**Advances in Medical Glaucoma Management: Video 2: New Drug Classes**

*Supplementary Study Guide*

**Presenters**
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- Confirmed video shoot: Saturday, October 15, 3:00-5:00pm

**PART 1: Why New Drugs Are Needed**

What are some of the problems or challenges with current medical therapy of glaucoma?

- **The aim in medical therapy of glaucoma is to reduce the burden of treatment and inhibit optic neuropathy.** At this point, the only way we know how to do this in humans is by lowering IOP. PGAs lower IOP effectively, yet most glaucoma patients require more than one medication—or medication plus a laser or surgical treatment—to bring IOP down into their particular “safe” zone. Used once a day, they produce an IOP reduction of about 30%-3

Since the introduction of PGAs, the number of penetrating drainage surgeries for glaucoma performed annually has reportedly dropped.\(^4\)-\(^6\) That said, since monotherapy is insufficient to achieve adequate IOP lowering in a majority of patients, additional agents are desirable to provide greater IOP-lowering efficacy, either by themselves or in combination with existing drugs.

- **Nonadherence**—prevalent among glaucoma patients—undercuts clinical efforts to control the disease. In effect, a patient who discontinues treatment is in the same boat as a patient who goes untreated, something good clinicians strive vigorously to avoid. As such, nonadherence—and the factors that contribute to it—merits greater clinical attention and discussion within the medical community than it receives.

- **Significant barriers to compliance exist for patients with glaucoma, including situational/environmental factors, the medication regimen, patient factors, and provider factors.** Proper adherence to topical ocular medication requires that patients fill their prescriptions and instill the proper dosage into the ocular cul-de-sac at the appropriate time every day. Anything that interferes with the medication contacting the eye can be thought of as nonadherence, including not filling the prescription, taking a drug holiday, missing doses, or allowing for too little (compressing) or too much (spreading) time between doses. Patients with arthritis or other physical comorbidities may have trouble steadying their hand or squeezing the dropper, resulting in the drop missing the eye.

- **Studies across a range of populations show that medication nonadherence and dosing errors are widespread among patients being treated for glaucoma.** A 2005 literature review showed that up to 80% of patients deviate significantly from their prescribed antiglaucoma treatment regimen.\(^8\) Self-report rates of nonadherence are generally lower but also range widely, from 28% to 59%.\(^9\) Roughly 1 in 13 newly
diagnosed patients never filled their first antiglaucoma prescription. Among newly diagnosed patients who fill their prescriptions, persistence (defined as starting and continuing therapy as prescribed for a certain period of time) has been estimated at 50% at 6 months and about 31% at 12 months. Other estimates suggest that about 50% are adherent at 12 months.

- In a particular patient or group of patients, one class of medication may lose its effectiveness over time, a pharmacological effect known as tachyphylaxis. The PGAs are quite resistant to development of tachyphylaxis, but adjunctive therapy for additional pressure reduction can become necessary due to progression of the disease. When a patient requires three or four medications for IOP control, the therapeutic burden—primarily the complexity of the treatment regimen rather than just its cost, since many of the glaucoma drugs are now available as generics—increases significantly.

- Despite the therapeutic importance of manipulating the trabecular meshwork pathway in the treatment of POAG, few IOP-lowering medications directly target the trabecular meshwork/Schlemm’s canal. Of the several classes of glaucoma medications now in common clinical use, three—CAIs (systemic or topical), alpha-2 adrenergic agonists, and β-blockers (ie, β adrenergic antagonists)—are secretory suppressants that decrease aqueous humor production, and one—PGAs—lowers IOP primarily by enhancing uveoscleral aqueous outflow (alpha-2 adrenergic agonists are also associated with decreased episcleral venous pressure or increased uveoscleral outflow). Pilocarpine, one of the earliest glaucoma medications, lowers IOP by contracting the ciliary muscle and thus indirectly enhancing trabecular outflow; but the miotic has long fallen out of favor due to ocular and systemic adverse effects as well as frequent dosing.

