

Glaucoma Drugs in the Pipeline

Physicians share which coming therapies they are most eager to use in their practices.

**BY MALIK Y. KAHOOK, MD; PAUL L. KAUFMAN, MD; ROBERT J. NOECKER, MD, MBA;
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PAUL L. KAUFMAN, MD

Latanoprostene bunod (Vesneo; Bausch + Lomb [a Valeant Pharmaceuticals company]) is an exciting drug for me personally. It is a nitric oxide-donating prostaglandin F₂- α analogue that reduces IOP in patients with glaucoma and ocular hypertension. My research group had helped to delineate the ocular hypotensive mechanism for both prostaglandin analogues and nitric oxide-donating compounds in nonhuman primates, and decades ago, I was on scientific advisory boards for other companies that were looking very carefully at this kind of technology but passed on it. Subsequently, I was on the scientific advisory board that urged Bausch + Lomb to go after this compound, and now, here we are. The company recently submitted a new drug application to the FDA.

In a phase 2 trial, once-daily latanoprostene bunod 0.024% reduced IOP significantly more than latanoprost with comparable side effects.¹ Last year, the primary endpoint of noninferiority to timolol maleate 0.5% was achieved in two phase 3 studies. Additionally, the drug reduced mean IOP by 7.5 to 9.1 mm Hg from baseline between 2 and 12 weeks of treatment. This IOP effect was statistically superior ($P < .05$) to that of timolol in both studies. The safety of latanoprostene bunod was comparable to latanoprost, with the most common adverse event's being mild hyperemia, which occurred at a similar rate across all treatment groups.¹

I anticipate that this drug will eventually be used as a first-line therapy: one molecule in one bottle administered once daily acting on both the uveoscleral pathway (by altering the extracellular matrix in the ciliary muscle and the sclera) and the trabecular meshwork outflow pathways (by inhibiting actomyosin contractility in trabecular meshwork cells and thereby relaxing the meshwork). The strong efficacy and the simplified therapeutic regimen agent may also keep some patients out of the OR, because they are more likely to adhere to the simplified prescribed therapy.

MALIK Y. KAHOOK, MD

Sustained-release travoprost (OTX-TP; Ocular Therapeutix) is an intracanalicular depot composed of polyethylene glycol hydrogel and drug-containing microparticles. Once the drug is inserted into the tear drainage system, the hydrogel expands to conform to the surrounding tissue. The drug is then released into the tear film in a controlled fashion to lower IOP over an extended period of time. To date, clinical studies of OTX-TP have shown up to 3 months of statistically significant IOP-lowering efficacy.²

Poor adherence to glaucoma therapy is one of the major reasons why I am excited about OTX-TP. Using a drug depot that bypasses forgetfulness, physical limitations, and many other of the major contributors to poor adherence with topical therapies would be a game-changer for glaucoma patients around the world. It remains to be seen if future data from OTX-TP will remain consistent with the early publicly available data. Also of interest, however, is how this form of drug delivery will compare to other punctal plug drug delivery vehicles as well as injectable depots that are currently in studies for treating glaucoma.

ROBERT J. NOECKER, MD, MBA

I am looking forward to the approval of Inotek Pharmaceuticals' trabodenoson and Aerie Pharmaceuticals' Rhopressa and Roclatan.

Trabodenoson is a selective adenosine mimetic, a novel mechanism for IOP control designed to directly protect retinal ganglion cells through a neuroprotective effect. According to Inotek, a phase 3 trial of trabodenoson is expected to commence in the fourth quarter of this year. The compound targets one of four known receptors for the naturally occurring adenosine A1 receptor. When stimulated, this receptor is reported to upregulate proteases in the trabecular meshwork,

TABLE. STATUS OF GLAUCOMA DRUGS IN THE PIPELINE

Product	Company	Type of Drug	Status
Rhopressa	Aerie	Once-daily eye drop that inhibits Rho kinase and norepinephrine transporter	Rocket 2 efficacy results expected in the third quarter of 2015; Rocket 4 scheduled to start in the third quarter of this year
Roclatan	Aerie	A single-drop fixed-dose combination of Rhopressa and latanoprost	Phase 3 trial (Mercury 1) expected to begin in the third quarter of this year
Bimatoprost SR	Allergan	Sustained-release implant	Phase 3 trials underway
Latanoprostene bunod (Vesneo)	Bausch + Lomb	Novel nitric oxide-donating prostaglandin F ₂ - α analogue	New drug application submitted to the FDA
Trabodenoson	Inotek	A potent and highly selective adenosine mimetic acting only at the A ₁ receptor subtype	Phase 3 trial expected to commence in the fourth quarter of this year
OTX-TP	Ocular Therapeutix	Sustained-release travoprost punctal plug	Phase 2 clinical trials underway

specifically matrix metalloprotease-2, which digests and removes hydrolyzed proteins that clog the trabecular meshwork and restrict the normal outflow of aqueous humor.³ Once cleared, the trabecular meshwork can regain its normal pressure-regulating function.⁴

In a phase 1/2 clinical study in elderly but healthy volunteers, 2 weeks of twice-daily dosing of up to 3.2 mg in a single eye and once-daily dosing of up to 3.2 mg in both eyes did not cause significant side effects.⁵ At the highest doses tested, no maximum tolerable dose was determined, because there were no appreciable local effects in the eye and no systemic effects of the drug were detected. Specifically, the adenosine mimetic lacked the hyperemia associated with prostaglandin analogues and other glaucoma drugs in development.

