Japan to treat choroidal neovascularization (CNV) in rats. They successfully delivered phosphorothioate oligonucleotides to inhibit VEGF.³⁰ Direct intravitreal administration of liposomes is a more definitive method of posterior segment drug delivery than topical administration, but it is more invasive and associated with greater risks of bleeding and infection. Furthermore, frequent injections may be required depending on the half-life of the pharmacologic agent.

IONTOPHORESIS

Iontophoresis is a noninvasive technique in which a small electric current is applied to enhance ionized drug penetration into tissue.^{33,34} The drug is applied with a weak electric current that drives charged molecules across the sclera and into the choroid, retina, and vitreous body.³³ A ground electrode of the opposite charge is placed elsewhere on the

body to complete the circuit. The drug serves as the conductor of the current through the tissue. Transcorneal and transscleral iontophoresis have been studied with a variety of ophthalmic drugs in animals and to a limited extent in humans. Iontophoresis is noninvasive and therefore avoids the risks of surgical implantation or intravitreal injections, and it does not affect drug half-life.³⁵

Animal studies have shown that transscleral iontophoresis can be used to deliver therapeutic levels of bioactive proteins to the retina and the choroid, which may offer a viable and less invasive alternative for delivering anti-VEGF agents.^{36,37} Human studies involving healthy volunteers showed no clinically significant ophthalmologic changes following transscleral iontophoresis.³⁸ A burning sensation was noted by a few subjects at the applicator site at higher current levels. Iontophoresis has the advantage of being noninvasive and therefore avoids the risks of surgical implantation or intravitreal injection.

TRANSSCLERAL DRUG DELIVERY

Transscleral drug delivery is another transport mechanism for posterior drug delivery with topical drops. Because the sclera is made up of fibrous tissue, it offers less resistance to permeability of drugs than the cornea, allowing improved absorption and increased retinal and intravitreal concentrations.³⁹ Molecules up to approximately 70 kDa can readily penetrate the sclera, whereas the size limit to pass through the cornea is less than 1 kDa. In addition, the sclera provides a large surface area of 17 cm², comprising 95% of the surface area of the human eye. This area provides a large region for transscleral drug absorption and allows delivery of neuroprotective agents, antioxidants, or angiostatic agents to specific regions of the retina.⁴⁰ Even large molecules such as tissue plasminogen activator have been shown to reach significant intraocular drug levels in the posterior segment.⁴¹⁻⁴³

OT-551 (Othera Pharmaceuticals) is a topical antioxidant that was investigated as a treatment for dry AMD. The drug is a small lipophilic molecule that readily penetrates the cornea and is converted by ocular esterases to TEMPOL-H (TP-H), an active metabolite that is a potent free-radical scavenger. In animal studies, topical therapy has resulted in excellent ocular bioavailability, with significant levels of TP-H achieved in the retina.⁴⁴

The drug OT-551 was shown to possess antiinflammatory, antiangiogenic, and antioxidant properties. OT-551 has also been shown to protect against oxidative damage in vitro, protect against light damage in vivo, suppress photoreceptor cell death in animal models, and block angiogenesis stimulated by growth factors.⁴⁵ Based on these preclinical data, OT-551 was investigated as a therapy for geographic atrophy for AMD. A 2-year, phase 2

trial, known as the OT-551 Multicenter Evaluation of Geographic Atrophy (OMEGA) study, was halted after 18 months due to an apparent lack of efficacy in preventing the enlargement rate of GA in AMD.

Mecamylamine (ATG003), a nicotinic antagonist that was approved by the US Food and Drug Administration as an antihypertensive and as a smoking-cessation medication, was developed by CoMentis, Inc. A phase 1 trial in patients with neovascular AMD has been completed, and a phase 2 trial is currently enrolling patients. Inhibition of the nAChR pathway blockade may inhibit angiogenesis, and thus the use of mecamylamine may be an effective adjunct to anti-VEGF treatment, including ranibizumab.⁴⁵

For neovascular AMD, the anti-VEGF agent pazopanib, developed by GlaxoSmithKline, has completed both phase 1 safety and efficacy trials and is currently being evaluated in several phase 2 trials. Pazopanib blocks tyrosine kinase receptors including VEGF receptors 1, 2, and 3, PDGFR, c-Kit, and fibroblast growth factor receptor 1, and has been shown to inhibit CNV in a mouse model.⁴⁶ By blocking multiple receptors, this agent may inhibit new blood vessel development and induce regression of established CNV.

THE EMERGING ROLE OF TOPICAL DRUG DELIVERY TO THE POSTERIOR SEGMENT

Effective treatment of ocular diseases is a formidable challenge for physicians because of the nature of the diseases and the presence of ocular barriers precluding delivery to the posterior segment. An ideal therapy should maintain effective levels of drug for long durations following a single application.