- In patients with OAG and ocular hypertension, maintaining long-term IOP control is important to reduce the risk of progression and prevent vision loss from the chronic disease. However, it has proved difficult to achieve adequate IOP control with a single agent, especially in the long run. Adjunctive therapy is common and often necessary for patients to achieve their individual target IOP levels, but the use of multiple drops increases therapeutic burden and risk of side effects. In some cases, patients continue to lose vision despite a seemingly good response to the medical treatment. Studies have suggested that additional risk factors, such as IOP fluctuation over the course of 24 hours and low OPP, may be important for long-term glaucoma control. It is thought that increased IOP and decreased systemic blood pressure during sleeping hours may result in reduced OPP, compromising blood flow and perfusion to the retina and optic nerve head and contributing to the neuronal damage in OAG.

- These challenges in medical glaucoma therapy point to an unmet need for medications with novel mechanisms of action (MOAs) that provide sustained IOP control and at the same time are well tolerated.

PART 2: PGA plus NO donor (latanoprostene bunod)
Some of the medications that have been developed to fill these unmet needs in glaucoma care include the PGA plus NO donor latanoprostene bunod, cytoskeletal agents/ROCK inhibitors, and adenosine receptor agonists. Optic nerve regeneration is also being investigated. What is the mechanism of action of these latanoprostene bunod?

- Latanoprostene bunod ophthalmic solution 0.024% is a nitric oxide (NO)-donating prostaglandin F2α receptor agonist indicated for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Latanoprostene bunod has a unique dual mechanism of action, achieved not by blending two different drugs in the same bottle as is the case of current combination preparations but by chemically fusing two moieties—latanoprost and an NO donor—into one molecule. When instilled in the eye, latanoprostene bunod is rapidly metabolized to latanoprost acid, a PGA, and butanediol mononitrate, the NO donor; both moieties are active and responsible for the molecule’s pharmacological activities.27

- While latanoprost should increase uveoscleral outflow like other PGAs do, the NO donor is believed to contribute to IOP lowering by increasing aqueous outflow through the trabecular meshwork.28 The conventional trabecular meshwork pathway is the primary route of aqueous outflow in the human eye and the site of extra resistance that results in elevated pressure in POAG.29 Although its mechanism of action is not fully elucidated, NO appears to work by direct action on the trabecular meshwork to increase outflow facility. Specifically, it likely works as a signaling molecule that is part of the trabecular meshwork’s natural response to deformation stemming from the pressure differential between the anterior chamber and Schlemm’s canal. In this scenario, NO signals the trabecular meshwork cells to adjust to their contractile tone so that collectively the meshwork maintains a preset deformation and intraocular pressure. NO is thought to suppress the Rho signaling pathway, which when activated, contracts the trabecular meshwork to increase outflow resistance. Thus, if IOP rises, meshwork deformation is greater, endothelial NO synthase is upregulated, and more NO is released, causing the TM cells individually and the TM as a whole to relax. The effect is that outflow resistance decreases to reduce the IOP toward its preset norm. NO markers have been shown to be reduced in the aqueous humor of eyes with POAG, suggesting that glaucomatous eyes have less endogenous NO than non-glaucomatous eyes.30 Latanoprostene bunod supplements endogenous NO, decreasing resistance to trabecular outflow by relaxing contracted trabecular meshwork cellS.28

What are some of the key findings from clinical trials of latanoprostene bunod?

- In two phase 3, randomized, multicenter, double-masked, parallel-group studies (N = 831), latanoprostene bunod produced greater mean diurnal IOP reductions than timolol 0.5%31 and superior IOP reduction compared to timolol 0.5% for all time points at month 3.32 The most common ocular adverse reactions were conjunctival hyperemia (5.8%), eye irritation (4.3%), eye pain (3.1%), and instillation site pain (2.1%). In addition, in a phase 2, randomized, multicenter, single-masked, parallel-
group study (N = 413), latanoprostene bunod produced significantly greater IOP lowering and comparable side effects compared to latanoprost 0.005%.\textsuperscript{33}

What is the foreseeable niche in clinical care for latanoprostene bunod?

- If approved, latanoprostene bunod may have an important place in the initial treatment of a patient, where the general goal is to achieve successful IOP control with a single agent. Since latanoprostene bunod has been shown to be effective at reducing IOP without increasing the risk of side effects, it has the potential to replace the current PGAs as the first go-to drug for patients with open-angle glaucoma or ocular hypertension.
- Latanoprostene bunod may also be beneficial for patients that are already on a prostaglandin but need additional IOP reduction. Instead of adding one more topical medication drop, we can now choose to substitute latanoprostene bunod, which is one molecule with two mechanisms of action, for the primary prostaglandin.

