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NEW TREATMENTS FOR OPEN-ANGLE GLAUCOMA AND OCULAR HYPERTENSION:

AN UPDATE ON NEW THERAPEUTIC OPTIONS

PART 1 OF 2

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New Treatments for Open-Angle Glaucoma and Ocular Hypertension:

An Update on New Therapeutic Options PART 1 of 2

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CONTENT SOURCE

This continuing medical education (CME)/continuing education (CE) activity captures content from a roundtable discussion that occurred on June 27, 2018.

ACTIVITY DESCRIPTION

Topical pharmacologic therapy is the mainstay primary treatment for patients with primary open-angle glaucoma (POAG) and ocular hypertension. Unfortunately, many patients need to be on multiple medications and different classes of drugs before there is adequate IOP control. And for some patients, visual field loss will progress despite adequate IOP control. Until recently, no new topical pharmacologic treatments had been approved in the United States for more than a decade. Two new formulations were approved in late 2017. Ophthalmologists and other health care providers may not be familiar with potential new treatments for glaucoma, the latest clinical studies evaluating treatment, or the mechanism of action of topical medications.

TARGET AUDIENCE

This certified CME/CE activity is designed for specialists and other allied eye care practitioners involved in the management of glaucoma and associated disorders.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- **Explain** how novel therapeutics differ in their methods of action from other topical medications.
- **Evaluate** the safety and efficacy of latanoprostene bunod for ocular hypertension and POAG.
- **Describe** how a healthy eye manages IOP in contrast with an unhealthy eye.

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1. PLEASE RATE YOUR CONFIDENCE IN YOUR ABILITY TO APPLY UPDATES IN GLAUCOMA TREATMENT IN THE CLINIC (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NOT AT ALL CONFIDENT AND 5 BEING EXTREMELY CONFIDENT).

a. 1
b. 2
c. 3
d. 4
e. 5

2. PLEASE RATE HOW OFTEN YOU INTEND TO APPLY ADVANCED GLAUCOMA TREATMENT TO "REAL-WORLD" PATIENT MANAGEMENT (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NEVER AND 5 BEING ALWAYS).

a. 1
b. 2
c. 3
d. 4
e. 5

3. PROSTAGLANDIN ANALOGUES (PGAs) REMAIN THE STANDARD FIRST-LINE TREATMENT OVER SELECTIVE LASER TRABECULOPLASTY (SLT) BECAUSE _____.

a. PGAs are more effective than SLT.
b. PGAs are easier to get approved by insurance companies.
c. Patients are fearful of surgery and more comfortable with pharmacotherapy.
d. Patient compliance is better with PGAs than SLT.

4. WHAT PERCENTAGE OF PATIENTS WITH GLAUCOMA HAVE MILD TO MODERATE DRY EYE DISEASE?

a. 33%
b. 30%
c. 26%
d. 24%

5. NITRIC OXIDE LOWERS IOP BY _____.

a. Decreasing aqueous production.
b. Relaxing the trabecular meshwork.
c. Reducing episcleral venous pressure.
d. Inhibiting the norepinephrine transporter pathway.

6. IN VOYAGER, RESEARCHERS REPORTED ONCE-DAILY LATANOPROSTENE BUNOD LOWERED IOP BY UP TO _____ MORE THAN ONCE-DAILY LATANOPROST.

a. 0.5 mm Hg
b. 1 mm Hg
c. 1.5 mm Hg
d. 2 mm Hg

7. THE APOLLO STUDY FOUND LATANOPROSTENE BUNOD LEADS TO HYPEREMIA IN _____ OF PATIENTS.

a. 3%
b. 4%
c. 5%
d. 6%

8. WHICH STATEMENT BEST DESCRIBES NETARSUDIL?

a. Netarsudil works best as a single agent and not combined with a PGA.
b. Netarsudil only has a single mechanism of action.
c. Netarsudil can lower IOP by 3 to 4 mm Hg.
d. Netarsudil does not cause conjunctival hyperemia.

9. TYPICALLY, PATIENTS WITH EARLY PARACENTRAL VISION LOSS AND OPEN-ANGLE GLAUCOMA EXHIBIT WHICH OF THE FOLLOWING FEATURES?

a. High blood pressure
b. Untreated IOP > 30 mm Hg
c. Untreated IOP ~ 21 mm Hg
d. Male gender

10. ACCORDING TO THE PANELISTS, PATIENTS WHO ARE SUFFERING FROM HYPEREMIA SHOULD BE SWITCHED FROM A BRANDED PGA TO _____.

a. Netarsudil.
b. Latanoprostene bunod.
c. Generic latanoprost.
d. Brimonidine.