Drug delivery to the posterior segment by the topical route is limited in the amount of effective drug delivered, although permeability enhancers may make this route of delivery more effective in the future. There has been considerable effort in the development of transscleral drug delivery systems; however, these modes have yet to demonstrate a clinical benefit over intravitreal delivery for treating retinal diseases.

Drug delivery by periocular route can potentially overcome many of these limitations and provide sustained drug levels in a number of ocular pathologies. Novel delivery approaches using sustained-release intravitreal implants will likely provide much-needed benefit for patients with conditions resistant to more conservative therapy, although long-term data on ocular tissue response to continuous corticosteroid exposure is lacking.

Periocular depot injections of microparticulate-encapsulated drugs or transscleral iontophoresis may also allow transscleral drug transfer into the eye and provide a technique less invasive than intravitreal injection or sustained-release implants.

For neovascular AMD, however, frequent injections of anti-VEGF compounds are the current standard of care. Unmet needs in this population include therapies that reduce the treatment burden and improve visual acuity in a greater percentage of patients. Transporter targeted delivery, microspheres, liquid drug delivery systems (Verisome, Icon Bioscience Inc.)⁴⁷ and thermoresponsive hydrogels⁴⁸ are also strategies that show promise for incorporation with many pharmacologic drug molecules. Colloidal carriers can substantially improve current therapy and may emerge as an alternative for periocular administration.

In the future, the efforts of pharmaceutical researchers will likely be placed on achieving noninvasive, sustained drug release for eye disorders of the posterior segment. ■

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Update on Endophthalmitis After Anti-VEGF Injection

Standardized preparation may be a factor in low infection rate.

BY ANDREW A. MOSHFEGHI, MD, MBA

In 2005, with the approval of the first pharmacologic agent for inhibition of vascular endothelial growth factor (VEGF) to treat neovascularization secondary to age-related macular degeneration (AMD), the anti-VEGF era in ophthalmology began. This era has been marked by the rapid adoption of pharmacologic therapy for neovascular AMD by physicians. Intravitreal injections are given on a frequent basis, often as frequently as monthly. The primary indication for anti-VEGF therapy is for treatment of neovascular AMD, but anti-VEGF injections are also given for other conditions, including central and branch retinal vein occlusions, diabetic macular edema, proliferative diabetic retinopathy, cystoid macular edema, and neovascular glaucoma. Figure 1 shows the increase in the number of anti-VEGF intravitreal injections given at Bascom Palmer Eye Institute's clinics over 4 years.

With these increases in patient volume and number of injections has come increased concern about potential

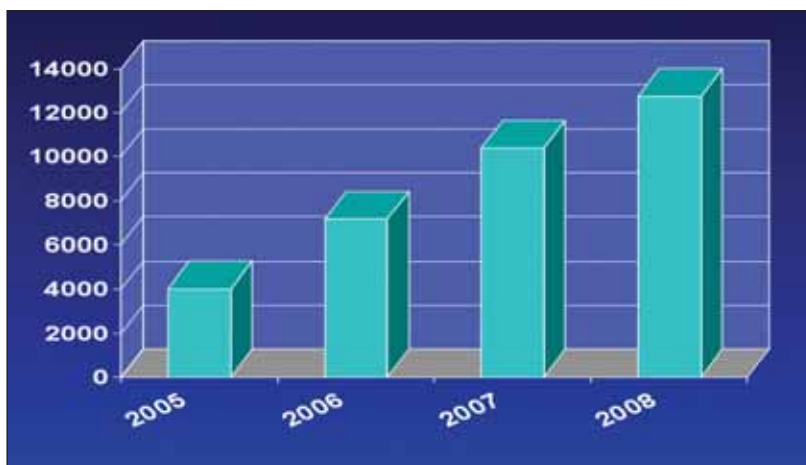


Figure 1. The increase in the number of anti-VEGF injections at BPEI over 4 years.

complications. Rare complications of intravitreal injections include iatrogenic cataract and retinal detachment. More common, although still rare, is the potentially devastating possibility of intraocular infection, or endophthalmitis.

In order to guard against this much-feared complication, it is helpful to have useful information about its incidence. Therefore, we undertook a retrospective study of the incidence of endophthalmitis after intravitreal

anti-VEGF injection at the Bascom Palmer Eye Institute. A full report will be forthcoming in the peer reviewed literature, but preliminary results of the study were presented recently at the Angiogenesis 2010 meeting.¹ This article summarizes some of the information presented there.

