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Emerging Trabecular Outflow Drugs

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Glaucoma is a progressive optic neuropathy that is a leading cause of irreversible blindness worldwide.[1] Elevated intraocular pressure (IOP) is commonly associated with glaucoma, and multiple longitudinal studies have demonstrated that lowering IOP in patients can slow optic nerve degeneration and preserve vision.[2] Although medications are available to reduce elevated IOP, the most commonly prescribed drugs do not address the underlying cause of elevated IOP in glaucoma, the deteriorating function of the trabecular outflow pathway.

The trabecular outflow pathway is the primary draining tissue for the aqueous humor in the eye. It consists of 3 structures, the trabecular meshwork (TM), juxtacanalicular tissue, and Schlemm's canal. In a healthy eye, IOP is maintained within a narrow range through dynamic regulation of trabecular outflow resistance. In a glaucomatous eye, elevated IOP is due to an abnormally high resistance to outflow in the trabecular outflow pathway.[3] The causes of increased outflow resistance are not fully understood, but it has been hypothesized to involve an increase in the contractile tone and stiffness of the TM and changes in extracellular matrix composition and/or a change in the conductance of Schlemm's canal.[4]

There is a significant need for glaucoma drugs that specifically target the physiologic cause of elevated IOP and thereby enhance trabecular outflow. The tissues of the trabecular outflow pathway are avascular and rely on the aqueous humor to supply nutrients, growth factors, and antioxidants. The most widely prescribed glaucoma drugs, the prostaglandin analogues (PGAs), lower IOP by increasing the aqueous drainage through the unconventional uveoscleral outflow pathway.[5] The older, non-PGA drug classes, the beta blockers, alpha agonists, and carbonic anhydrase inhibitors, lower IOP by decreasing the production of aqueous humor.[5] By shunting the aqueous humor through the uveoscleral pathway or decreasing the aqueous production, the commonly used glaucoma medications actually decrease the outflow of aqueous humor through the diseased TM. Thus, while protecting the optic nerve from damage by lowering IOP, current medications may be allowing further degradation of the trabecular outflow pathway.

PGAs have become the initial therapy of choice for most physicians because they are generally more effective at lowering IOP and better tolerated than non-PGA drugs, and they offer a once-daily dosing regimen. Although PGAs often provide adequate efficacy as an initial therapy, nearly half of all patients started on PGA monotherapy ultimately require 1 or more non-PGA drugs to be added to their treatment regimen. This is the primary reason why half of all prescriptions are still written for non-PGA products.[6] It does not appear that PGAs become less effective at promoting the uveoscleral outflow over time. IOPs continue to rise over time because the function of the trabecular outflow pathway continues to deteriorate over time.

Fortunately, several new drug classes that target the trabecular outflow pathway have entered clinical development (Table 1). The drug class with the longest history in the clinic is the class of selective Rho kinase inhibitors. Rho kinase is a serine/threonine kinase whose activity increases actomyosin contraction in smooth muscle cells, including the smooth muscle-like cells of the TM. The therapeutic potential of Rho kinase inhibitors was initially demonstrated in preclinical studies using the Rho kinase inhibitor Y-27632, which was shown to relax precontracted TM tissue *ex vivo*,[7] increase trabecular outflow in perfused enucleated porcine eyes,[8] and lower IOP in live rabbits upon topical ocular application.[9]

According to clinical trial registries in the U.S., Europe, and Japan, 7 different selective Rho kinase inhibitors have been tested in human clinical trials.[10] The most studied compound of this class is Aerie Pharmaceuticals' AR-12286. Although Aerie has replaced AR-12286 with the Rho kinase/norepinephrine transporter (ROCK/NET) inhibitor AR-13324 as its lead trabecular outflow drug (see below), much was learned about the potential clinical utility of selective Rho kinase inhibitors from AR-12286 clinical studies. For example, transient hyperemia is a class effect of Rho kinase inhibitors that results from relaxation of the smooth muscle cells of conjunctival blood vessels. A 28-day study of AR-12286 in patients with elevated IOP showed that transient hyperemia associated with Rho kinase inhibition could be effectively managed by dosing the drug once-daily in the evening to allow the hyperemia to resolve overnight.[11] Specifically, once-daily P.M. dosing of 0.5% AR-12286 achieved IOP reductions of 2.9 to 6.1 mmHg, similar to twice-daily dosing of 0.25% AR-12286. However, the hyperemia incidence with the once-daily P.M. dosing regimen was only 11% compared with 46% for the twice-daily dosing regimen.

