

IMPLANTABLE DRUG DELIVERY: A LOOK AT PHARMACOKINETICS



Novel approaches are showing promise for addressing treatment burden in retinal disease.

BY CHARLES C. WYKOFF, MD, PHD, FASRS, FACS

The pharmacokinetics, pharmacodynamics, and delivery methods of intraocular drugs are important considerations in the management of retinal disease and in drug development. The successful delivery of novel therapeutics to the retina has been a challenge for development programs, and while various methods have been explored, many have led to subtherapeutic levels of drug delivered to the target tissue.¹

Currently, the most common retinal drug delivery method is intravitreal injection, widely used for delivering anti-VEGF biologics for the treatment of a host of exudative retinal diseases, including wet AMD and diabetic macular edema (DME). However, in many patients, frequent anti-VEGF injections are required, which can present meaningful treatment and adherence burdens. As such, adherence rates are often suboptimal, and injections are frequently administered at longer intervals than may be ideal, limiting their effectiveness and compromising long-term patient outcomes.¹

Additionally, while regular injections may be feasible for compounds such as anti-VEGF proteins, which have half-lives on the order of days, this approach is less feasible for small-molecule drugs, which typically have much shorter intraocular half-lives and may require unrealistic dosing frequencies.¹ To address this need, several implantable sustained drug delivery methods are currently under investigation for retinal pathologies. These methods hold promise to reduce treatment burden and maximize long-term visual outcomes through increased adherence and reduced disease fluctuation with more consistent delivery of drug at therapeutic levels.

WET AMD

Although anti-VEGF therapy constituted a paradigm shift in the treatment of wet AMD, therapeutic outcomes in routine clinical practice often lag behind those achieved in clinical trials, and reduced frequency of injections appears to be a key factor.² A large-scale study of practice

data found that only about one-third of eyes treated with anti-VEGF agents had injection intervals of less than 8 weeks by the end of the first year of treatment and more than 40% had discontinued treatment by year 3. These reductions in treatment frequency may translate to poorer visual acuity outcomes over time.³

Despite the widespread use of anti-VEGF therapy, our understanding of the pharmacokinetics at the patient level remains limited, hindering our ability to create optimal dosing strategies for individual patients. For example, the optimal frequency of administration likely depends on the agent's half-life, which may vary between patients due to factors that could affect individual clearance rates.⁴

Tyrosine kinase inhibitors (TKIs) are under investigation as a new treatment approach for wet AMD that differ from available anti-VEGF biologics in their intracellular multitarget inhibition of tyrosine kinase receptors, including VEGF receptors. Many of the TKIs in development have demonstrated promising pharmacokinetic profiles; two late-stage programs with clinical data to date are

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MACULAR TELANGIECTASIA TYPE 2

The use of ciliary neurotrophic factor (CNTF) has been found to significantly slow the progression of retinal degeneration in two randomized prospective trials involving patients with macular telangiectasia (MacTel) type 2.¹ From a pharmacokinetic standpoint, however, delivery of CNTF has some challenges. Its intraocular half-life is extremely short (estimated between 1 to 3 minutes), making treatment with bolus injections of CNTF non-viable. Additionally, it is a protein, making it challenging to use in polymer release systems, which are traditionally optimized for the delivery of small molecules, and it does not readily penetrate the blood-retina barrier.²

To address these issues, an encapsulated cell technology, revakinagene tarorectel-lwey (Encelto, Neurotech Pharmaceuticals), has been developed to continuously deliver CNTF inside the vitreous cavity and can remain productive for many years. The therapy consists of a semipermeable polymer membrane capsule

that contains a genetically engineered human retinal pigment epithelial cell line designed to express CNTF at a consistent rate. The capsule is surgically implanted into the vitreous cavity and anchored to the overlying sclera using a prolene suture.

Early studies of revakinagene tarorectel-lwey found that it consistently produced CNTF over a 2-year period.² More recently, revakinagene tarorectel-lwey demonstrated efficacy in MacTel patients in two phase 3 clinical trials, and safety studies have demonstrated it is generally well tolerated.³ The device was recently approved by the FDA for use in patients with MacTel type 2.⁴

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EYP-1901 (Duravyu, Eyepoint Pharmaceuticals), which releases vorolanib,^{5,6} and OTX-TKI (Axpaxli, Ocular Therapeutix), which releases axitinib.^{7,8} EYP-1901 has demonstrated zero-order kinetics in preclinical studies, with near steady-state drug levels achieved within 4 hours of dosing and maintained through 8 months.⁹ Preclinical studies of OTX-TKI have demonstrated steady-state drug levels and consistency in axitinib concentrations across retinal and choroidal tissues 6 months after a single injection of OTX-TKI.⁷ TKIs have also been investigated in nonproliferative diabetic retinopathy and DME.¹⁰

The port delivery system (PDS; Susvimo, Genentech/Roche) is a surgically implanted device designed for in-office refills and can deliver a continuous supply of ranibizumab to patients, with refills given in-office every 6 months in the phase 3 wet AMD trial.¹¹ Data from a population pharmacokinetics model showed release of ranibizumab from the PDS with an estimated half-life of 106 days.¹² The PDS is currently FDA-approved for the treatment of wet AMD and DME.¹¹

DIABETIC MACULAR EDEMA

At a population level, patients with DME have demonstrated lower adherence rates with treatment than patients with wet AMD, and approximately two-thirds of patients with DME experience at least one barrier to treatment or attending a medical visit.¹³ Patients with DME who receive anti-VEGF therapy have been reported to require a median of 15 or 16 injections over a 2-year period,¹⁴ further highlighting the need for strategies that can reduce the number of treatments in this patient population.

One approach that has been explored for bridging this gap

is the use of a fluocinolone acetonide intravitreal implant (Iluvien, ANI Pharmaceuticals), which is indicated for the treatment of DME in patients who have not manifested an IOP response to prior corticosteroid treatment. This implant is nonbiodegradable and can release fluocinolone acetonide for up to 3 years, potentially reducing retinal thickness fluctuations.¹⁵ Most importantly for this therapeutic, the ongoing prospective, randomized NEW DAY trial is analyzing its use for first-line therapy in eyes with DME compared with 2 mg aflibercept (Eylea, Regeneron).¹⁶

The dexamethasone intravitreal implant (Ozurdex, Abbvie) is also approved for the treatment of DME and uses a propriety drug delivery system with a polymer matrix.¹⁷ Preclinical pharmacokinetic models with and without vitrectomy have indicated the presence of dexamethasone for a minimum of 31 days.¹⁸

In patients with DME and diabetic retinopathy treated with the PDS, pharmacokinetic data showed that continuous delivery was achieved over an every-24-week refill interval. The PDS facilitates continuous drug release into the vitreous through passive diffusion.¹⁹

LOOKING AHEAD

Beyond sustained-release implants, other strategies being explored to enhance the intraocular pharmacokinetics of retinal therapies include gene therapies; the relatively simplistic approach of dose escalation, which has been found to reduce the number of required intravitreal injections in some cases; the use of micro- and nanoparticles; and periocular routes of administration, such as suprachoroidal delivery.²⁰

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A NEW TECHNIQUE FOR MYOPIC TRACTION MACULOPATHY



Learn about wristwatch macular buckling and how we have optimized the procedure.

BY NIKOLOZ LABAURI, MD; TEKLA MAMAGISHVILI, MD; MONIKA ZALINIAN, MD; AND SUPRIYA DABIR, MD, PHD

Myopic traction maculopathy (MTM) involves a spectrum of pathological changes to the macula in high myopia and is caused by two main mechanisms: 1) internal traction due to a posterior hyaloid membrane, rigid vasculature of the neurosensory retina, and/or an epiretinal membrane and 2) external outpouching of the thinned posterior scleral wall (ie, posterior staphyloma).¹ MTM comprises numerous posterior retinal abnormalities and can manifest in isolation or combined with posterior vitreoschisis, epiretinal membrane, foveoschisis, lamellar macular hole, full-thickness macular hole, and/or posterior retinal detachment.²

Surgical treatment focuses on addressing the causative mechanisms of MTM and takes two main approaches: 1) an internal approach with pars plana vitrectomy to relieve internal traction by removing the vitreous, epiretinal membrane, or internal limiting membrane and 2) an external approach with posterior scleral indentation (macular buckling) to shorten the axial length of the eye and oppose the sclera, choroid, and retinal pigment epithelium posteriorly toward the photoreceptors of the neurosensory retina.³⁻⁷ MTM can be observed or treated either with macular buckling, vitrectomy, or a combination of both.

Here, we describe a novel device and implantation technique—wristwatch macular buckling—that has proven successful in our OR.

THE PROCEDURE

The device, assembled by the operating surgeon prior to implantation, is made of solid silicone rubber that is trephined with a 7 mm corneal punch to harvest a round 7 mm silicone rubber head (Figure 1A). It has a concave internal surface and a preplaced 2.5 mm groove on its external surface made for the silicone band placement.

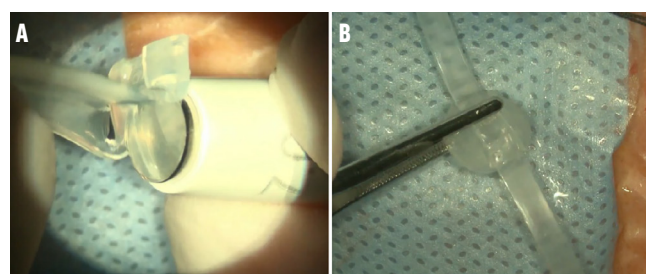


Figure 1. A 7 mm corneal trephine cuts a round indenting head from the silicone (A). The assembled buckling device resembles a wristwatch (B).

Use a 2 mm crescent knife to make partial-thickness tunnels at both ends of the external groove, through which the silicone band is passed and firmly fixated. The assembled device resembles a wristwatch, hence its name (Figure 1B).

Perform a circumferential 360° conjunctival peritomy to isolate and sling (using 4-0 silk traction sutures) all recti muscles. Pass the proximal end of the silicone band under the superior oblique and superior rectus muscles and bring it from the superotemporal to the superonasal quadrant. Next, pass the distal end of the silicone band under the lateral rectus and the inferior oblique muscles. Repeat these steps with the inferior rectus. Pull the proximal and distal ends of the silicone band nasally to slide the indenting 7 mm head across the sclera and bring it under the foveal projection.

Confirm the appropriate position of the buckle head through transvitreal observation. Then, use a 2 mm crescent knife to make two partial-thickness scleral tunnels in an oblique fashion in the superonasal and inferonasal quadrants. Pass both ends of the band through the appropriate scleral tunnels and secure them using a Watzke sleeve. Lastly, adjust both ends of the band to center the head of the implant under the fovea while applying mild indentation over the macular region to flatten the posterior staphyloma and

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Tactics aimed at enhancing the pharmacokinetics of existing and future retinal therapeutics have the potential to meaningfully improve patients' lives. This space is evolving, and it is exciting to participate in the development of these therapies, especially in concert with the potential role for remote monitoring approaches, such as home OCT. ■

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