PART 3: Cytoskeletal Agents/ROCK Inhibitors

What are some of the cytoskeletal agents/ROCK inhibitors in development?

- Rhopressa: Netarsudil mesylate 0.02\%, also known as AR-13324, is a Rho kinase (ROCK) and norepinephrine transporter (NET) inhibitor and another medication in a phase 3 trial (Rocket 4) that may change the landscape of medical glaucoma treatment. It is thought that netarsudil reduces IOP by three separate mechanisms: increasing trabecular outflow through ROCK inhibition, decreasing aqueous production through NET inhibition, and reducing episcleral venous pressure, presumably through NET inhibition.\textsuperscript{34}
- Roclatan: A fixed combination of netarsudil 0.02\% and latanoprost 0.005\% is also in phase 3 trials (Mercury 1 and 2). With an additional mechanism of action to latanoprost, the combination drug has the potential to reduce IOP to an even greater degree.
- Rhopressa and Roclatan are not the first cytoskeletal agents—nonselective adrenergic agonists, such as epinephrine, presumably lower IOP by modifying the cytoskeleton in the trabecular meshwork cells. Epinephrine and related agents used to be a common treatment for glaucoma, but they are no longer used because of local and potentially systemic side effects. In Japan, a ROCK inhibitor known as ripasudil has been in clinical use for about a year. That agent demonstrates modest but sustained IOP-lowering effects, and, most recently, was shown to provide additive efficacy in combination with timolol or latanoprost.\textsuperscript{35-37} Nor are Rhopressa and Roclatan likely to be the last cytoskeletal agents that we will see: second-generation ROCK and norepinephrine transporter inhibitors are now in preclinical development.

What is the mechanism of action of the ROCK inhibitors?
• Trabecular meshwork cells are highly contractile due to an abundance of actin filaments, a primary cytoskeleton component that drives cell contractility via interaction with motor proteins such as myosin. Activation of the Rho pathway tightens actomyosin networks, contracting the cells and strengthening cell-extracellular matrix adhesion. Overall, this makes the trabecular meshwork, especially the juxtacanalicular tissue more resistive to the outflow of aqueous humor. ROCK inhibition reduces actomyosin contractility and relaxes the meshwork, allowing aqueous to pass through more easily.

• Interestingly, Rhopressa is claimed to have two additional effects. Besides ROCK, it may also inhibit norepinephrine transporters, leading to reduced reuptake of norepinephrine and thus a higher extracellular concentration of the neurotransmitter at neurovascular or neuroepithelial synapses. This would increase norepinephrine stimulation in the ciliary epithelium, putatively resulting in decreased aqueous humor formation. Further and unique among glaucoma medications, Rhopressa is also claimed to reduce episcleral venous pressure. This latter effect, demonstrated most recently in an animal study, may allow Rhopressa to consistently reduce IOP, even in patients with normal to mildly elevated baseline IOPs.

What are the key findings from clinical trials of ROCK inhibitors?

• The manufacturer previously announced that in a phase 1 study of 18 normotensive individuals (mean IOP 16 mm Hg; range 12 to 21 mmHg) Rhopressa reduced mean IOP to 11 mm Hg, a reduction of just over 30%. These additional mechanisms beyond ROCK inhibition require further confirmation in animal and human studies.

• In two phase 3 studies (Rocket 1 and 2), Rhopressa was shown to be non-inferior to timolol in patients with baseline pressures between 20 and 25 mmHg, which, according to the Baltimore eye study, represents approximately 80% of diagnosed glaucoma patients.

• Rhopressa reportedly demonstrated a useful IOP-lowering effect in a phase 2b clinical trial completed in 2013. Mean IOP reduction was 5.7 and 6.2 mm Hg, respectively, on days 28 and 14; the mean IOP-lowering effect was consistent regardless of the patients’ baseline pressures. In the first phase 3 registration clinical trial (Rocket 1 study) comparing once daily Rhopressa with twice-daily timolol, however, Rhopressa failed to meet the primary endpoint of non-inferiority to timolol in patients with a baseline IOP ranging from above 20 mm Hg to below 27 mm Hg. Further analysis of Rocket 1 results indicates that, had the high end of the baseline IOP range be set 1 mmHg lower, at 26 mmHg, Rhopressa would have shown non-inferiority at all time points and numerical superiority over timolol at the majority of time points. A second phase 3 registration clinical study (Rocket 2) is ongoing, and the FDA has agreed to reset the high end of the primary endpoint range to include patients with a baseline IOP ranging from above 20 mmHg to under 25 mmHg. The previous endpoint range of above 20 mmHg to under 27 mm Hg will be a secondary endpoint range.
What is the foreseeable niche in clinical care for the ROCK inhibitors?

