

IMPLANTS AND INJECTABLES

An overview of devices in development.

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During the past few years, there has been an incredible proliferation of technology in the pharmaceutical and surgical areas of glaucoma. The driving force behind these advances is the quest to improve patients' adherence to prescribed medical therapy while maintaining a high quality of life.

Noncompliance is a key contributor to disease progression, and multiple studies have shown that a majority of patients do not take their glaucoma medications as prescribed by their doctor. In a study of more than 5,500 managed care patients, 90% were noncompliant, and more than 50% failed to refill their initial prescription in the first year.¹ A separate trial found that patients administered their glaucoma medications only 7 out of 10 days on average.² Moreover, in a hospital-based trial, 41% of patients who were compliant indicated that they had difficulty paying for their medications.³

More than 40% of patients with definite or suspected glaucoma may fail to return for follow-up appointments on schedule.⁴ Up to 80% of patients may not take medication as prescribed,⁵ and more than 30% of patients do not refill their initial prescription regardless of the specific medication.⁶ Persistence with glaucoma medical therapy is generally considered to be poor, with studies reporting that less than 25% of patients use their eye drops continuously for 12 months. Individuals' persistence may also fluctuate over time.⁷



AT A GLANCE

- The challenges posed by long-term medical therapy for both practitioners and patients have prompted researchers and companies to explore sustained-delivery systems for IOP-lowering drugs.
- Most of these platforms are still in early development, but a few have entered later phases of research.

“ [The goal is] to improve patients' adherence to prescribed medical therapy while maintaining a high quality of life.”

Several published studies suggest that medical compliance among glaucoma patients is poor and that between 20% and 66% of them do not use their medication as prescribed. The prevalence of noncompliance may vary, depending on the patient's age, systemic and economic conditions, level of education, understanding of glaucomatous progression, motivation, and confidence in his or her



Figure 1. Gonioscopic view of a Bimatoprost SR implant in the inferior angle.



doctor. The complexity of the therapeutic regimen also plays an important role in compliance.

The challenges that long-term medical therapy poses for both practitioners and patients have prompted researchers and companies to explore alternative delivery systems for IOP-lowering drugs. Most of these platforms are still in early development, but a few have entered later phases of research. This article focuses on injectable and implantable devices.

THE CONTENDERS

Allergan

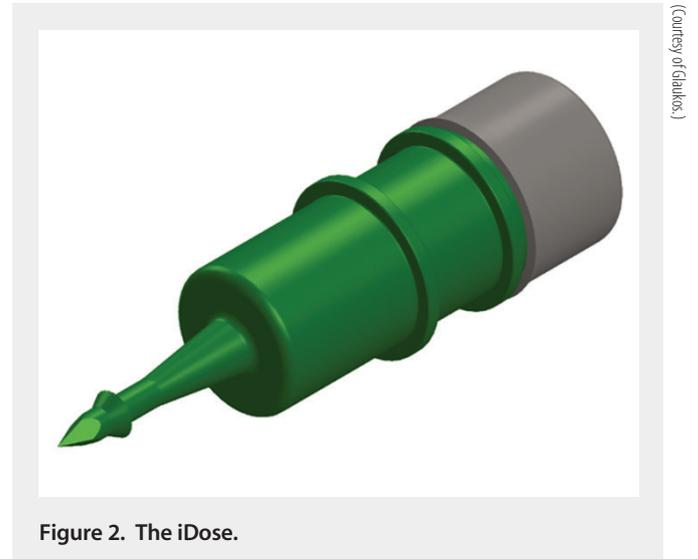
Allergan is currently studying the release of bimatoprost into the eye via a biodegradable implant. The Bimatoprost SR (Figure 1) is placed in the anterior chamber via an injector system using a 27-gauge needle in a fashion similar to the creation of a standard paracentesis. The amount of active drug contained in the implant is also approximately equivalent to the amount in one drop of commercially available bimatoprost (10- μ g dose). The low concentration of active medication is possible because the compound does not have to penetrate the cornea. The lack of external drug exposure reduces the risk of side effects, including lash growth, periocular pigmentary changes, and alterations in the lid margin.

The Bimatoprost SR is currently in phase 3 clinical trials. In phase 2 trials, the device produced a mean IOP reduction of 7.2 to 9.5 mm Hg from baseline in 75 eyes 4 months after the injection. Patients' fellow eyes received once-daily topical bimatoprost 0.03% and experienced an IOP reduction of 8.4 mm Hg at 4 months. 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.⁸

Glaukos

Glaukos recently completed enrollment in the phase 2 clinical trial of the iDose travoprost intraocular implant in glaucoma patients. The device is designed to continuously release therapeutic levels of medication from within the eye for extended periods of time. The implant is filled with a formulation of travoprost specific to the device and capped with a membrane designed for continuous controlled drug elution into the anterior chamber. When the medication has been exhausted, the implant can be removed and replaced in the same minimally invasive fashion.