11. A RECENTLY PUBLISHED META-ANALYSIS FOUND THAT _____ AND TOPICAL MEDICATION DEMONSTRATED SIMILAR SUCCESS RATES IN IOP REDUCTION FOR PATIENTS WITH OPEN-ANGLE GLAUCOMA.

a. Microincisional glaucoma surgery
b. Argon laser trabeculoplasty
c. SLT
d. Incisional surgery

12. _____ IS CONSIDERED A VALUABLE MARKER BY THE PANELISTS FOR PREDICTING PATIENT RESPONSE TO PGAs.

a. Baseline IOP
b. Corneal hysteresis
c. Presence of dry eye disease
d. Patient age

New Treatments for Open-Angle Glaucoma and Ocular Hypertension:

An Update on New Therapeutic Options PART 1 of 2

Glaucoma, a progressive disease, is the leading cause of irreversible blindness worldwide.[1] Approximately 3 million people in the United States are undergoing glaucoma treatment.[2] In today's clinical setting, prostaglandin analogues (PGAs) are routinely used as the first-line treatment for the majority of patients. These treatments are not always successful at maintaining ideal IOP or in preventing visual field deterioration, however, leading many patients to be prescribed multiple medications before their IOP has stabilized.

Compliance and medication costs remain significant challenges for glaucoma specialists and their patients. Glaucoma specialists must understand the novel agents, combination therapies, and sustained-delivery modalities currently available and in the pipeline in order to provide the most effective patient care. The following roundtable discusses novel therapeutics and their safety, efficacy, and differences as well as cases in which these novel agents may be most effective.

— Nathan Radcliffe, MD, Moderator

GLAUCOMA TREATMENT IN THE FIRST-LINE SETTING

Q | NATHAN RADCLIFFE, MD: What are the first-line treatments for a patient diagnosed with glaucoma in 2018? Are we using laser more than PGAs? How is glaucoma treatment evolving, and what is changing in 2018?

BEN GADDIE, OD: PGAs are an easy first-line treatment choice because of their generic availability. Glaucoma specialists are comfortable with generic PGA efficacy, even given the variance we see with some of the generics. However, it can be a hassle to obtain medications covered by insurance; treatment compliance is always an issue for patients, which is causing laser to emerge more and more as a first-line treatment option. I offer laser to every patient who begins therapy. I explain the differences and the relative parity between a PGA and selective laser trabeculoplasty (SLT) for initial therapy. Patients don't always believe that SLT is as effective as a PGA. We often need to provide patients with additional reassurance in these cases.

The use of laser is increasing due to recent studies showing its sustainability, repeatability, and good safety profile.[3-7] For example, a 2015 meta-analysis published in *BMC Ophthalmology* found that SLT and topical medication demonstrated similar success rates in IOP reduction for open-angle glaucoma.[3] As we become more comfortable with a prolonged, sustained SLT model, employing it as a first-line therapy will make sense for a lot of patients. But at the same time, patients are apprehensive about a primary surgical therapy. SLT does have its place, and its use will continue to increase as medication approval becomes more burdensome.

DR. RADCLIFFE: As much as I prefer to place patients on laser as early as possible, that doesn't translate to the real world because patients are much more comfortable with pharmacotherapy from a psychological standpoint. Conceptually, I prefer laser because it is the outflow pathway that we want to restore. Those of us who are in surgical referral practices don't always have the opportunity to choose the first-line medication.

Fortunately, we are now seeing pharmacotherapies that also are enhancing the trabecular outflow—Rho kinase (ROCK) inhibitors. There are two things I will do for a patient who is on three drops. The first thing I do is assess if the patient is on the best PGA possible. While latanoprost is cheap and well tolerated, I do not believe that the literature supports generic latanoprost as the most efficacious PGA, and I personally hold it to be the least effective. For patients not on a potent PGA (bimatoprost, travoprost, or latanoprostene bunod), I will switch from latanoprost before adding another medication. And secondly, I make sure the patient has tried the laser at least once before we move on to something more invasive.

DR. GADDIE: I am also a big proponent of making sure the patient is on the best PGA possible, and that usually involves a switch to a branded drug if they've been placed on the generic version. Many doctors don't have the stamina or the will to continue to advocate for the branded drug. But, you are correct; if you are going to switch to something more invasive, or add a combination medicine or laser therapy, I think you owe it to the patient to try a branded medication and observe the results. I am frequently surprised at the improvement in IOP control we obtain when we switch away from a generic. I definitely agree with that strategy.

DR. RADCLIFFE: I will often ask patients how much they pay for

their medication, and I can be surprised by either the cost of the generic or what the brand name costs. Sometimes generics are very expensive, and other times patients will a have drug plan that has a relationship with pharma or is in some other way unique, so their member patients don't pay significant costs for branded drugs. I don't want to miss giving the most powerful therapy I can in a patient who is able to get that medication affordably.

Surprisingly, new branded drugs that are first in class can be fully covered because, if a drug class only has one available agent, insurance policies dictate that it must have a reasonable coverage status (usually tier 1 or 2).

