

DRUG DELIVERY TO THE RETINA

Questions, thoughts, and opinions related to current and emerging drug delivery systems.

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Drug delivery systems that target retinal diseases continue to evolve. Improvements may appear to be slow in evolving, yet the progress that has taken place over the past decade is encouraging. We can now treat many retinal diseases and disorders in a much more effective manner using pharmacotherapy than we could in the past. These

improvements are largely due to the remarkable effectiveness of the latest generation of retinal pharmacotherapies.

Before 2005, most of the ophthalmologic medications used to treat retinal disorders were classified as small molecules. These agents included antibiotics, antivirals, and corticosteroids such as dexamethasone, triamcinolone, fluocinolone, and prednisolone. Today, the most effective retinal pharmacotherapies target the VEGF protein and fall into a class of therapeutics referred to as biologics or genetically engineered proteins.

According to the Scottish Intercollegiate Guideline Network,¹ the highest quality level 1 data originate from randomized clinical trials and meta-analyses. For example, in the treatment of exudative age-related macular degeneration (AMD), several extensive, large-scale studies have demonstrated clear effectiveness and patient benefit with the use of monthly or bimonthly injections of anti-VEGF biologics.²⁻⁵ Similarly, several studies have demonstrated an important role for the sustained release of small molecules in the management of retinal vascular disease.⁶⁻¹² The side-effect profile, especially with the use of sustained-released corticosteroids (cataract and glaucoma), must be carefully managed.^{10,13,14} Many questions regarding current and future pharmacotherapies for retinal disorders remain unanswered. This article briefly explores some of these questions.

ATTEMPTING TO ANSWER THE DIFFICULT QUESTIONS

Has profound improvement in sight-saving therapy come at a price?

The answer, unequivocally, is yes. In retina clinics today, many of our colleagues perform numerous repetitious intravitreal injections that primarily involve antiangiogenic agents with annual costs that can exceed \$18,000 per patient.¹⁵ This accounting does not include the tremendous

costs of the time burdens on our patients and their families, along with the tremendous burden on the health care infrastructure. Implants and devices are also extremely expensive, and the benefits of such therapies require careful consideration with regard to cost-effectiveness and cost-utility.

Which delivery platform is most commonly used for biologics?

A standard tuberculin syringe and a 30-gauge needle (Figure 1) together have an estimated per-visit drug delivery system cost of \$0.16. Although this seems like a rather simple delivery system—and it is—simple injections are highly efficient and extremely cost-effective. When this type of system is used by a trained expert, it results in low rates of adverse events (eg, cataract, retinal detachment, endophthalmitis).

Why have we not moved beyond these time-consuming injections?

The reasons are numerous. Changing a given practice pattern in health care generally takes time, and a new delivery system requires two key components: (1) that the system demonstrates greater efficacy and (2) that the system is at least equivalent in cost to or more cost-effective than an existing delivery system. New drug delivery systems that are equally effective but cost the same as or more than an existing system are likely to face steep challenges for successful integration into clinical practice.



AT A GLANCE

- Novel ophthalmic drug delivery systems will emerge that will minimize the degradation of biologic molecules while maintaining efficacy and therapeutic tissue levels.
- The choice of relevant preclinical animal models is critical in assessing these delivery systems.
- Insurers will carefully assess the cost effectiveness of new drug delivery systems with the goal of noninferior or improved efficacy combined with a reduction in overall health care expenditures.



Figure 1. The most common intraocular drug delivery system: intravitreal injection. Total cost is approximately \$0.16 per visit.

Will sustained-delivery systems used for small molecules also work for biologics?

Probably not. We have seen a remarkable improvement in drug delivery technology for small molecules, especially corticosteroids. Slow-release polymer-based systems have been shown to be effective in treating several retinal disorders and disease states in large randomized clinical trials. These systems reduce the burdens of regular injections and have sustained treatment effects. As mentioned above, these slow-release systems also have higher rates of medication-related side effects, such as cataract and glaucoma for corticosteroids.

On the other hand, biologics are not released (solubilized) from a polymeric structure as readily or quickly as are small molecules. As the larger biologic molecule is released or exposed to the environment from a polymer, the protein-based structure may be susceptible to proteases and enzymatic degradation, rendering it ineffective. Novel systems may overcome this barrier and enable a better sustained-release process that improves the patient experience while simultaneously lowering health care costs.

Will sustained-release systems for antiangiogenic compounds lead to worsening geographic atrophy (GA)?¹⁶

Originally, a pulse dose of drug (eg, monthly intravitreal injections) was viewed as a poor pharmacokinetic model

for treating a chronic disease such as neovascular AMD. Sustained delivery was considered to be more desirable. But does a small window of subtherapeutic VEGF suppression provide a beneficial impact on the choriocapillaris? Perhaps. But if the answer is truly yes, then sustained-release systems may lead to more long-term risk of GA. Perhaps a cyclic intraocular drug level is desirable. These questions remain unanswered.

