

FILL A NEED

Enhancing adherence to glaucoma therapy with punctal plug drug delivery platforms.

BY MALIK Y. KAHOOK, MD; JEFFREY R. SooHoo, MD; AND LEONARD K. SEIBOLD, MD



One of the major limitations of medical therapy for glaucoma is patients' poor adherence to physician-prescribed regimens. It has been estimated that the rate of nonadherence to topical glaucoma therapy is 40% or



higher.¹⁻³ Even with multiple methods of addressing the problem, such as memory aids and instillation devices, proper therapy remains a major unmet need for patients around the globe.

In response, over the past decade, several companies have attempted to develop therapeutic strategies that are indepen-

dent of patients and administered by the physician. These modalities include insert devices that reside on the ocular surface, slow-release medication depots that are injected into the eye, and punctal plugs that deliver drugs directly into the tear film. The last of these has received a great deal of attention during the past few years.

WHY PUNCTAL PLUGS?

Inserting a slow-release medication depot into the punctum provides several advantages. First, standard punctal plugs have been used to manage dry eye disease for decades. This history encourages more immediate acceptance by physicians and patients, because there is a track record of safety that does not exist with many other strategies for long-term ophthalmic depots.

Second, punctal plug delivery platforms are a minimally invasive intervention. Compared to intraocular injections, for example, they represent a low-risk approach that is on par with more traditional therapies such as topical drops.

Third, a punctal plug approach can leverage existing active pharmaceutical ingredients (APIs) that have a long track record of success and safety.

DRAWBACKS

Like any treatment modality, punctal plugs have drawbacks. For one thing, they are prone to fall out over time, which is not acceptable for the treatment of a chronic disease, when months often elapse between office visits. Overcoming this problem would require either enhanced

retention devices or the patient's awareness that a plug had fallen out of place. In the latter case, a visit to the physician should be scheduled to replace the plug or initiate an alternate therapy.

Another drawback to current designs is that drug delivery is passive, depending on tears to wash into the plug reservoir and transport the active drug back into the tear film. In cases of severe dry eye or lid anatomy pathologies, plugs may not be able to deliver a drug in a predictable manner.

Finally, current APIs may not be ideal for this type of delivery system, either owing to an inability to hold a large enough depot or because of differences in efficacy with pulsed dosing, as with topical drops, compared to the constant delivery of the same drug when retained in a depot.

TECHNOLOGIES

This article has described just a few of the pros and cons of using punctal plugs for the treatment of glaucoma and other ophthalmic diseases, but the drawbacks should be viewed as challenges to overcome rather than deterrents to using this method of treatment. There have been multiple attempts at delivering drugs with punctal plugs over the years, and many have come and



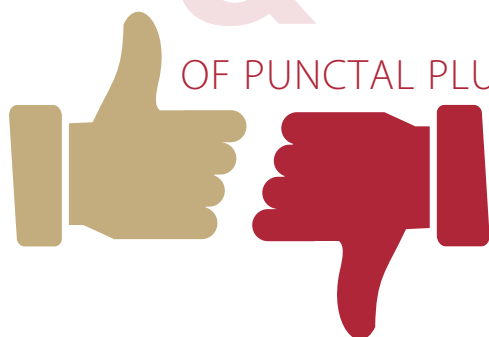
AT A GLANCE

- Poor adherence to glaucoma treatment is an ongoing problem. Patient-independent therapies that demonstrate long-term efficacy, such as punctal plugs, are one potential solution.
- Although the minimally invasive application, patients' and doctors' familiarity with punctal plugs, and their long-term safety record make this platform attractive, obstacles such as retention and consistent efficacy will have to be overcome.
- Several promising punctal plug drug delivery platforms are in active clinical trials and show some hope of becoming commercially available in the coming years.



Figure 1. The Evolute in situ (A). The device becomes visible when the eyelid is pulled down (B, C).