What will change in the next 3 to 5 years in terms of how we are addressing patients with glaucoma in the first-line setting?

LOUIS PASQUALE, MD: I am noticing that third-party payers are making the decisions. We will start patients on latanoprost, but then we run into issues due to pricing. New alternative forms of drug delivery will be more expensive than a bottle of latanoprost. I'm concerned that the answer to what will be changing in 3 to 5 years is not much unless a new drug enters the market with competitive pricing.

DR. RADCLIFFE: This is the problem with drug delivery. What we have available may work, but it isn't as accessible to us and to our patients. These are significant hurdles. It might only require one extra phone call to obtain a branded drug for a patient, but that can be a major hurdle when we see 70 patients a day who all need those calls to be made on their behalf.

Figure 1 illustrates the traditional classes of drugs we have in our armamentarium. Let's discuss PGAs. Speaking about the molecules themselves, are all PGAs the same, or are there significant differences between them?

DR. PASQUALE: I don't see major differences between PGAs, such as latanoprost, travoprost, tafluprost, and bimatoprost.

Bimatoprost switched from 0.03% to 0.01% without a dramatic reduction in efficacy, which was interesting, although there was a reduction in ocular discomfort in patients.[8] I've found latanoprost to be generally well tolerated by patients, even though it has one of the higher concentrations of preservatives of all the drops. For patients who have challenges with ocular surface disease and preservatives, travoprost is alternatively preserved with SofZia (Alcon) as opposed to benzalkonium chloride, and tafluprost is preservative-free. Travoprost maybe be a better drug choice for some patients, and tafluprost may be a good preservative-free option.

Preservatives are an issue; the active ingredient does not present as much of an issue for me. Approximately 33% of patients with open-angle glaucoma have mild to moderate dry eye disease, with about 26% reporting severe dry eye.[9] The more medications a patient is on, the more likely they are to report dry eye symptoms.[10] Those patients will likely benefit from preservative-free or a non-benzalkonium chloride-preserved formulation.

DR. GADDIE: In terms of PGAs, I do see a difference in some patients,

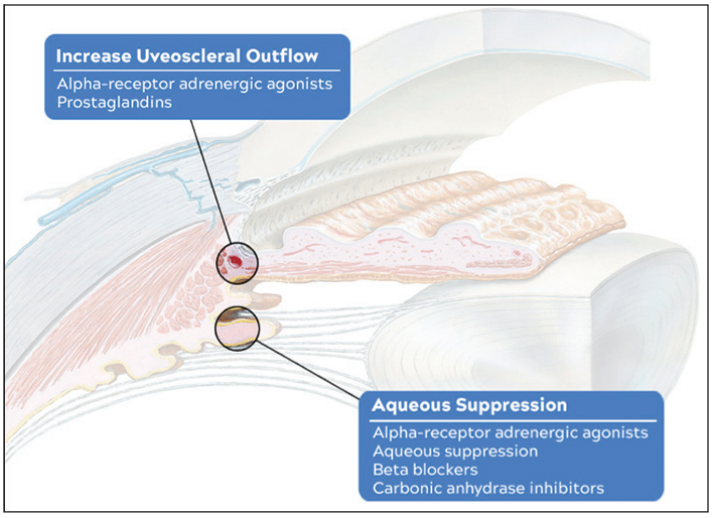

Figure 1. Common classes of glaucoma medications have previously addressed uveoscleral outflow and aqueous suppression, with the prostaglandin class of drugs becoming a preferred first-line option.

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and there are some differences that I can't necessarily authentically comment on. A study from the XLT Study Group published in 2003 compared latanoprost, bimatoprost, and travoprost over 12 weeks in 410 patients.[11] The group found no statistical difference between generic and branded PGAs. Latanoprost seemed to be more tolerable than the others, with fewer reports of ocular surface events and fewer reports of hyperemia in latanoprost-treated patients.

Anecdotally, while treating patients, I've noticed that bimatoprost seems more efficacious than the others. There are some data supporting this. A 2004 review study in *Advances in Therapy*[12] compared bimatoprost to latanoprost for IOP-lowering efficacy and found that mean IOP was lower among patients on bimatoprost when compared to those on latanoprost. Overall, both drugs were well tolerated, but bimatoprost had greater efficacy.[12]

In my mostly private practice setting, we receive samples of branded drugs. If I have a patient on generic latanoprost and feel as though their IOP is not at target or they are experiencing progression, I will use a sample of one of the branded products to see if it is an issue with the generic medication or just part of their disease. Sometimes their pressure goes up even when they are on treatment. I use the sample as a failsafe to ensure that we are not dealing with a prostaglandin variability issue; I determine this before I add an additional copay, an additional side effect profile, and an additional dosing rather then possibly run into the compliance issues and all the things that go along with another medication. If we do need adjunctive therapy, my preference is to use a combination. I know that may be more aggressive, but my experience has been that, if I need one adjunctive drug, the chances are good that I am going to need a second adjunctive drug in the short term. I prefer the therapy to be as efficient as possible.