- Rhopressa may provide patients with a new once-daily alternative without the systemic side effects of beta-blockers, alpha agonists, or CAIs.
- Roclatan may be more effective because it encompasses all currently known IOP-modifying parameters: aqueous humor formation, uveoscleral outflow, conventional outflow, and episcleral venous pressure. The phase 3 clinical trials of Roclatan have yet to begin, but phase 2b data suggests that this putatively quadruple-action agent has the potential to be very effective.34

PART 4: Adenosine Receptor Agonists

What are the agents in development for the class of adenosine receptor agonists?

- Another glaucoma drug being studied in phase 3 clinical trials is trabodenoson (previously INO-8875), a highly selective adenosine type 1 receptor agonist. Trabodenoson also targets the trabecular meshwork and lowers IOP by enhancing trabecular outflow.

What is the mechanism of action of the adenosine receptor agonists?

- Like NO and ROCK inhibitors, adenosine receptor agonists act specifically on the trabecular meshwork. It is thought that adenosine-mimetics lower IOP by enhancing the aqueous outflow via the conventional pathway, although precisely how has not been fully elucidated. For outflow facility to increase significantly, clearly some kind of physical change must occur in the juxtacanalicular region of the trabecular meshwork and the inner wall of Schlemm’s canal.
- Even so, questions remain about what exactly these changes are and how such changes can be brought about by activation of adenosine receptors. Stimulation of the A1 adenosine receptor in the trabecular meshwork causes a meaningful improvement in metabolic activity there, which helps to clear the pathway for the aqueous humor to flow out of the eye (lowering IOP). This metabolic activity takes the form of an increase or upregulation of proteases (such as Protease A or matrix metalloprotease-2 [MMP-2]) that digest and remove accumulated proteins that, in a glaucomatous eye, can block the healthy flow of aqueous humor from the eye. This metabolic activity is a naturally occurring process that is enhanced by treatment with trabodenoson. It is believed that this process does not radically change the way that the trabecular meshwork controls eye pressure.

What are some of the key findings from clinical trials of adenosine receptor agonists?

- Trabodenoson is a first-in-class drug entering phase 3 clinical trials. In phase 2 trials, trabodenoson monotherapy significantly reduced IOP in patients with glaucoma and ocular hypertension.15 Its IOP-lowering efficacy, after 28 days of treatment, was found to be in the range of the PGAs.38
What is the foreseeable niche in clinical care for adenosine receptor agonists?

- Since trabodenoson enhances aqueous outflow via conventional outflow pathway (similar action to pilocarpine), it may provide some of the pharmacologic benefits of pilocarpine without having some of the side-effects of cholinergic agonists such as pilocarpine. For example, cholinergic agonists may be additive for IOP lowering to uveoscleral outflow drugs (e.g. prostaglandins) and aqueous suppressants (e.g. timolol). Also cholinergic agents are thought to blunt IOP spikes more effectively than aqueous suppressant medications since they work on outflow via the conventional trabecular meshwork outflow mechanism.

PART 5: Optic Nerve Regeneration

How promising an approach is optic nerve regeneration?

- Animal studies give us reason to be optimistic about nerve regeneration therapy. In genetically modified animals, synergistically acting therapies have been shown to tip the balance away from inhibition and toward growth promotion in damaged neural cells, resulting in axonal regeneration along the optic nerve fiber, synaptic reconnection within the brain, and limited visual restoration. To date, however, these interventions are too invasive and inflammatory for application to humans. Much work remains to be done before we achieve our key goal: axonal regeneration without the inflammatory problems we see in laboratory animals. Ideally, combining neuroprotective and nerve regeneration modalities—a “protect and repair” approach—would hold the greatest opportunity for success.

References:


