UPDATE ON SUSTAINED-RELEASE DRUG THERAPIES

These therapies have the potential to change the glaucoma treatment paradigm.

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Glaucoma may be effectively treated with topical eye medications, but patients' poor adherence limits the success of this form of intervention. Studies repeatedly show poor rates of medication refill.[1,2] One study of glaucoma monotherapy found that 25% of patients took less than 75% of their doses and that almost 20% of patients took less than 50% of their doses, even when they knew they were being electronically monitored.[3]

Sustained-release drug delivery has the potential to profoundly improve glaucoma care by lowering IOP and eliminating much of the adherence problem. Receiving an injection by an ophthalmologist once every few months rather than self-administering eye drops multiple times per day could revolutionize the glaucoma treatment paradigm.

Currently, there are no FDA-approved and clinically available sustained-release drug delivery systems for glaucoma. The most evolved examples of commercially available ophthalmic sustained-release drug therapies are the corticosteroid implants, which include Retisert (fluocinolone acetonide; Bausch + Lomb; approved in 2005), Ozurdex (dexamethasone; Allergan; approved in 2010), and Iluvien (fluocinolone acetonide; Alimera; approved in 2014). Many companies are developing sustained-release products for glaucoma, but most of the available data have not been published in peer-reviewed journals.

PLATFORMS DELIVERED INSIDE THE EYE

Allergan is currently performing phase 3 clinical trials on its bimatoprost sustained-release implant (bimatoprost SR), which is a depot implant injected into the anterior chamber. Phase 2 trials of the implant showed a mean IOP reduction from baseline of 7.2 to 9.5 mm Hg in 75 eyes 4 months after the injection. The fellow eyes received once-daily topical bimatoprost 0.03% and experienced an IOP reduction of 8.4 mm Hg.[4] The implant lowered IOP in 92% of patients at 4 months and 71% at 6 months. There were no serious adverse ocular events, and the most common adverse events were related to the injection procedure.

Another depot implant that is injected intracamerally and targets the anterior chamber is ENV515 by Envisia Therpeutics. The company is a spinoff of Liquidia Technologies, which develops nanotechnology-based health care products and uses a proprietary system for molding nano- and microparticles called PRINT (Particle Replication in Nonwetting Templates). ENV515 is a biodegradable polymer drug delivery system that uses an extended-release formulation of travoprost.[5] A phase 2a open-label, 28-day dose-ranging study of 21 patients yielded 6.7 mm Hg or 28% IOP lowering at day 25 in one group, which was comparable to once-daily Travatan Z (travoprost ophthalmic solution; Alcon) dosing in the fellow

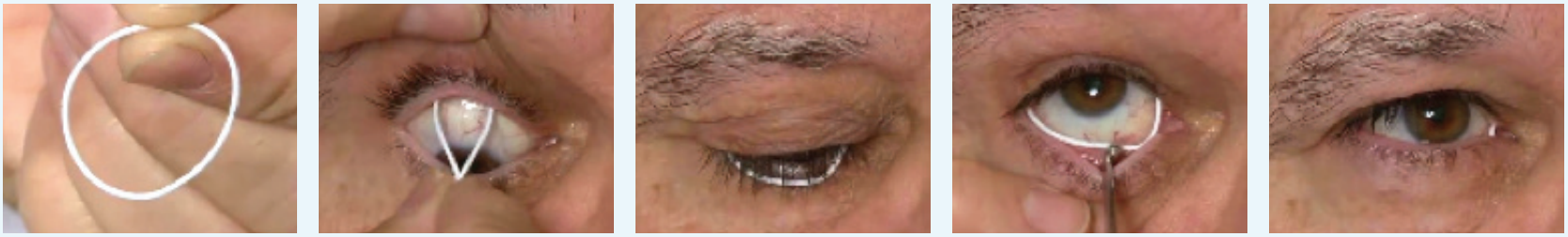

Figure . The Helios ring.

eye. Envisia is planning to advance to a 12-month study to evaluate the long-term IOP lowering of ENV515.[6]

GrayBug is developing a microparticle controlled-release drug delivery system for the treatment of age-related macular degeneration (AMD) and glaucoma based on technology the company licensed from the Wilmer Eye Institute of Johns Hopkins School of Medicine in Baltimore. Particles injected through the conjunctiva as a gel in a viscous vehicle aggregate form a depot. In the glaucoma space, GrayBug is developing compounds with both IOP-lowering activity and neuroprotective benefits. In animal models, the company has achieved IOP reduction lasting months with subconjunctival administration of the depot drug using two generic medications.