DR. RADCLIFFE: Corneal hysteresis may explain patients who seem to be nonresponders to drugs because, although their pressure

"This is the problem with drug delivery. What we have available may work, but it isn't as accessible to us and to our patients. These are significant hurdles. It might only require one extra phone call to obtain a branded drug for a patient, but that can be a major hurdle when we see 70 patients a day who all need those calls to be made on their behalf."

—Dr. Radcliffe

may be changing, their corneal properties don't display much of a change on Goldmann tonometry. Studies have shown that corneal hysteresis is a valuable tool for predicting patient response to PGAs. Patients with higher IOP have lower corneal hysteresis and are more likely to progress as shown by visual field exams.[13-16]

One study that I conducted looked at the relationship between corneal hysteresis and the magnitude of IOP reduction with PGAs.[17] We found that, if a patient had a low hysteresis of 7 mm Hg, a PGA could reduce IOP by 29%. However, if that patient had a high hysteresis of 12 mm Hg or more, that same medication would only reduce IOP by about 8%. It has been hypothesized that patients with high corneal hysteresis may make up to 30% of patients in clinical trials who are classified as nonresponders.[18-20]

I used to believe that, if someone didn't respond to medication, switching medications to a more powerful PGA would elicit a better response. But interestingly, we now know that you can't tell who is really responding and who just has a cornea that will easily show change. Therefore, I always strive to use what I view to be the most powerful PGA possible during initial therapy.

DR. GADDIE: Nonresponsiveness to PGAs is often cornea-related, especially if you do a follow-up with SLT and still achieve the same response. I'm curious about those patients who are well controlled on a PGA. They switch medications and then, within 6 months, they're varying up. Is that a coincidence, or does this have something to do with corneal hysteresis as well?

DR. RADCLIFFE: What we generally found is that a high hysteresis is a cornea that doesn't show much change in any setting.

NOVEL GLAUCOMA MEDICATIONS IN THE CLINIC

Q | **DR. RADCLIFFE:** There are two new outflow mechanisms in glaucoma, one being nitric oxide with latanoprostene bunod (Vyzulta, Bausch + Lomb), a PGA, and the other being trabecular outflow with netarsudil (Rhopressa, Aerie Pharmaceuticals). Figure 2 demonstrates how these two new medications fit into and with our current classes of drugs. Can you describe the mechanisms of action with those drugs and what they might mean for treating patients with glaucoma?

DR. PASQUALE: Latanoprostene bunod is an organonitrate that is chemically linked to a latanoprost moiety. The organonitrate is converted to nitric oxide that produces trabecular meshwork (TM) relaxation. This provides for somewhere between a 1-mm Hg and a 2.5-mm Hg reduction of IOP. Preclinical animal models have shown that nitric oxide directly lowers IOP.[21] We put mice in a chamber that contained 40 parts per million (ppm) nitric oxide. Those mice had a lower IOP than mice that did not get exposed to that inhaled nitric oxide, and they demonstrated improved outflow facility.[21]

Interestingly, netarsudil works in a similar fashion, and there is histological evidence that netarsudil actually relaxes TM endothelial cells.[22,23] Netarsudil lowers IOP through ROCK and norepinephrine transporter (NET) inhibition. The ROCK inhibitor enhances the trabecular outflow and reduces episcleral venous pressure, and the NET inhibitor decreases aqueous production, which causes a further reduction of IOP.[23-27] Thus, direct relaxation of the TM cells works via the nitric oxide signaling pathway. Netarsudil works a little farther downstream, and nitric oxide works upstream by directly causing relaxation of cellular contractile elements.

DR. GADDIE: I want to ensure I understood that correctly. They both work through the signaling—one upstream, one downstream—but directly on trabecular endothelial cell relaxation?

DR. PASQUALE: Correct.

DR. GADDIE: Is there a different signaling pathway, or is it the same pathway?

DR. PASQUALE: Ultimately the same pathway gets stimulated.