The 150-patient, multicenter, randomized, double-blind phase 2 trial evaluated two models of the iDose delivery system with different travoprost elution rates in comparison to a topical timolol maleate ophthalmic solution, 0.5%. The trial, which focused on safety and efficacy in lowering IOP in patients with open-angle glaucoma, will be unmasked after 12 weeks of follow-up, with analysis expected later this year. The results will help the company



(courtesy of Glaukos.)

Figure 2. The iDose.

decide whether to conduct expanded phase 3 trials.

The iDose is a titanium implant that is comparable in size to Glaukos' proprietary devices for microinvasive glaucoma surgery (Figure 2).

Envisia Therapeutics

Envisia Therapeutics has created customized delivery vehicles for prostaglandin analogues and other ophthalmic agents. The company's PRINT technology produces biodegradable nanometer-scale vehicles designed to be injected intracamerally to provide 24-hour IOP control for up to 6 months from a single dose.

Phase 2 studies with travoprost showed IOP lowering similar to that achieved with travoprost ophthalmic solution 0.004% (Travatan Z; Alcon). An ongoing safety trial has reported no serious adverse events over 11 months and less hyperemia than is typical of topically administered prostaglandin analogues. ENV515 has also demonstrated an IOP-lowering effect comparable to that of prestudy topical prostaglandin analogues (Xalatan [Pfizer] and Lumigan [Allergan]) and in-study topical timolol maleate 0.5% ophthalmic solution (daily eye drops). A single low dose of ENV515 decreased the mean 8 AM IOP by 6.7 ± 3.7 mm Hg or 25% over 11 months (average of all 8 AM IOP measurements over 11 months). The mean 8 AM IOP after a single low dose of ENV515 was 19.5 mm Hg over the 11-month period. The most common adverse event was early-onset transient hyperemia related to the dosing procedure.⁹

Amorphex Therapeutics

Amorphex Therapeutics has developed a topical ophthalmic drug delivery device (Figure 3). Made of a biocompatible soft elastomeric material, the device sits on the surface of the sclera underneath the eyelid. The

(Courtesy of Amorphex Therapeutics.)



Figure 3. Drug delivery device from Amorphex Therapeutics.

company has tested various drops individually and as a combination, including timolol maleate, prostaglandins, pilocarpine, brimonidine, and even some anti-inflammatories and antibiotics. The device has the ability to hold a large amount of medication and deliver it for months. It is fairly simple to replace, a process that can be done at home and takes less than a minute.

The technology is currently in phase 2a trials and has demonstrated more than a 35% reduction in IOP in a prostaglandin study in dogs. Amorphex has secured a regulatory path with the FDA to gain approval.¹⁰

Graybug

Graybug is developing an injectable platform, encapsulating novel agents in microparticles that form a resorbable drug depot in the vitreous. Initial dosing will be every 6 months, but recent animal data support once-yearly dosing.¹¹

The company is developing two related technologies. One is an injectable drug depot that can be tuned for different agents, various delivery sites within the eye, and different delivery durations. The second technology comprises novel forms of familiar drugs that have been optimized for depot delivery. According to Graybug, it is possible to deliver a prostaglandin-timolol combination, for example, or an IOP-lowering agent plus a neuroprotective agent.

A phase 1 clinical trial in wet age-related macular degeneration has begun, and the company plans to launch its first glaucoma trial in 2018.

pSivida

The Durasert (pSivida) is a bioerodible insert that is roughly the size of a grain of rice. The device is designed to be injected into the subconjunctival space via a modified 27-gauge system and to deliver latanoprost for up to 12 months. The insert is currently in phase 1/2 trials. It is a modification of the approved technology licensed by Alimera Sciences for the Iluvien implant, which delivers a

steroid to the posterior segment for up to 3 years. There is also the possibility of injecting sustained-release neuroprotective agents with the same injector system, a goal that has eluded companies for years. The insert would not need to be surgically removed, according to pSivida.

Replenish

The programmable Ophthalmic MicroPump System (Replenish) is designed to deliver nanoliters of drug directly into the anterior chamber or pars plana. The platform is surgically implanted similarly to a glaucoma drainage device, and it can be refilled with a 31-gauge needle in the clinic. Current studies have demonstrated a good safety profile in canine models without excess inflammation or scarring at 12 months.¹² The device also has the potential to assist in the long-term treatment of retinal pathology via sustained-release therapeutic agents, potentially decreasing the need for repeat intravitreal injections.

CONCLUSION

Without a doubt, the emphasis of research and development for glaucoma medical therapy is on reducing the burden of eye drops on patients in hopes of better controlling disease progression. New drug delivery devices combined with advances in laser treatments and microinvasive glaucoma surgery may spare patients a life sentence of topical drops. ■

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