

Challenges of Trial Design for Extended Drug Delivery

A virtual round table with industry.

**WITH KEN GREEN, PhD (ALIMERA SCIENCES); YEHIA HASHAD, MD (ALLERGAN);
AND ROMAN RUBIO, MD (GENENTECH)**

The ongoing burden of frequent intravitreal injections has made the prospect of extended drug delivery to the posterior segment an attractive goal. Several devices for sustained delivery have been developed or are in the process of development, as detailed in the article by David M. Boyer, MD, on page 52. In order to understand some of the challenges involved in developing devices or vehicles for long-term drug delivery to the posterior segment, Retina Today interviewed executives at 3 ophthalmic companies who have extended-release products in development or in the marketplace. Their replies are presented here as a virtual round table.

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 2 things. That is why extensive preclinical testing is crucial to our understanding of both the intricacies of the drug delivery system process and the safety of a particular drug in combination with the delivery system. We have found that medications may work well with certain drug delivery technologies but not work well with others. 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 (AMD) and diabetic macular edema (DME), as well as the potentially more acute condition of retinal vein occlusion (RVO). Therefore, we have to consider the ability of a sustained-release technology to address the need for a relatively shorter period of sustained delivery as well as for a permanent one. For a more acute disease such as branch RVO 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.

A highly targeted therapeutic agent, such as an anti-VEGF antibody, may be the perfect treatment to use for early DME, but in people in whom the disease has transitioned to this more inflammatory state, anti-VEGF therapy may not be as effective. An agent with a larger spectrum of activity is needed, and right now a corticosteroid is the only such option. 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 (PD) and pharmacokinetics (PK) 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.

Dr. Rubio: The process that Genentech uses in identifying a sustained delivery technology for potential use with ranibizumab focuses on several considerations. We are always focused on the patient, first and foremost, and want to make sure that a particular drug delivery technology is able to meet the need that exists in treating retinal diseases with our current platform—that is to say, the need to address regular and, in many cases, frequent intravitreal injections for the treatment of AMD, DME, and RVO. We want to ensure that we are able to build on the success that we have achieved to date with regu-

latory approvals for use of ranibizumab in AMD, DME, and RVO, meaning that for a particular sustained delivery technology, we would want to consider the ability of that technology to address each of these 3 disease states. We also want to ensure that a drug delivery technology is able to provide a significant advance over the current mode and frequency of administration, which currently is intravitreal injection requiring regular monitoring. Lastly, we want to make sure that the science behind a particular technology is sound, in that it has been well thought out and is capable of being used with ranibizumab, a large molecule, in a way that can address the unmet needs of patients with retinal disease.

Dr. Green: In our case, we licensed a delivery technology that already had the active pharmaceutical ingredient (API) associated with it. Our technology, Iluvien, is nonbioerodable and releases drug for at least 3 years. We licensed the delivery technology from pSivida Corp., which had previously developed the Retisert (fluocinolone acetonide intravitreal implant 0.59 mg, Bausch + Lomb) delivery system. Iluvien is the second generation, if you will, using the same API and the same sort of release mechanism, in which the corticosteroid permeates through a polyvinyl alcohol (PVA) matrix and slowly leeches out. The difference is that Retisert is sutured into the pars plana and Iluvien is not. Iluvien is injected in an office-based procedure.

RT: What kinds of decision-making go into the choice of a biodegradable vs nonbiodegradable vs genetic vs nanotechnology, etc., delivery system?

Dr. Hashad: The decision to pursue a biodegradable vs nonbiodegradable delivery system is dependent on disease state, duration of therapy, and patient population. Not all patients respond in the same way, so a biodegradable implant can allow better individualization of the treatment and avoidance of overtreatment. The biodegradability of Ozurdex (dexamethasone intravitreal implant, Allergan) 0.7 mg eliminates the need to surgically remove the implant and allows repeated injections.

The drug-delivery platform also plays an important role in selecting the compound. At Allergan, we have domain expertise with several drug delivery platforms. Integrating the abilities of these platforms with the properties of the drug dictates which platform we choose. Although many may appreciate the complexity of innovating a sustained delivery system for the back of the eye, few may appreciate the manufacturing and development considerations involved. Each platform and compound brings different manufacturing requirements

and considerations for sterility, low endotoxin levels and quality control. In order to meet regulatory and compliance requirements, all of these must be taken into consideration. This requires a high degree of technical competence.