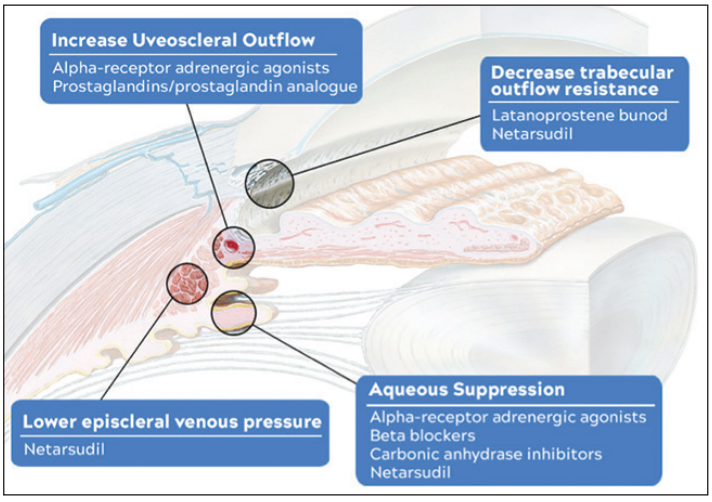

Figure 2. Recently approved glaucoma medications work through signaling directly on the trabecular endothelial cell relaxation, providing clinicians with four potential pharmaceutical targets.

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But netarsudil's ROCK inhibition also translates to reduced episcleral venous pressure; further netarsudil also reduces aqueous humor production via NET inhibition.

DR. RADCLIFFE: Latanoprostene bunod has a higher concentration of latanoprost than latanoprost itself. It's about four or five times higher. How do we know that the pressure lowering you get in latanoprostene bunod is activating that nitric oxide pathway?

DR. PASQUALE: Data have been published that indirectly address this question by showing that inhaled nitric oxide lowers IOP directly in mice.[21] We showed that it did so through the nitric oxide pathway using soluble guanylate cyclase knockout mice. Soluble guanylate cyclase is the intracellular receptor for nitric oxide that mediates downstream smooth muscle cell relaxation. The wild-type mice, exposed to nitric oxide, showed about a 2-mm Hg lowering of IOP when exposed to 40 ppm nitric oxide in an experimental chamber. Soluble guanylate cyclase knockout mice who inhaled nitric oxide at 40 ppm did not have a reduction in IOP (Muenster et al, *Invest Ophthalmol Vis Sci* 2018).

Secondly, we used lambs to study the effect of nitric oxide on IOP. We placed goggles on these animals to serve as a local chamber where we controlled the ambient concentration of nitric oxide concentration. We found that nitric oxide in the goggle lowered IOP in a concentration-dependent manner.[21] Indirect, preclinical data indicate that nitric oxide directly lowers IOP, albeit very modestly, by 1 mm Hg to 3 mm Hg. Looking at clinical studies, VOYAGER suggested that latanoprostene bunod was more effective than latanoprost in patients with ocular hypertension and early-stage, open-angle glaucoma.[28] In VOYAGER, 413 patients were randomly assigned to latanoprostene bunod or latanoprost. Patients on latanoprostene bunod had significantly greater reductions in IOP compared with latanoprost at the primary endpoint. Latanoprostene bunod once daily reduced IOP 1 mm Hg to 1.5 mm Hg more than latanoprost once daily. The authors concluded that once-daily latanoprostene bunod was the most effective regimen, with significantly greater IOP-lowering effects and comparable side effects compared to latanoprost. That is the best evidence that we have.

DR. GADDIE: If you return to the dose-ranging studies for latanoprost, they found that increasing concentrations yielded no further IOP response. The increased concentration did lead to greater pain, redness, and hyperemia.[29]

DR. RADCLIFFE: What are the clinical implications of drugs targeting the TM, such as netarsudil and latanoprostene bunod? Is it possible that by targeting this tissue we alter the disease itself rather than simply lower IOP?

DR. PASQUALE: Having a true TM drug would be a huge development in the treatment of glaucoma. A paper just recently published in *Nature Genetics*, which leveraged data from the UK Biobank, identified 112 genomic loci associated with IOP, 68 of which were novel.[30] They all have very small effects on the IOP level. You don't find one gene that changes eye pressure by 2 mm Hg or 3 mm Hg; rather, these loci change eye pressure by somewhere between 0.2 mm Hg to 0.4 mm Hg. But, collectively, these genes are strongly associated with the risk of developing primary open-angle glaucoma (POAG). We don't fully understand how these genes affect TM function, but many of them must be doing something. These results indicate that IOP is in the causal pathway of POAG.

Interestingly, this panel of IOP genetic biomarkers is also associated with normal-tension glaucoma, suggesting that TM dysfunction plays a role in this POAG subtype. Therefore, having drugs that improve TM function is key. The only such drug we've had so far is pilocarpine, which is widely known to have significant challenging side effects such as miosis, induced myopia, and retinal detachment. To have another drug in that space is welcome.

Drugs that improve nitric oxide signaling are exciting because some patients with POAG may have impaired nitric oxide signaling as a root cause of their disease. One of the genes for POAG and IOP is a gene called *caveolin*.[31] Caveolin sits right next to nitric oxide synthase 3 on biological membranes to regulate nitric oxide production. Therefore, if POAG is a disease of impaired nitric oxide signaling and you're using a drug that improves nitric oxide signaling, such as netarsudil or latanoprostene bunod, that's great.