LOW RATES OF INFECTION

The purpose of the study was to determine the safety of intravitreal anti-VEGF injections: specifically, to identify the rate of culture-proven endophthalmitis after intravitreal anti-VEGF injections, and to characterize the cases of treated endophthalmitis encountered during this period.

The anti-VEGF era was defined as the period beginning in 2005 with the regulatory approval of pegaptanib sodium.² That approval was followed by reports of off-label use of bevacizumab for treatment of wet AMD,³ and then by the regulatory approval of ranibizumab.^{4,5}

Our study reviewed data from January 1, 2005, through December 31, 2008. To determine the rate of infection, the denominator we used was all intravitreal anti-VEGF injections performed at the Bascom Palmer Eye Institute by Bascom Palmer retina specialists during that period. The numerator was all cases of clinically suspected endophthalmitis: that is, any case that the physician treated as endophthalmitis, not necessarily culture-positive cases. Standard management for endophthalmitis was intravitreal injection of antibiotics or pars plana vitrectomy with intravitreal injection of antibiotics.

During the period under study, 34,278 intravitreal anti-VEGF injections were administered at the four Bascom Palmer Eye Institute sites. Nine cases of clinically suspected and treated endophthalmitis were identified. Five were culture positive on vitreous tap, and four were culture negative. The rate of suspected and treated endophthalmitis among 34,278 total cases was therefore 0.026%, and the rate of culture-positive cases was 0.015%.

Of the nine cases of clinically suspected endophthalmitis, five eyes (56%) had been treated with bevacizumab ($5/22,030 = 0.023\%$), four (44%) with ranibizumab ($4/10,329 = 0.038\%$), and none with pegaptanib.

Two cases (0.009%) were culture-positive after bevacizumab injection, and three (0.03%) after ranibizumab injection (Figure 2).

ACHIEVING A LOW INFECTION RATE

With minor exceptions, the preparation and antibiotic prophylaxis protocols for intravitreal anti-VEGF injections at Bascom Palmer Eye Institute are standardized among all physicians. This standardization may be one factor that has helped us to achieve a low rate of infection after anti-VEGF injection.

No preinjection antibiotic prophylaxis is given: that is,



Figure 2. Representative slit-lamp photograph of a patient with endophthalmitis 1 day following an intravitreal anti-VEGF injection.

antibiotics are not started in the days before the patient's clinic visit.

The preparation is performed by registered nurses in dedicated injection rooms to facilitate patient flow. An eyelid speculum is affixed. The prep technique includes application of 5% povidone-iodine on the conjunctival surface; periocular application of povidone-iodine swab to the eyelids, lashes and adnexa; and topical application of cotton swabs soaked with 4% lidocaine. The cotton swabs are pressed against the sclera in the area of the anticipated injection site, both to soften the eye and to administer the anesthetic. After that, a drop of 5% povidone-iodine is placed on the injection site. This swab-betadine cycle is repeated three times. After the third time, the physician, wearing clean but nonsterile gloves, administers the injection. At the conclusion, typically a drop of antibiotic is placed on the eye, and the eyelid speculum is removed. Intraocular pressure is checked at the conclusion of the injection. Anterior chamber paracenteses are not performed.

Use of postoperative antibiotics varies among physicians at our center. For a large portion of the period of time described in our study, patients were prescribed a topical antibiotic four times daily for 3 days following the injection. Over the past 2 years, a large proportion of Bascom Palmer physicians have opted not to use postoperative antibiotics. (I am among the minority who still prescribe postoperative antibiotics.) It is notable that the Diabetic Retinopathy Clinical Research Network, in recent clinical trials involving the use of anti-VEGF agents,⁶ has not made it mandatory to use postoperative antibiotics.

DISCUSSION AND CONCLUSIONS

The rates of infection in our series of more than 34,000 anti-VEGF intravitreal injections were very low (0.03%) and are comparable with rates reported in other series of anti-VEGF intravitreal injections similar

to ours,⁶⁻⁹ and in the phase 3 clinical trials of pegaptanib¹ and ranibizumab.^{3,4}

Streptococcal species were the most common infectious agents identified in our series and were associated with poorer outcomes than the one staphylococcal infection.

No significant differences were seen between the rates of infection with the anti-VEGF agents included, except that there were no infections in the relatively small number of cases in which pegaptanib was given. The data do not suggest an additional level of risk because of the extra steps involved in the pharmacy preparation of bevacizumab; in fact, the percentage of infections was lower with bevacizumab than ranibizumab, although not statistically significantly so.

One potential strength of this series compared with other large series using pooled data from multiple centers is that, with minor exceptions, the preparation and antibiotic prophylaxis techniques at our center are standardized. With pooled data, it can be difficult to tease out the techniques behind the numbers. The greater homogeneity of our data may make our results easier to interpret. ■

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