Dr. Rubio: We are continually evaluating drug delivery technologies as we become aware of them, or as companies contact us with technologies they have in development. We are aware that drug delivery companies are making great strides with sustained delivery technologies in the preclinical setting that have potential to be used with ranibizumab, and we focus on the evaluation of these in a few key areas: First, what is the potential safety profile of a given technology when used in combination with ranibizumab (ie, does the drug delivery technology have an established safety profile or is the technology novel without a proven track record of safety in patients)? Second, what is the technology's performance from a drug delivery standpoint? From this perspective, we focus on the ability of a technology to deliver ranibizumab for a minimum of 4 months, which is the target duration we have set for delivery of therapeutic levels of ranibizumab to the retina. Third, what is the compatibility of the technology with ranibizumab within the eye at physiologic conditions for sustained periods of time?

Dr. Green: Nonbioerodable technology has 2 valuable characteristics for extended drug delivery: It can achieve durations and release kinetics that cannot be achieved with bioerodable implants. With this technology there is hardly any burst; it has near-zero-order release kinetics. Part of our hypothesis in adopting this technology was related to the primary ophthalmic side effect of long-term steroid administration, namely elevation of intraocular pressure (IOP). If we could control the release kinetics such that we achieved a near-zero-order release, and have the point of release as far posterior as possible, we believed that would optimize delivery to the macula, which is important in the treatment of DME, and also in mitigating IOP elevation.

The primary route of aqueous flow in the posterior segment is anteriorly: around the lens, through the pupil and out the trabecular meshwork. But about 15% of aqueous production is actually pumped out of the back of the eye by the retinal pigment epithelium (RPE). Our theory was that if we could release the steroid in a controlled manner, far posterior in the eye, utilizing this minor current flowing out the posterior route, we could mitigate the IOP side effect. The clinical trial data suggest that this is exactly what we did. There was a dramatic mitigation of the incidence of surgery to treat elevated IOP with Iluvien, compared with Retisert. We have also published human

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—Roman Rubio, MD

data comparing anterior chamber levels in the human eye of Retisert vs Iluvien showing a significantly higher level of steroid in the aqueous with Retisert than with Iluvien.

RT: What are some of the logistical issues in licensing or bringing the chosen delivery system in-house?

Dr. Hashad: The technology innovator often possesses specific expertise that it is important to retain; however, many innovators of these new technologies are small and have limited experience in developing these systems commercially. By in-licensing and bringing the technology in house at a company like Allergan, we can leverage our disease models, pharmacokinetic, and safety expertise, chemistry manufacturing controls (CMC), regulatory and manufacturing experience, and resources to expedite development of the concept into a commercial therapeutic to benefit patients.

Dr. Rubio: In terms of the actual process of in-licensing, I would refer you to my colleagues within the Genentech or Roche partnering groups. With regard to technologies that we have shown interest in, however, we have a licensing agreement with ForSight Vision4 for a refillable port delivery system, a technology which is a durable implant that, has the potential to deliver ranibizumab over a sustained period of time within the eye.

Dr. Green: When we first licensed the technology, it had not undergone clinical trials. The company from which we licensed the technology made the clinical supplies in the beginning. Their expertise lies in inventing delivery technologies, and our expertise is developing drugs, so it was a perfect marriage. They supplied the clinical supplies while the trial was ongoing. Toward the end of the clinical trial we transitioned to a commercial manufacturing site, which is where the product is now made.

RT: What steps do you have to take preclinically to determine that this drug and delivery system make a

good combination—to identify the effects of the delivery system on the drug's action, for instance?

Dr. Hashad: Preclinically, we evaluate whether the drug compound and delivery system in combination provide the requisite disposition and PK we desire. In addition, we assess the PD, safety, and efficacy, at least in an animal model. Those data are then used to further optimize the drug delivery system, as well as the compound, to meet the intended product profile. Where we have an active research program and are analoging around a pharmacophore (the group of atoms in a drug molecule that are responsible for the drug's action), the feedback from initial in vivo observation allows us to optimize and select the most promising compound candidates for the various drug delivery platforms.

Dr. Rubio: From a preclinical perspective, one of our first considerations is to ensure that a robust safety profile is established. From a performance perspective, we want to understand the ability of the technology when used in combination with ranibizumab to have a favorable PK profile when delivering ranibizumab over a sustained period of time. We want to understand the basic performance of the technology to be able to mimic the PK profile that has been established with ranibizumab in its currently approved liquid platform when administered intravitreally. Finally, we focus on the ability of the technology to be manufactured in a consistent way that is scalable in order to support the clinical development program needed to support approval, as well as ultimate commercialization.

Dr. Green: For a long-term delivery system, the toxicology program must be designed to mimic what could happen in clinical practice, over the life of a patient. Separate from the toxicology studies, the animal PK studies gave us the first indication that our hypothesis about having a lower anterior chamber exposure was correct. Animal studies are invaluable in assessing the potential of a delivery technology in the eye.

