Glaucoma is a domestic and global health care challenge that affects approximately 3 million Americans and is a leading cause of blindness around the world.1 An aging population, available diagnostic modalities that may identify disease progression in a more sensitive fashion, and a better understanding of progression rates from randomized trials may all influence physicians to intervene earlier and more aggressively. There is good reason to do both: in the Early Manifest Glaucoma Trial (EMGT), approximately half of untreated patients exhibited signs of disease progression after 4 years.1 Even for treated patients, achieving long-term IOP control can be challenging. The Ocular Hypertensive Treatment Study (OHTS) demonstrated that achieving an IOP reduction of 20% to 24 mm Hg or less in approximately 40% of patients required two or more medications at the 60-month visit.2

With this sobering prelude, there is excitement in the air as multiple new therapeutic options work through the FDA approval process. A new class of glaucoma agents has not been introduced since the prostaglandins approximately 2 decades ago.3 This article focuses on the three agents furthest along the drug development pipeline, based on the order of their projected approval.

LATANOPROSTENE BUNOD
Latanoprostene bunod ophthalmic solution 0.024% (Vyzulta; Bausch + Lomb) is a nitrous oxide (NO)-donating prostaglandin F2α analogue reported to have a dual mechanism of action, increasing both uveoscleral and trabecular outflow.4 An important endogenous mediator in the body, NO has critical roles in the cardiovascular system and is a well-known mediator of smooth muscle relaxation and vasodilatation.5 NO enzymes are found throughout ocular tissues, and they have multiple roles, including relaxation of the trabecular meshwork, regulation of Schlemm canal volume, secretion (inflow), and vasodilation of ocular blood vessels.6 Studies demonstrate that, in eyes with open-angle glaucoma, there are lower levels of NO activity in the trabecular meshwork, Schlemm canal, and the ciliary musculature.7 NO has many interesting effects in open-angle glaucoma: it mediates many of the disease’s ocular effects, including the maintenance of IOP through soluble guanylate cyclase, and it increases the second messenger cyclic guanosine monophosphate.8

The primary mechanism by which prostaglandins (latanoprost acid) lower IOP in the eye is via the uveoscleral pathway, but discoveries of the secondary effect of NO on the trabecular meshwork outflow are relatively new. Through the conventional pathway, NO is said to increase aqueous humor outflow via the trabecular meshwork and Schlemm canal pathway by relaxing the former and regulating the volume of the latter.9 In pivotal phase 3 trials (Apollo and Lunar), treatment with a single dose of the drug demonstrated an IOP reduction range of 7.5 to 9.1 mm Hg from baseline at between 2 and 12 weeks of treatment with no evidence of tachyphylaxis at 1 year.10 No significant safety findings were reported. Side effects were typical of a prostaglandin analogue.
NETARSUDIL

Netarsudil ophthalmic solution 0.02% (Rhopressa; Aerie Pharmaceuticals) is the first Rho kinase (ROCK) inhibitor to advance to regulatory submission in the United States. The drug is a small-molecule inhibitor of both ROCK and norepinephrine transporter, and it is thought to have three principal mechanisms of action. ROCK inhibition increases outflow through the trabecular meshwork and lowers episcleral venous pressure, while norepinephrine transporter inhibition decreases inflow by reducing the production of fluid. Clinical research suggests that the drug could be a useful option for both initial and adjunctive therapy, particularly in the large number of patients who first present with low- or normal-tension glaucoma. In a phase 2b trial, a single dose of netarsudil produced a consistent reduction in IOP regardless of starting pressure. It reduced IOP by 5.2 to 6.6 mm Hg across all time points. This decrease was approximately 1 mm Hg less than with latanoprost, but the two agents were statistically equivalent in patients with starting pressures below 26 mm Hg. (See Watch it Now.)

The most frequently reported adverse event associated with netarsudil was conjunctival hyperemia. This effect was generally mild and transient, usually milder in the morning than immediately after evening installation, and it declined over time. In the first phase 3 clinical trial (Rocket 1), non-inferiority to twice-daily timolol was not met, although the data may have been skewed by lack of response among patients with a high initial IOP. Netarsudil was actually superior to timolol among a subset of patients with an initial IOP below 26 mm Hg.

The second study, Rocket 2, clearly demonstrated non-inferiority. The 12-month interim analysis of the first 118 patients in Rocket 2 showed a sustained IOP reduction with no evidence of tachyphylaxis. The most commonly reported adverse event was hyperemia (30% increase from baseline, 76% mild, 81% sporadic). There were no serious adverse events related to therapy. Aerie is also conducting two phase 3 trials (Mercury 1 and Mercury 2) of a fixed combination of netarsudil with latanoprost. This move follows a successful phase 2b trial that compared two concentrations of the fixed-dose combination to both netarsudil and latanoprost in a trial design that followed the FDA’s requirements for fixed-dose combinations.

In this study, the fixed-dose combination (Roclatan 0.02%) achieved statistical superiority over the individual components at all time points (P < .001). The IOP-lowering effect of the fixed-dose combination was unprecedented. For example, on day 29, 50% of the Roclatan patients had IOP reductions of greater than 35% compared to 17% for Rhopressa alone and 28% for latanoprost alone. Most recently, topline efficacy results were released on the first phase 3 study (Mercury 1). The study achieved its primary efficacy endpoint demonstrating statistical superiority of the fixed-dose combination over each of its components. The IOP-lowering effect of Roclatan was 1 to 3 mm Hg greater than monotherapy with either latanoprost or netarsudil throughout the study, with subjects having maximum baseline IOPs ranging from 20 to 36 mm Hg. 

TRABODENOSON

Trabodenoson (Inotek Pharmaceutical) is a first-in-class, highly selective adenosine mimetic targeting the adenosine A1 subreceptor. Trabodenoson is reported to lower IOP by augmenting the natural function of the trabecular meshwork. In phase 2 trials, treatment with the drug reduced IOP in patients with primary open-angle glaucoma and those with ocular hypertension, with a diurnal IOP reduction ranging from 3.5 to 5 mm Hg and at an average of 4.1 mm Hg. Efficacy continued to improve with longer duration of therapy and up to the highest dose tested, indicating that higher doses may provide additional IOP lowering. To date, no dose-limiting toxicity has been observed, and no significant dose-related ocular or systemic side effects have occurred. The data through phase 2 demonstrate no drug-related hyperemia. The first phase 3 study of trabodenoson (MATrX-1) is underway, with three active doses being tested: 3% and 6% daily and 4.5% twice a day. The statistical comparator in the trial is placebo, and a timolol 0.5% twice-daily arm serves as an internal control. Data from this trial are expected by the end of 2016, and the program will continue with a second phase 3 trial (MATrX-2) and a long-term safety study (MATrX-3), using the dose with the optimized clinical profile from MATrX-1. Inotek is also
conducting a phase 2 trial of trabodenoson in fixed-dose combination with latanoprost. With the potential approval of these three innovative compounds, physicians’ challenging job of reducing glaucomatous progression might become just a bit easier.

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14. Bacharach J. AR-13324 ophthalmic solution 0.02%: top-line results of two phase 3 clinical studies in patients with open-angle glaucoma and ocular hypertension. Poster presented at: American Glaucoma Society Annual Meeting; March 3-6, 2016; Fort Lauderdale, FL.

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