DR. RADCLIFFE: My understanding of all the safety data that we have, as well as from reading the label for latanoprostene bunod, is that the warnings and contraindications are latanoprost contraindications. I don't see any identified safety issue with adding this aspect of nitric oxide going for the TM. Is that consistent with your understanding?

DR. PASQUALE: Yes, it is. I have put patients on both drugs, and I'm not seeing anything untoward so far. I'm not seeing anything related to the organonitrate that raises any alarm bells regarding latanoprostene bunod use.

DR. GADDIE: I am seeing two things. First, this is purely observational, but they don't seem to have as much hyperemia as I see with a traditional PGA. Second, almost all patients noticed some burning on installation, and that is not something that you typically hear your PGA patients complain about unless they have severe dry eye.

DR. RADCLIFFE: In the APOLLO and LUNAR studies, the mean IOP reduction was 7.5 mm Hg to 9.1 mm Hg from baseline between 2 and 12 weeks of treatment.[32,33] The hyperemia rate for latanoprostene bunod was 3% in APOLLO and 9% in LUNAR, with an average of 6%.[32,33] That rate is low given that some of the PGAs go up to 40% on hyperemia. I took a drop myself and noticed a little bit of stinging, but I haven't had anyone complain to me about it. It is good to know that we are not taking any systemic risks by going after this new approach.

Moving on, netarsudil was thought of as an adjunctive agent because its pressure lowering is in the 20% range. And, as far as we know, there is no problem with combining netarsudil with any PGA. What are we seeing there in terms of benefits, efficacy, and tolerability?

"We need to either put the drug in the eye or effectively put it on the cornea. The problem with punctal plugs and rings is that you are taking the drug away from its pathway to its site of action. By displacing the drug from the cornea, you are leaving efficacy on the table. You are turning a PGA into a beta blocker in terms of IOP lowering because the drug is not going across the cornea."

—Dr. Pasquale

DR. PASQUALE: In terms of efficacy, I have been really impressed with netarsudil. In fact, I have used it on patients who are on maximal medical therapy and who are considering more invasive procedures. Some of these patients actually failed latanoprostene bunod. I exchange the brimonidine tartrate (Alphagan P, Allergan) for the netarsudil, and I have seen improved IOP control.

That said, I have had one patient who had severe redness and could not tolerate the medication. Other side effects of netarsudil, which we are just now learning about, include conjunctival hemorrhages at the margin and corneal verticillata. However, it has been well tolerated overall, and it has given patients pretty significant IOP reductions of 3 mm Hg to 4 mm Hg. These findings are consistent with a study published by Kazemi et al.[34] Another advantage is it is a once-daily drug as compared with other agents that are dosed up to three times per day. This dosing may help with compliance, which is always an issue.

DR. RADCLIFFE: Interesting. For the patients who say their vision is improved, I wonder if some of those patients were carbonic anhydrase inhibitor patients who got rid of their blurred vision side effects.

DR. GADDIE: My experience has been similar to Dr. Pasquale's. Netarsudil provides good efficacy, especially in patients that maybe were on a twice-daily brimonidine or beta blocker or topical carbonic anhydrase inhibitors. A large number of my patients have had an allergic reaction to brimonidine and can't take either brinzolamide/brimonidine (Simbrinza, Alcon) or brimonidine/timolol (Combigan, Allergan). Being able to substitute these medications with netarsudil has been useful. The hyperemia is there, but it is manageable in patients who are already on a PGA.

I am using netarsudil in the same manner that someone would use the future drug netarsudil/latanoprost (Roclatan, Aerie Pharmaceuticals). Combination netarsudil/latanoprost is in the pipeline and will hopefully come to market soon. In a phase 3 safety study of 718 patients, once-daily netarsudil/latanoprost demonstrated superiority over netarsudil and latanoprost individually. The combination arm had a mean IOP of 16 mm Hg or lower in 60% of patients.[35] The dosing makes sense. I would use it in patients who are already on a PGA and need an adjunctive single agent.

DR. RADCLIFFE: Interestingly, both latanoprostene bunod and netarsudil have some data that suggest they work well at low baseline IOP. Latanoprostene bunod had a recent study that was done in Japan where the baseline pressures were lower.[36] In all of the ROCKET studies, what you saw with netarsudil was that it was very consistent at lowering the pressure, regardless of baseline IOP. In the phase 3 ROCKET 2 registration trial, netarsudil demonstrated noninferiority of IOP lowering compared with timolol.[37] The pivotal phase 3 ROCKET 4 trial also found noninferiority to timolol for patients with baseline IOPs ranging from 20 mm Hg to below 25 mm Hg. Netarsudil demonstrated similar noninferiority in prespecified secondary endpoint ranges of above 20 mm Hg to below 27 mm Hg and at a range of above 20 mm Hg to below 28 mm Hg.