Another AR-12286 clinical study demonstrated that Rho kinase inhibition can be used successfully in combination with PGAs to achieve a greater IOP lowering than PGA therapy alone.[12] In patients with elevated IOP, a fixed-dose

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Table 1. Recent Clinical Development of Trabecular Outflow Drugs

Drug class/molecule	*Company*	*Phase 2 data references*
ROCK inhibitors		
AR-12286	Aerie	11, 12, 19
ATS-907	Altheos	n.a.
AMA-0076	Amakem	n.a.
INS-117548	Inspire/Merck	n.a.
K-115	Kowa	13
DE-104	Santen	n.a.
SNJ-1656	Senju/Novartis	20
Adenosine A1 agonists		
INO-8875	Inotek	15
ROCK/NET inhibitors		
AR-13324	Aerie	18

ROCK, Rho kinase; NET, norepinephrine transporter; n.a., not available.

combination of 0.5% AR-12286 and 0.004% travoprost achieved IOP reductions of 9 to 12 mmHg when dosed once-daily in the evening and produced a reduction in diurnal IOP that was 2 mmHg greater than travoprost alone. The incidence and severity of hyperemia for the fixed-dose combination was similar to travoprost monotherapy. Given that physicians often need to prescribe non-PGA drugs as add-on therapy to PGAs, it is important that the Rho kinase mechanism of action is compatible with the PGA mechanism of action.

Phase 2 clinical study results have recently been published for another selective Rho kinase inhibitor, K-115, from Kowa.[13] In patients with elevated IOP, twice-daily dosing of 0.4% K-115 achieved IOP reductions of 3.1 to 4.5 mmHg. A 65% incidence of transient, mild hyperemia was reported for this concentration. The 0.4% concentration of K-115 has been advanced to Phase 3 studies in Japan.

Adenosine A_1 receptor agonists represent another new drug class that targets the trabecular outflow pathway. Adenosine A_1 agonists are thought to increase the trabecular outflow by reducing the cell volume and increasing the expression of matrix metalloproteinases.[14] The clinical study results from a 28-day Phase 2 trial have recently been presented for the adenosine A_1 agonist trabodenoson (INO-8875).[15] In patients with elevated IOP, twice-daily dosing of 500 μg trabodenoson produced IOP reductions of 4.9 to 6.5 mmHg. A transient, mild hyperemia was observed, although the incidence of hyperemia was not reported.

The newest class of trabecular outflow drugs is the dual-action ROCK/NET class. ROCK/NET inhibitors are single molecules that act through a dual mechanism of action, simultaneously inhibiting Rho Kinase to increase trabecular outflow and inhibiting the NET to reduce the production of aqueous humor.[16,17] Aerie Pharmaceuticals' AR-13324 is the first compound of this class to be tested in the clinic and has replaced AR-12286 as Aerie's lead trabecular outflow drug. In a 7-day clinical trial in patients with elevated IOP, once-daily A.M. dosing of AR-13324 (0.01%, 0.02%, or 0.04%) produced IOP reductions ranging from 5.6 to 7.2 mmHg.[18] The morning dosing regimen produced transient, mild to moderate hyperemia with an incidence of 29% for the 0.02% concentration (the top of the dose–response curve) on day 7. The 0.01% and 0.02% concentrations of AR-13324 have been advanced to a 28-day Phase 2b study to evaluate the efficacy and tolerability of AR-13324 when dosed once-daily in the evening. In addition, clinical development has begun for PG324, a fixed-dose combination product that combines AR-13324 with latanoprost.

Physicians have long desired a drug that could effectively treat the source of elevated IOP in glaucoma, the diseased trabecular outflow pathway. Once available, it will be possible to address potential benefits that may be unique to a trabecular outflow drug. Does improving the flow of nutrients and growth factors to the trabecular outflow pathway stop or even reverse its degeneration? Is it important that trabecular outflow drugs be used early in the course of treatment, before the outflow pathway is damaged beyond repair? Does improving trabecular outflow restore the normal ability of the TM to dampen spikes in IOP and thereby provide greater protection to the optic nerve? Fortunately, significant progress is being made toward bringing an effective and well-tolerated trabecular outflow drug to the practice of glaucoma medicine.

Author Disclosure Statement

Casey C. Kopczynski is the Chief Scientific Officer and Cofounder at Aerie Pharmaceuticals. Aerie is developing the trabecular outflow drug AR-13324 mentioned in the editorial. As an employee of Aerie, he is an owner of Aerie stock as well as an owner of options to purchase stock. David L. Epstein is the founder of Aerie Pharmaceuticals and a former member of the Board of Directors. He is the owner of Aerie stock as well as an owner of options to purchase stock.

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