PROS & CONS OF PUNCTAL PLUGS



Punctal plugs have been in use for decades, so they have the advantages of familiarity and a history of safety.

This minimally invasive intervention represents a low-risk approach compared to intraocular injections, for example.

Punctal plug delivery platforms can leverage existing active pharmaceutical ingredients that have a long track record of success and safety.

Punctal plugs are prone to fall out over time, which is not acceptable for the treatment of a chronic disease, when months often elapse between office visits.

Drug delivery is passive and potentially unpredictable.

Current active pharmaceutical ingredients may not be ideal for this type of delivery system.

gone without being able to overcome the limitations described. Several promising technologies in active clinical trials, however, show some hope of becoming commercially available in the coming years.

Mati Therapeutics, a startup company that is continuing work begun at QLT, is developing a long-term punctal plug delivery system (Evolute; Figure 1) that has completed multiple clinical trials for the treatment of glaucoma and other ophthalmic diseases. Earlier studies with this system at QLT revealed success in lowering IOP and improved retention of the plug by way of device refinement over time. In one press release, the company reported plug retention ranging

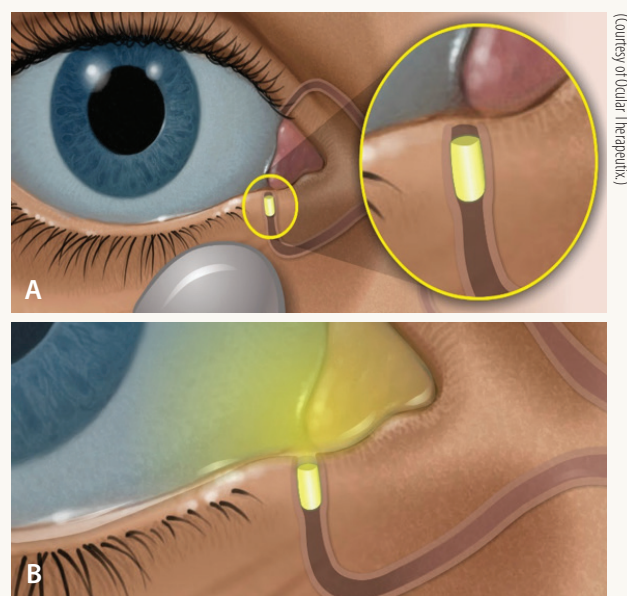


Figure 2. OTX-TP is moisture activated and formfitting upon insertion. It swells to fit comfortably and securely in the canaliculus, according to Ocular Therapeutix (A). Over time, the company's hydrogel reportedly enables OTX-TP to release travoprost for up to 90 days (B).

“

Ongoing clinical trials will be informative in comparing punctal plug therapies with currently available topical medications.”

from 48% to more than 95%, depending on the duration of follow-up and whether the plug was placed in the upper or low punctum.⁴ Mati is currently engaged in a phase 2 trial of a latanoprost-delivering plug, with timolol as the active comparator.

Ocular Therapeutix has a proprietary polymer-based punctal plug drug delivery platform. Medication depots with this platform have included therapies for glaucoma, using travoprost as the API, with reported retention of 88% at 75 days.⁵ The company is also working with ocular allergy and postcataract surgery steroid depots. The travoprost plug (OTX-TP) is currently in phase 3 trials comparing it to placebo (Figures 2 and 3).

A punctal plug delivery system from Eximore Technologies leverages a nonbiodegradable, nonsilicone polymer composite device to allow the delivery of APIs to the tear film. Data on this platform are not widely

available, but in vitro and preclinical studies reported to date show promise.⁶

Overall, the IOP-lowering efficacy of the various platforms has not been rigorously tested and reported. To date, with sparse information available, pressure-lowering efficacy appears to range from slightly less than with a β -blocker to almost on par with a prostaglandin analogue.

