ENVISIONING NEW HORIZONS IN OCULAR DRUG DELIVERY

In this article, Jay S Duker, MD, Chief Operating Officer at EyePoint Pharmaceuticals, discusses the history and future of ocular drug delivery, with a special focus on posterior segment diseases and the battle to overcome significant patient and caregiver burdens.

A BRIEF HISTORY OF OCULAR DRUG DELIVERY

In the ophthalmic space, practitioners are lucky to have a wide range of quality medications at their disposal. Topical drop-based medications have long been characterised by strong efficacy and tolerability profiles. Relevant examples include antibiotic drops for conjunctivitis, intraocular pressure modulators for glaucoma and steroidal agents for the treatment of dry eye disease. These medications have played a pivotal role in making positive care outcomes more predictable, safe and accessible around the world.

Unfortunately, no drug delivery system is perfect. Eye drops, for instance, present clear challenges and trade-offs. For example, although drops are generally effective, safe and tolerable, many patients consider them inconvenient and consider self-administration of them burdensome. This is especially true for products that require twice- or thrice-daily dosing, which represent a large share of the popular and affordable options on the market today.

Additionally, because the human eye possesses so many anatomical defence mechanisms, drug penetration is difficult. As a result, eye drops are primarily effective only in the eye's anterior segment, making them less viable for treating pathologies of the posterior segment, which houses the retina, macular, choroid and other structures that facilitate sight. Unfortunately, diseases that manifest here, including age-related macular degeneration (AMD), diabetic retinopathy and diabetic macular oedema, have a significant, often devastating, impact on patient vision.

In light of these factors, ophthalmologists sometimes turn to systemic drugs to mitigate posterior segment disease progression. These drugs can be delivered intravenously or orally. These modalities slow disease progression and can preserve visual acuity longer but can also incur systemic side effects – an unacceptable cost for many patients.

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INTRAOCULAR INJECTIONS – BENEFITS, LIMITATIONS AND EMERGING IMPERATIVES

The advent of intraocular injections, which allow practitioners to deliver compounds directly to tissues at the back of the eye, represented a watershed moment in ophthalmology. For the first time, retinal specialists could deliver sight-preserving therapies in a relatively safe, controlled manner to the target tissues. Today, intraocular injection-based products – specifically, anti-vascular endothelial growth factor (anti-VEGF) agents – are considered the gold standard of care for treating these diseases, including the "wet" variety of AMD, which is characterised by new blood vessel growth and subsequent leakage in the centre of the retina and, fortunately, can be slowed with prompt medical intervention.

Still, in the world of medicine, few (if any) solutions are perfect. Although this drug delivery method provides distinct advantages, it also presents real limitations. First, the window of therapeutic action for these drugs is relatively short, requiring patients to return to their doctor each or every other month, often indefinitely. Additionally, contemporary evidence suggests that, for wet AMD and diabetic retinopathy, just one or two missed doses can cause vision loss. This was made

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especially clear during the early covid-19 pandemic, when societal disruption led to decreased treatment compliance and, subsequently, adverse outcomes for thousands of vulnerable patients.

Accordingly, ophthalmic researchers and clinical leaders have set their sights on an urgent imperative in drug delivery – facilitating safe and effective posterior segment therapy while reducing logistical burdens for our most vulnerable patients and their caregivers. If this vision can be made a reality, we can theoretically improve patient compliance, preserve vision for longer periods of time, positively impact patient quality of life and minimise the burdens on caregivers, healthcare systems and the economy at large.

NOVEL APPROACHES FOR INTRAOCULAR DRUG DELIVERY

To meet this important imperative and overcome significant and costly limitations, drug manufacturers are approaching the problem from diverse developmental angles. One conceptually straightforward approach involves increasing medication dosage fourfold at the initial injection in order to reduce the number of total injections required (EYLEA® – Regeneron, NY, US). Phase II trial data presented in February 2022 indicates that this may be a viable approach.

Figure 1: An implantable ophthalmic drug delivery device on a dime to show size.

Another approach involves a surgical procedure wherein a refillable port device is surgically placed in the wall of the eye; the port is loaded with anti-VEGF, releases it slowly over the course of six months and is then refilled at the doctor's office (SUSVIMO™ and LUCENTIS® – Roche, Basel, Switzerland). Intraocular injections are still required but at a reduced frequency. The US FDA approved this first-of-its-kind device in October 2021.