That's not how most medications usually work. Typically, you observe better pressure reduction if you start with a high baseline pressure. I do think these study results are notable. What I have seen with netarsudil is that it still performs in patients who have already been on many other medical therapies. That's unique, and that has been encouraging. In terms of the side effect profile, most of the hyperemia in the study was fairly mild, even though it was up to 50%. That's fairly consistent with what I'm seeing in my patients. Many of our patients already have a little bit of hyperemia, so that's an issue, but it doesn't get any worse.

SUSTAINED-RELEASE DEVICES

Q | **DR. RADCLIFFE:** Studies have shown that sustained-release devices, such as contact lenses, punctal inserts, and bio-adhesive metrics, are all viable options that improve drug delivery and may help overcome compliance issues.[38,39] Are we ready to start implementing sustained-release devices, such as a silicone punctal plug-based system delivering a PGA, in the clinic? Is there another sustained-release modality that appeals to you? How long would a sustained-release device need to last to make it a success in your practice?

DR. GADDIE: Sustained drug delivery is an exciting field and something that, from a compliance standpoint, will be a huge victory in glaucoma treatment. I don't think punctal plugs are the answer, however. In some ways punctal plugs make sense, such as in their apposition to the ocular surface and the elution of glaucoma medications that it receives. Could you have a punctal plug that also secretes the drug? That could be a viable option in maybe 20% of patients.

The same could be said for the ocular ring. I don't know how many patients would opt for that, although it looks like it is comfortable and well tolerated.[40] I also wonder how many patients will want sustained injections via an intracameral approach. My patients with

"You want to start the patient on a medication that will work for them, that is true. We often don't realize it, but we are often asking too much from new medications and putting them in an unfair position. Physicians practicing in tertiary glaucoma surgical practices only use new medications on the desperate cases, which isn't indicative of the medications' true utility and power. It is important to pay attention to our own behaviors and make sure we have realistic expectations of these new medications. And, of course, the earlier in the disease we begin treating patients, whether with a laser response or a PGA, the better patients tend to respond."

—Dr. Radcliffe

age-related macular degeneration rarely complain about injections, so maybe there is hope that injection would be accepted and tolerated by glaucoma patients. I continue to believe pharmacotherapy and laser are going to have the predominant stage for the next 5 years.

DR. PASQUALE: We need to either put the drug in the eye or effectively put it on the cornea. The problem with punctal plugs and rings is that you are taking the drug away from its pathway to its site of action. By displacing the drug from the cornea, you are leaving efficacy on the table. You are turning a PGA into a beta blocker in terms of IOP lowering because the drug is not going across the cornea.

Conceptually, in order for drug delivery to be successful, we need a device that effectively puts the drug on the cornea, like a piezoelectric device, or a contact lens, or a device that puts the drug right in the eye, like the bimatoprost sustained-release implant. The bimatoprost implant is impressive because it is impregnated with a drop of bimatoprost, which can release over a 4- to 6-month time period and provide reasonable IOP-lowering ability.[41] It shows you how ineffective we are at delivering drugs across the cornea.

The questions are will patients be tolerant of that, and how many times can we do it? I don't know the answers to those questions. I can tell you that patients with age-related macular degeneration are tolerant of injections because they know that they have a vision-threatening disease and, without the injections, they will lose their eyesight. That is not what is on the table here with glaucoma treatment. I think there's a misconception in terms of patients' acceptance that comes into play. Patients are going to be less accepting of this modality, which is why, I think, the real winners will be a contact lens or piezoelectric device.

DR. RADCLIFFE: We will probably need to change our mindset in order to use sustained-release devices. The same question comes up with microinvasive glaucoma surgery. We all perform it very frequently now with cataract surgery because it is such an easy decision when you are already taking out a cataract to also try to lower the pressure. But if you take a patient with borderline pressure who is otherwise doing fine, that patient rarely accepts what they perceive to be an invasive intervention, such as an injection or surgical procedure. The patient psychology is very different in those cases.

CASE 1: COMBINING SLT, LATANOPROSTENE BUNOD, AND NETARSUDIL

Q | **DR. RADCLIFFE:** I treated a 36-year-old phakic man with POAG who was on fixed-combination dorzolamide/timolol. His compliance had been a little off, and he had recently been found to have a very high pressure of 36 mm Hg. That pressure decreased to 28 mm Hg with improved compliance. When I saw him, we found that his disease had progressed, and he had at least moderate glaucoma. I decided that he could be a great candidate for engaging the TM. We performed SLT and switched his medication to latanoprostene bunod and netarsudil. We didn't just double down on the TM; we tripled down on it. He had a good response, and his pressure is now in the teens. What are your takeaways from this case?

