Highlights from *RT*’s Feature Series: The Path to the Retina

Drug delivery devices remain a hot topic of interest to many retina specialists.

The management of posterior segment eye disease has changed dramatically over the past decade. Previously, surgical procedures (either incisional or laser) were the gold standard for pathologies like age-related macular degeneration, diabetic macular edema (DME), and retinal vein occlusion. In the 2000s, however, a wave of agents ushered in a new era of pharmacotherapeutic management of posterior segment diseases. It was during this time period that anti-vascular endothelial growth factor (anti-VEGF) agents emerged as a strategy to slow or stop the progression of age-related macular degeneration. Since that time, studies have evaluated the various anti-VEGF agents for DME, central and branch retinal vein occlusion, and a host of other pathologies.

A well-known drawback to the medical management of retinal pathologies is that patients are often subject to frequent if not monthly injections, creating a practical and economic burden for treating physicians, patients, and their families. Because of this, there is significant interest in devising strategies to reduce the “shot burden” while maintaining the safety and efficacy of intravitreal agents.

In his article, Dr. Boyer noted that although topical delivery to the posterior segment is difficult to achieve, “the topical route remains attractive because of the ease of access and application.” Nevertheless, there are several devices in development or in use that might change how drugs are delivered to the back of the eye.

**TOPOICAL DELIVERY**

In his article, Dr. Boyer noted that although topical delivery to the posterior segment is difficult to achieve, “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 that are being investigated for posterior segment effects after topical delivery include the nonsteroidal antiinflammatory drug nepafenac, the multitargeted kinase inhibitor produg TG100801, the nicotinic antagonist mecamylamine, the tyrosine kinase inhibitor pazopanib, the aminosterol compound squalamine, and the antisense

**AN UPDATE ON THE PIPELINE**

Affecting sustained delivery of a therapeutic agent to the posterior segment is no easy task. According to David S. Boyer, MD, several strategies have been tried to varying degrees of success. Each strategy has obvious potential but also some notable drawbacks: “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.”

Nevertheless, there are several devices in development or in use that might change how drugs are delivered to the back of the eye.
Several of these agents are still in the animal testing phase (nepafenac and TG100801), although each of these has demonstrated biologic plausibility, both in penetrating through the cornea and in delivering therapeutic effect. A human trial of squalamine, sponsored by its manufacturer Ohr Pharmaceutical Inc., is currently enrolling patients. The drug is thought to inhibit several growth factors involved in neovascularization.

**TRANSSCLERAL DELIVERY**

This could seem advantageous for drug delivery, because the agent would be proximal to the choroid and retinal pigment epithelium. “Although periocular injection is in general safer than intravitreal injection, there are numerous barriers to absorption through this route, as the drug must pass through the episclera, sclera, choroid, Bruch membrane, and [retinal pigment epithelium]. 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.”

This method of drug delivery has attracted particular attention because of the potential to infuse rather large biopeptides (ie, anti-VEGF agents) through the sclera. Early studies with proprietary devices suggest increased bioavailability and sustained duration of activity.

**INTRAOCULAR IMPLANTS**

There are currently a few intraocular implants already available on the US market. This category has been in use since 1996, when the Vitrasert (ganciclovir intravitreal implant; Bausch + Lomb) gained approval for treatment of cytomegalovirus secondary to HIV/AIDS infection.

“[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 ensure 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 candidates in development are a surgically implanted device using encapsulated cell technology (several versions containing differing agents are in development by Neurotech); the iluvien injectable implant (fluocinolone acetonide, Alimera Sciences); I-Vation (Merck), a drug-eluting polymer emitting triamcinolone acetonide; a microelectromechanical system with a refillable port; and the Port Delivery System, which has already gone through phase 1 clinical trials using an anti-VEGF agent. The bioerodable Ozurdex (dexamethasone, Allergan) implant has indications for treatment of uveitis, DME, and macular edema secondary to venous occlusion.

**OTHER APPROACHES**

According to Dr. Boyer, a number of novel strategies for affecting sustained or improved drug delivery to the posterior segment are in development. Some notable examples include iontophoresis, or the use of an electrical current to accelerate drug delivery through corneal tissue; suprachoroidal injection via specially designed microneedles; microcannulas for drug deposition to the suprachoroidal space; and gene therapy designed to program the body’s cells to produce therapeutic proteins.

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THE COMPLEXITY OF TRIAL DESIGN

The complexity of navigating the US regulatory system has been a source of angst for those in the pharmaceutical and device industries for a number of years. Estimates suggest it may take 8 to 12 years and an investment close to $1 billion to bring a product to market—and this accounts only for successful candidates, because the actual failure rate is unknown. But if bringing a drug or device to market is complicated enough, what happens when a product contains elements of both?