In contrast to the bimatoprost SR and ENV515 injectable implants, Icon Bioscience combines a drug with a carrier platform called Verisome into a true liquid injection that can be placed in the posterior or anterior segment. Icon's most evolved product is IBI-10090, which combines dexamethasone and Verisome for treating uveitis and postsurgical inflammation. IBI-10090 is in phase 3 trials, and a glaucoma product is in the preclinical phase.[7]

PLATFORMS DELIVERED OUTSIDE THE EYE

The Helios (ForSight Vision5) is a bimatoprost-laden polymer-matrix insert embedded in a compliant ring (Figure). The ring is positioned under the upper and lower eyelids and rests on the conjunctiva. It is visible only at the caruncle once it is in place. The ring is designed to be replaced by a physician every 6 months. In a phase 2 randomized, double-masked controlled study, the Helios insert lowered IOP but less than did topical timolol 0.5% dosed twice daily in eyes with an unmedicated insert.[8] Ninety percent of subjects who tried the implant were comfortable, and those who rejected it typically did so within a few days of its placement. A limited sample size of 50 to 60 patients in each arm may have affected the analysis. A much larger phase 3 trial is therefore planned.

TODDD (Topical Ophthalmic Drug Delivery Device; Vista Scientific) is a nonerodible solid matrix that is worn under the eyelid in the superior fornix and may be embedded with a drug. The National Eye Institute supported the development of the platform through grants, but no information regarding clinical trials has been released.

The long-standing precedent of punctal plugs' safety for the treatment of dry eye disease makes embedding a drug in a punctal plug an area of interest for sustained-release glaucoma therapy. Ocular Therapeutix and Mati Therapeutics are already performing clinical trials relating to this route. Their punctal plugs differ in that the Ocular Therapeutix device, OTX-TP, is an intracanalicular depot that dissolves over time, whereas the Mati Therapeutics device, L-PPDS (latanoprost-punctal plug delivery system), is a drug-eluting punctal plug. OTX-TP releases travoprost and is visible via fluorescence. L-PPDS releases latanoprost and is grossly visible. As a superficial punctal plug, it can be pulled out relatively easily, whereas the deeper canalicular depot may require flushing the canaliculus with saline or other maneuvers if removal is needed.

More than 570 patients have been treated in various dose-ranging phase 2 studies with L-PPDS. A US-based, randomized, multicenter trial of 100 patients comparing a 95-µg formulation with timolol for up to 14 weeks is ongoing. Information from past trials indicates a 20% IOP reduction at 12 weeks with L-PPDS.[9] Recent iterations of this device have shown improved retention.[10]

Ocular Therapeutix reported results from a phase 2b trial comparing OTX-TP with saline drops to placebo with timolol.[11] The average change from baseline in the OTX-TP treatment group was 5.6 mm Hg versus 6.7 mm Hg in the timolol arm. Retention of the OTX-TP device was 91% at 60 days and 48% at 90 days.

CONCLUSION

The groundwork is being laid for exciting new glaucoma treatments to become available in the coming years. Topical agents are effective, but patients' problems with adherence have limited therapeutic success, resulting in blindness in some individuals who discontinue treatment for extended periods. Depot drugs may improve adherence, and early studies show better tolerability compared to drops. Nonetheless, any side effects may prove challenging to address if they arise after the administration of depot systems.

The adoption of these new mechanisms of drug administration will require interest on the part of patients and physicians. Selective laser trabeculoplasty is a relatively quick and low-risk procedure with little discomfort. Nonetheless, many patients approach this treatment with

AT A GLANCE

- There are currently no FDA-approved and clinically available sustained-release drug delivery systems for glaucoma.
- Several companies are developing sustained-release devices that can be placed inside or outside of the eye. It is hoped these treatments will improve patients' adherence to therapy.
- Once approved, the success of sustained-release drug delivery systems will depend on the physicians' and patients' confidence in the treatment.

trepidation, which raises the question of how patients will feel about receiving an injection or other physician intervention multiple times per year. If the FDA approves sustained-release drug delivery systems, their ultimate success may be based on how they are presented to patients. Widespread adoption will depend on the confidence of physicians and patients in the efficacy and safety of these new treatment modalities. ■

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