Gene therapy, which could theoretically induce ocular cells to endogenously create and deploy anti-VEGF proteins, represents another interesting avenue of innovation. Early efficacy data appears promising but, as an industry, we are very much in the early stages of gene therapy, and concerns about associated ocular inflammation need to be explored and addressed.

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For years now, ophthalmic research has also focused on the concept of sustained drug delivery, which may unlock new avenues for controlling therapeutic results and increasing patient compliance. Sustained drug delivery's proof of concept has been validated in the treatment of several ocular diseases, such as sustained delivery of ganciclovir for cytomegalovirus (CMV) retinitis; fluocinolone acetonide for chronic non-infectious uveitis (RETISERT® – Bausch + Lomb, NY, US; YUTIQ® – EyePoint Pharmaceuticals, MA, US); and, in 2020, bimatoprost for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension (DURYSTA™ – Allergan, Dublin, Ireland).

In recent years, a novel, implant-based methodology has been in development for releasing anti-VEGF medication at a slow, steady rate over a long period of time (Figures 1 & 2). This technology is being developed both to extend the time between patient visits and to facilitate steady-state medication release, which may help physicians control disease progression in a more even, predictable way.

Figure 2: Injector used to insert the ophthalmic implants.

EXPLORING FACTORS FOR TECHNOLOGY SELECTION

Taken together, these research initiatives offer practitioners several distinct and valuable options when it comes to drug delivery. Implants, sustained-release therapies, gene therapies and other delivery technologies will all likely have an eventual role to play in ophthalmic care, and individual clinicians will undoubtedly choose based on their patients' specific situations, needs and constraints.

There is also an inherent cost-benefit analysis to be made regarding each approach. Gene therapy, for instance, represents a fascinating avenue of pursuit but its novelty makes it expensive to implement, at least until uptake becomes more widespread across pathologies. Additionally, because gene therapy works at an endogenous level, adverse events can be costly and difficult, if not impossible, to remediate, whereas injections can be slowed or halted in response to problems that arise during the course of treatment.

A key cost-benefit question is "What is the ideal sweet spot for duration of therapy?" Research conducted by EyePoint Pharmaceuticals has indicated that most retinal physicians are looking for a six-month treatment option for wet AMD, with the feeling that treatment periods longer than six months may increase the risk of patients failing to make their follow-up visits. Additionally, six-month check-ins are beneficial for monitoring wet AMD progression in the patient's other eye and for detecting potential new ocular problems.

However, as previously stated, the reality on the ground is complex, rapidly evolving and best addressed by a diverse range of tools with distinct utilities and advantages. As with many domains in medicine, there will likely never be a "one-size-fits-all" solution, which is why the march of innovation carries on indefinitely.

FINAL THOUGHTS

The world of ophthalmic research is in a pivotal and transformative period. Although we have long had effective and efficient treatment options in the world of eye-drop-based therapy for anterior segment conditions, posterior segment drug delivery has been plagued with challenges for just as long. However, in the last decade, new technologies, discoveries and innovations – the result of, and testament to, the brilliance and hard work of researchers in the field – have created exciting new possibilities for superior drug delivery and, subsequently, improvements to standards of care. As new delivery methods are piloted, trialled and approved, we can finally look forward to a new era for the treatment of wet AMD and other serious diseases of the posterior segment. Unmistakably, a brighter future is in sight.

ABOUT THE COMPANY

EyePoint Pharmaceuticals is a pharmaceutical company committed to developing and commercialising therapeutics to help improve the lives of patients with serious eye disorders. The company's pipeline leverages its proprietary Durasert® technology for sustained intraocular drug delivery, including EYP-1901, a potential six-month intravitreal anti-VEGF treatment initially targeting wet AMD. The company has two commercial products: YUTIQ® (fluocinolone acetonide) for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye, and DEXYCU® (dexamethasone) for the treatment of postoperative inflammation following ocular surgery. DEXYCU is now sold in the US by ImprimisRx (Carlsbad, CA, US), a division of Harrow Health.

ABOUT THE AUTHOR

Jay Duker, MD, Chief Operating Officer at EyePoint Pharmaceuticals, is a leading retinal disease expert with more than 30 years' experience in the field of ophthalmology, focused on improving eyesight and preventing blindness. Dr Duker has held roles in clinical, research, business, start-ups and academic settings.