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 independent 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 gone.

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

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.
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 |

**PROS & CONS OF PUNCTAL PLUGS**

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<th>PROS</th>
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<td>Punctal plugs have been in use for decades, so they have the advantages of familiarity and a history of safety.</td>
<td>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.</td>
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<td>This minimally invasive intervention represents a low-risk approach compared to intraocular injections, for example.</td>
<td>Drug delivery is passive and potentially unpredictable.</td>
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<td>Punctal plug delivery platforms can leverage existing active pharmaceutical ingredients that have a long track record of success and safety.</td>
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Figure 1. The Evolve in situ (A). The device becomes visible when the eyelid is pulled down (B, C).

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).
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.