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?

Dr. Hashad: The rationale for developing drug delivery systems should be based on well-defined clinical need. In terms of clinical trial design, early clinical trials must not only assess safety, but also provide clinical confirmation

of bioavailability and preclinical PK and PD data. Any unexpected characteristics from the delivery system—for example, dose dumping that could result in unacceptable higher exposures—should also be identified and addressed during the preclinical phase. These data are critical to determining optimal dose, duration of effect, and the release rate of the drug over time prior to advancing into later stage development and trials.

As with any late-stage drug development, the primary focus of these clinical trials is on safety and efficacy. When evaluating a sustained-release drug delivery system there are additional factors that are assessed in these trials including the safety of not only the drug, but also the drug delivery system and its method of administration. We also evaluate the intensity and duration of therapeutic effect throughout the targeted treatment timeframe.

Dr. Rubio: Within the clinical setting, the focus is similar to what I just described in the preclinical setting, however a number of additional measures are focused on as well. Our first focus is on the establishment of an acceptable safety and PK profile for the drug delivery technology when used in combination with ranibizumab in a phase 1 trial. We also want to evaluate the PD performance of the technology, looking at parameters such as optical coherence tomography (OCT) to assess the ability of the sustained delivery of ranibizumab to resolve macular edema. Lastly, we begin to evaluate efficacy, the primary focus in phase 2 trials, to be able to understand whether the early signs of both PK and PD established in a phase 1 trial are capable of being translated into efficacy within the setting of a large phase 3 program.

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.

Dr. Green: There were 2 issues that made the design of the phase 3 FAME trials for Iluvien somewhat different. One had to do with the nature of testing a drug that is injected intravitreally to treat a retinal disease. A clinical trial must have a control arm. With a drug that requires an intravitreal injection, we could not ethically perform a clinical trial in which we would inject blank Iluvien pellets into control subjects. This dilemma has been faced

by other drug developers pursuing intravitreally injected therapies over multiyear periods.

Therefore, we had to design the trials with 2 investigators at each site. The administering investigator knew whether the device was being injected or whether a blunt injector was being pushed against the patient's eye, while the assessing investigator was masked to the injection status. That investigator did not know if the patient was in the active or control group.

The second consideration had to do with the status of existing therapies for DME. At the time this trial was performed, there were no approved pharmacotherapies for DME; ranibizumab was not yet approved for that indication. The standard of care was laser photocoagulation. However, although laser photocoagulation was the de facto standard of care, it does not have regulatory approval with an indication for treating DME. So from a regulatory perspective, laser could not serve as a control in the trials.

To address this, we set up the trial so that patients enrolled in the study could not have laser for 6 weeks. After 6 weeks it was possible to administer rescue laser. Again, this was where the trial design depended on having 2 investigators at each site. The assessing investigator, who did not know whether the patient was in the active or control group, made decisions about laser and other treatments that might be necessary.

Before our phase 3 trials, chronic DME was not fully understood or recognized. The reason it emerged in our trials was the requirement that patients had to have at least 1 macular laser treatment before entering the trial. By comparison, in the phase 3 trials of ranibizumab about 35% of patients were treatment-naïve at baseline. Because of this requirement in the FAME trials, our study population was enriched with people who had longer-term disease. One of the preplanned analyses was to look at the primary outcome as a function of the duration of disease. That is where this dramatic effect emerged, and it was replicated in both trials. So then we began to focus on chronic DME.

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, CMC can prove challenging when seeking approval of a new delivery platform and may require a high level of technical expertise, especially with biologics.

Dr. Rubio: The challenge faced by many of these newer drug-delivery technologies is that well-defined pathways and accompanying endpoints required by the FDA for approval have yet to be well established. Very close dialogue and interaction with the FDA to define acceptable efficacy and safety endpoints is required.

Dr. Green: Our initial applications in both Europe and the US were based on the full population. As the submission has matured, the focus has turned to the chronic DME subgroup mentioned above.

We did not get approval in Europe on the full DME population; the approval there is for chronic DME considered insufficiently responsive to available therapies. That indication perfectly matches how Iluvien is going to be used. It is not going to be used in a treatment-naïve patient, and we do not promote it that way.

At the time we submitted our dossier, there was an approved pharmacotherapy in Europe; ranibizumab was approved there for treatment of DME. It was not approved at that time for DME in the US.

In the US, the first pharmacotherapy for DME was approved in August last year. We have resubmitted our response, and we have a new Prescription Drug User Fee Act (PDUFA) date of October 17, 2013. ■

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