In two completed phase 2 trials, the single eye drop formulation of trabodenoson significantly lowered IOP in patients who were no longer using glaucoma medications.⁶ When trabodenoson was added to latanoprost, those patients whose IOP remained elevated on a prostaglandin analogue alone also had a significant reduction in IOP. This IOP-lowering effect was significant whether the drug was dosed once or twice daily. In these efficacy trials, trabodenoson was well tolerated, and no systemic effects were observed.

If the good efficacy and lack of side effects prevail in the phase 3 trials, I believe trabodenoson—with once-daily dosing and a mechanism that complements the currently available glaucoma drugs—could be a welcome tool for managing IOP in patients who need a second drug to reach therapeutic IOP-lowering targets or for

those intolerant of or unresponsive to current therapies.

Rhopressa is a Rho kinase and norepinephrine transporter inhibitor that is believed to lower IOP by the “triple action” of reducing aqueous production, increasing trabecular outflow, and decreasing episcleral venous pressure. A rabbit study demonstrated significant lowering of episcleral venous pressure at various concentrations.⁷ In a phase 2 trial, once-daily AR-13324 0.02% lowered IOP by 5.7 mm Hg from the unmedicated baseline.⁸

For its phase 3 registration trial, Rocket 1, Rhopressa did not meet its primary efficacy endpoint based upon IOP measurements at the end of weeks 2 and 6 and day 90.⁹ The Rocket 1 study included 182 patients in the Rhopressa once-daily arm and 188 patients in the timolol twice-daily arm. The baseline IOPs ranged from above 20 mm Hg to below 27 mm Hg. The results showed a slight loss of efficacy at week 6 and on day 90. In the Rhopressa arm, 36 patients (approximately 20%) showed signs of loss of efficacy during the study. The primary adverse event was hyperemia, which was experienced by approximately 35% of the Rhopressa patients, of which 80% was reported as mild.⁹

The FDA recently agreed to allow Aerie to change the primary endpoint range of its second phase 3 registration trial (Rocket 2) to include patients with baseline IOPs ranging from above 20 mm Hg to below 25 mm Hg, the same range in which Rocket 1 demonstrated success. The former range for the primary endpoint of above 20 mm Hg to below 27 mm Hg will now represent a secondary endpoint range for Rocket 2.

Aerie's Roclatan, a combination of Rhopressa and

latanoprost, was also evaluated in a phase 2b clinical trial of 297 patients. Roclatan lowered mean diurnal IOP on day 29 by 34% from a baseline of 25.1 to 16.5 mm Hg.¹⁰ Roclatan's IOP-lowering effect exceeded that of latanoprost by 1.6 to 3.2 mm Hg across each time point evaluated during the study, and these results were statistically significant at all time points. The most common adverse event with Roclatan was hyperemia, which was reported in 40% of patients and scored as mild for most of them.¹⁰

Aerie's new drugs promise the potential that our current glaucoma treatment algorithms may change in the future. With its ability to alter episcleral venous pressure, Rhopressa may benefit patients with normal-tension glaucoma. The combination drug Roclatan, will provide a new way to treat patients with high IOPs on single eye drop therapy that is significantly different than what is available now. For patients who need higher degrees of IOP lowering or who have not maintained target IOPs with other agents, this drug will be a welcome solution.

NATHAN M. RADCLIFFE, MD

From the moment I decide to write a prescription for a patient, multiple events may interfere with the intended result of lowering his or her IOP. Often, paper prescriptions are lost or never filled, or they are rejected by the patient's insurance plan. Electronic prescriptions are lost in cyberspace. Eye drops may not be used. Alternatively, the eye drop may fall on the cheek instead of in the eye, or too many drops may be delivered to the eye, emptying the bottle prior to when a refill is allowed. If the drop actually makes it to the eye, almost one-third of patients stop using the medication due to local side effects.¹¹ Even those few patients who successfully pass all of these hurdles may end up suffering from the long-term effects of topical eye drop use.

Finally, there is a potential solution in the pipeline to these problems. Allergan has formulated a sustained-release implant capable of delivering bimatoprost for many months after a single intracameral injection. By placing the medication closer to the intended target, topical and periocular side effects may be significantly reduced or eliminated, and efficacy may be enhanced. Most importantly, the paradigm of daily or multidaily eye drop administration is changing. This shift can only bring great things for the future of glaucoma management.

A phase 3 trial of the bimatoprost implant is currently underway. In the phase 2 trial, patients received the implant in one eye and topical bimatoprost in the contralateral eye. The data suggest that the efficacy of the implant is comparable to that of daily topical bimatoprost with a duration of 4 to 6 months.¹² ■

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