Innovative drug delivery systems now in development are in high demand and promise to offer features including a rechargeable system; safe and relatively simple insertion in the eye; long-term stability; simple removal; greater cost-effectiveness, and improved patient quality of life.

Will insurers approve and pay for new retinal drug delivery systems that cost more than the current system?

Not likely, if the two systems being compared are equally effective, unless the new system lowers the total drug cost or provider cost or significantly reduces side effects (ie, improves quality).

Does drug delivery that originates from the outside of the retinal pigment epithelium (RPE) barrier differ from drug delivery from within the RPE barrier?

With respect to pharmacokinetics, the answer is clearly yes. The choroidal blood flow and absence of an intervening blood-retina barrier creates access for rapid egress of drugs from the eye. Thus, sustained-release systems are important for targeting delivery to either the RPE or neurosensory retina using transscleral or suprachoroidal delivery.¹⁷ Microneedle technology enables easy access to the suprachoroidal space without surgical dissection.^{18,19} An advantage of catheter-based delivery to the suprachoroidal space is that a bolus of drug can be placed in a specific area.²⁰ Other risks, such as damage or injury to the RPE, Bruch membrane, and choroidal vasculature, also must be considered when the suprachoroidal space is accessed using either technology.

What are the best preclinical model systems for studying new drug delivery systems?

There are no perfect preclinical model systems. Perhaps there has been an overreliance on or too much relative scientific weight attributed to small rodent (ie, mouse) models for studying a drug that is intended to treat the human macula. Granted, the genetics of the mouse are well characterized, and thus a mouse may be a good preliminary animal model. However, study in larger animals is necessary for further analysis. Not only does a mouse not possess a true macula, but the diffusional kinetics of drugs delivered in or around a mouse eye differ dramatically from those around a human eye.

Definitive pharmacologic conclusions from data generated in small rodent models, especially assumptions about either pharmacokinetics or pharmacodynamics (outcome effects),

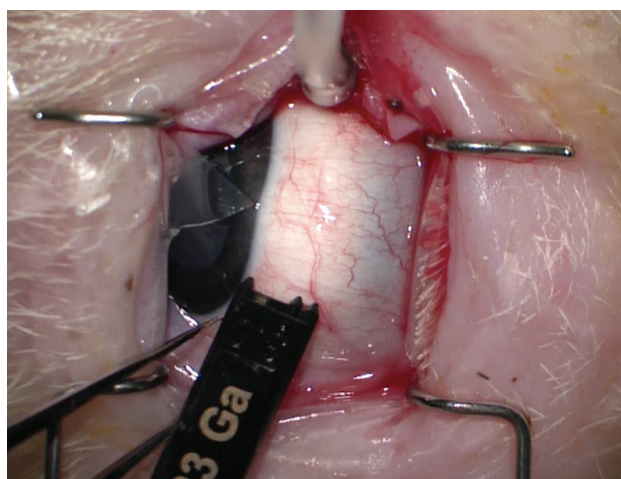


Figure 2. Preparing a standard three-port vitrectomy for a pharmacodynamics study using a pig model.

are inappropriate. Such conclusions may be fraught with uncertainty. Applied principles from the application of Fick's law of diffusional kinetics should be considered. In essence, this law characterizes the molar flux of a drug along a diffusional concentration gradient. Important variables, such as the distance of the diffusional gradient from the drug source and the time for diffusion to occur, affect diffusion. Also, the vascularity of the target tissue plays a major role in determining how much drug gets to it or is swept away into the systemic circulation.

In our experience, the pig represents one of the best models by which to study pharmacokinetics and selected cellular mechanics such as gene expression profiles (Figure 2).^{17,20-25} The porcine eye is roughly the same size as the human eye, and the sclera is of approximately the same thickness, albeit distributed differently.^{24,26} The crystalline lens is similar in size, and the retinal and choroidal vasculature are also similar. Additionally, there is a cone-dense region known as the area centralis in the pig, and the RPE closely resembles that in humans. Rabbits occasionally serve as an adequate model, although, due to some stark differences, there may be major challenges in translating pharmacokinetic data to humans. For example, rabbit retinal vasculature is very different (merangiotic). The lens is large relative to the size of the eye, and the sclera is thin.

CONCLUSION

Innovative research in our field has led to great strides in the development of effective pharmacotherapies for treating retinal diseases. Further improvements are soon to be realized through optimizing the pharmacokinetics of biologic agents used in or around the eye. Novel systems are emerging that may minimize the degradation of the biologic molecule while maintaining therapeutic efficacy and appropriate tissue levels. Such studies are being developed in preclinical animal models.

The effects of sustained-release systems will require long-term follow-up analysis that examines long-term side effects such as the issue of progressive GA in AMD. ■

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- Annex B: key to evidence statements and grades of recommendations. In: SIGN 50: A Guideline Developer's Handbook. Edinburgh: Scottish Intercollegiate Guidelines Network;2011:51. <http://www.sign.ac.uk/pdf/sign50nov2011.pdf>. Accessed August 9, 2016.
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