The editors of Retina Today interviewed executives at three companies currently developing drug delivery devices: Ken Green, PhD (Alimera Sciences); Yehia Hashad, MD (Allergan, Inc.); and Roman Rubio, MD (Genentech). The discussion that ensued revealed the careful planning necessary to steer a candidate drug delivery device through the pipeline. Following are some excerpts from the virtual roundtable.

Retina Today: What are some of the nuances of selecting and testing a drug delivery system?

Yehia Hashad, MD: A drug delivery system adds another variable into the equation of assessing safety and efficacy. If a treatment is determined to be unsafe or ineffective in a study using a new drug delivery system, one has to ask whether that is because of the drug, the delivery system or a combination of the two things. … Extensive preclinical modeling and testing are required to pair the optimal delivery technology with the right drug.

Roman Rubio, MD: Ranibizumab (Lucentis; Genentech) has regulatory approvals for treatment of chronic retinal diseases such as age-related macular degeneration and diabetic macular edema (DME), as well as the potentially more acute condition of retinal vein occlusion. … For a more acute disease such as branch retinal vein occlusion which has the possibility of spontaneous resolution, one would want to consider technologies that provide a less permanent solution, for example, a biodegradable delivery system. By contrast, a more permanent delivery technology, such as an implantable device, may be more attractive in terms of being able to provide a more permanent treatment option for chronic disease states.

Ken Green, PhD: To develop a long-acting drug-release technology, it is important to understand the characteristics of the disease you wish to treat. To treat herpetic keratitis, you would not think of multiyear delivery. But for DME, the US Food and Drug Administration (FDA) requires 3-year trial data. While we were developing Iluvien (fluocinolone acetonide intravitreal implant, Alimera Sciences), the FDA allowed us to submit after 2 years of follow-up, but we still had to run a 3-year trial and ultimately submit 3 years of data. We knew that a technology with the potential for multiyear delivery would minimize the number of intravitreal administrations required, so that should be an advantage. What we didn’t know but since have learned is, that in many patients, DME transitions after a period of time to a more inflammatory state that requires long-term therapy. The basis of our regulatory approval in Europe, and the basis of our current proposal to the FDA, is that our product is not for treatment of DME in general but for this subset of chronic DME. … Our data have shown that (A) this subset of DME exists, and (B) it is highly responsive to corticosteroid therapy. It appears that a continuous, very low exposure of corticosteroid is providing a unique benefit in chronic DME. This was not part of our original hypothesis; rather, it emerged with the results of the clinical trials.

RT: How do you identify a drug that might be appropriate for use in a sustained delivery mode? How do you identify a sustained-delivery vehicle that matches best with your chosen drug?

Dr. Hashad: When identifying a drug compound for a sustained delivery platform, a number of considerations are evaluated, including assessment of the pharmacodynamics and pharmacokinetics of the compound and the pharmacologic target. Essentially, we consider how much drug we need, the physical target and, once we get it there, how quickly it clears from the eye. Knowledge of the potency at the intended target paired with the compound’s pharmacodynamics and pharmacokinetics allows us to determine the feasibility of sustained release. From a formulation standpoint, we then look at the physical and chemical properties of the drug, including solubility, lipophilicity, excipient compatibility, stability and, in some instances, crystallinity. All of these factors help determine what kind of drugs would be best suited for a specific sustained-delivery vehicle platform. Ideally, an integrated cross-functional development team facilitates the optimization of drug properties and delivery systems for sustained delivery.

RT: How do you design a clinical trial to test a delivery system, as opposed to a drug (assuming the drug in question is an established therapy in standard delivery mode)? What are the special considerations in this type of trial design?

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**Dr. Rubio:** One of the key factors in the clinical evaluation is the ability of this sustained delivery technology to deliver drug over an extended period of time. As a result, longer observation periods, both from a safety and efficacy perspective, may make the trial longer than for a product that is dosed monthly, for example. The minimum amount of time for such trials, before being able to draw definitive conclusions around the performance of the device, would vary based on the target duration that one is evaluating.

**RT:** What kinds of regulatory challenges are (or will be) faced, getting approval for a new delivery mode for an established drug?

**Dr. Hashad:** In general, every new drug needs an adequately designed trial that is placebo-controlled, randomized, and multicenter to establish safety and efficacy. With new drug delivery platforms, this also is the case, but there are additional requirements that must be taken into consideration. Most drug delivery systems focus on reducing treatment burden or improving patient compliance. Regulatory authorities, however, do not consider either of those attributes as primary endpoints in a clinical study. Drug delivery systems are also viewed by regulatory authorities as combination products looking at both the drug and the delivery system. Often the components of combination products can be evaluated separately when historical data are available to support the history and safety of each component. Even with an established drug in a new delivery system, although historical data may play a supportive role for the drug, the primary focus of regulatory questions often centers on the drug and delivery system interaction when safety and efficacy are assessed.

In addition to regulatory issues, [chemistry, manufacturing, and controls] can prove challenging when seeking approval of a new delivery platform and may require a high level of technical expertise, especially with biologics.

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