CONCLUSION

As is true with many chronic illnesses, poor adherence to glaucoma treatment is an ongoing problem for patients and their treating physicians. Patient-independent therapies that demonstrate long-term efficacy, such as punctal plugs, are one potential solution. Although the minimally invasive application, patients' and doctors' familiarity with punctal plugs, and a long-term safety record make this platform attractive, obstacles such as retention and consistent efficacy will have to be overcome. Ongoing clinical trials will be informative in comparing punctal plug therapies with currently available topical medications. ■

1. Friedman DS, Hahn SR, Gelb L, et al. Doctor-patient communication, health-related beliefs, and adherence in glaucoma results from the Glaucoma Adherence and Persistency Study. *Ophthalmology*. 2008;115:1320-1327.

2. Friedman DS, Quigley HQ, Gelb L, et al. Using pharmacy claims data to study adherence to glaucoma medications: methodology of the Glaucoma Adherence and Persistency Study (GAPS). *Invest Ophthalmol Vis Sci*. 2007;48(11):5052-5057.

3. Quigley HA, Friedman DS, Hahn SR. Evaluation of practice patterns for the care of open-angle glaucoma compared with claims data: the Glaucoma Adherence and Persistency Study. *Ophthalmology*. 2007;114(9):1599-1606.

4. QLT shows positive efficacy trends from data in plug combinations in phase II studies for glaucoma using latanoprost punctal plug delivery system [press release]. Vancouver, British Columbia: QLT; October 24, 2012. <http://bit.ly/2xHm78>. Accessed August 28, 2017.

5. Ocular Therapeutix reports on topline results of phase 2b glaucoma clinical trial [press release]. Bedford, MA: Ocular Therapeutix; October 22, 2015. <http://bit.ly/2wj7F3X>. Accessed August 30, 2017.

6. Gebhart F. New technologies on horizon to redefine drug delivery. *Ophthalmology Times*. <http://bit.ly/2gjlubM>. Published July 15, 2017. Accessed August 28, 2017.

(Courtesy of Ocular Therapeutix.)

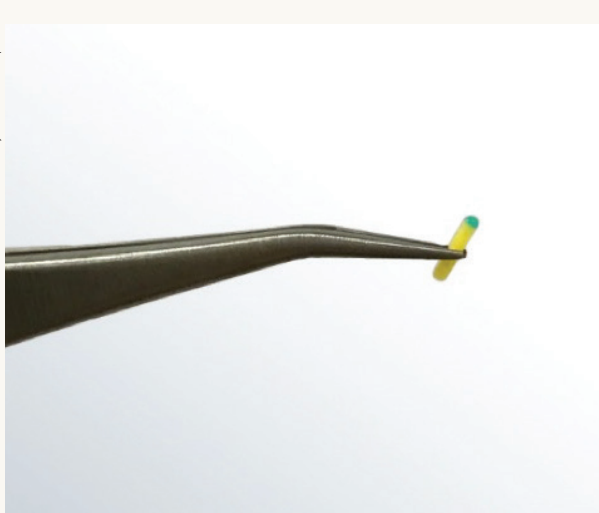


Figure 3. The OTX-TP in surgical forceps.

Malik Y. Kahook, MD

- Slater family endowed chair in ophthalmology; vice chair, clinical and translational research; director, Glaucoma Service; and codirector, Glaucoma Fellowship, Department of Ophthalmology, University of Colorado School of Medicine, Aurora, Colorado
- (720) 848-2020; malik.kahook@ucdenver.edu
- financial disclosure: owns patents in the field of punctal plugs for drug delivery to the eye

Leonard K. Seibold, MD

- associate professor of ophthalmology and codirector, Glaucoma Fellowship, University of Colorado School of Medicine, Aurora, Colorado
- leonard.seibold@ucdenver.edu
- financial interest: none acknowledged

Jeffrey R. Soohoo, MD

- assistant professor of ophthalmology and residency director, University of Colorado School of Medicine, Aurora, Colorado
- financial interest: none acknowledged