DR. PASQUALE: I am not surprised he had such a good response. This patient whom you described has never been exposed to an outflow agent, and you really tripled down. You treated his TM with laser, upstream nitric oxide signaling, and a ROCK inhibitor which enhances nitric oxide signaling downstream, and you observed a dramatic reduction of IOP.

I can give a similar anecdote. I treated a highly myopic male of a similar age. The patient had a giant retinal tear. He was aphakic, and the referring physician wanted to do a transscleral cyclophotocoagulation. The patient had a consistent pressure of 22 mm Hg on every medical intervention. I swapped out his latanoprost for latanoprostene bunod, and his pressure went from 22 mm Hg to 16 mm Hg. So, anecdotally you can see those kinds of responses.

DR. RADCLIFFE: I have seen some super responders, even on pilocarpine. The issue with pilocarpine was the tolerability, even if the patient responded well. Do you think we'll have that type of super responder with latanoprostene bunod?

DR. GADDIE: Whenever a new drug comes out, a new mechanism, we are all excited, and we use it on our most challenging patients, which can sometimes blunt your expectations for other patients. The greatest success I have had with super responders is treatment-naïve patients with an IOP baseline in the mid-20s.

DR. PASQUALE: You have taken treatment-naïve patients and gone directly to latanoprostene bunod and seen some great responses?

DR. GADDIE: That is correct, yes. The responses have been greater than I would expect from a PGA. Some of them have had sustained responses. The magnitude of it has been shocking.

DR. PASQUALE: That highlights an important point because you are on a different end of the care spectrum. I practice in a tertiary care world where I see referrals from other glaucoma specialists. My patients are on maximum medical therapy. I switch them to latanoprostene bunod or netarsudil, and it can be frustrating because the expected efficacy is understandably going to be attenuated. If the therapy doesn't work, then the drug gets a bad name. But is that a fair comparison? My staff and I are also fighting with the drug companies to get the patients these drugs, but many of these requests are denied. We are often requested to try another PGA before they will consider supporting latanoprostene bunod use.

DR. RADCLIFFE: You want to start the patient on a medication that will work for them; that is true. We often don't realize it, but we are often asking too much from new medications and putting them in an unfair position. Physicians practicing in tertiary glaucoma surgical practices only use new medications on the desperate cases, which isn't indicative of the medications' true utility and power. It is important to pay attention to our own behaviors and make sure we have realistic expectations of these new medications. And, of course, the earlier in the disease we begin treating patients, whether with a laser response or a PGA, the better patients tend to respond.

CASE 2: PARACENTRAL VISUAL FIELD LOSS IN EARLY DISEASE

Q | DR. RADCLIFFE: In what clinical scenario will latanoprostene bunod be most effective? Is the ideal latanoprostene bunod patient young or old? Is there any demographic information that could help parse patients for this medication?

DR. PASQUALE: Determining the ideal patient for latanoprostene bunod is independent of age and sex. I think it is a patient who experiences paracentral visual field loss early on in their disease. These patients have mean untreated IOP of about 21 mm Hg, low blood pressure, migraines, and Raynaud's phenomenon.[42] There is considerable genetic evidence that patients with early paracentral visual loss have impaired nitric oxide signaling.[43-45] Latanoprostene bunod and netarsudil would be ideal first-line agents for those patients. My anecdotal experience indicates that these patients need target pressures of less than 16 mm Hg.

DR. GADDIE: For me, I use latanoprostene bunod in high-risk patients who have, for example, damage in the temporal side of the macula, damage in the macular vulnerability zone area, or in patients prone to a central visual field defect. You want to start with the best therapeutic once-a-day option available. I agree that latanoprostene bunod could have some utility beyond what we are used to seeing with PGAs in patients with normal-tension glaucoma. Patients on generic latanoprost who need more therapy before adding another drop or going to laser could benefit from latanoprostene bunod. Lastly, I would use latanoprostene bunod as a last-ditch effort in patients on a PGA plus a combo. Maybe you have already done laser treatment, and you need to try one last option before moving on to surgery. Latanoprostene bunod would be my final attempt.

DR. RADCLIFFE: If you have a patient who is suffering from hyperemia, I recommend switching to latanoprostene bunod. It is effective, and the tolerability profile is good. That has been a patient-pleaser situation for me; I have found success with that. We often switch medications to achieve a lower pressure, but you can also switch medications because you're happy with the pressure, and you don't want to give that up but are looking for a tolerability benefit as well.

Thank you for your insights. I look forward to working with you in the future. ■

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NEW TREATMENTS FOR OPEN-ANGLE GLAUCOMA AND OCULAR HYPERTENSION: AN UPDATE ON NEW THERAPEUTIC OPTIONS, PART 1 OF 2

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Name _____ ❑ MD/DO participant ❑ non-MD participant

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Address _____

City _____ State _____ Zip _____

License Number _____ OE Tracker Number _____

DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this activity)
___ 0
___ 1-5
___ 6-10
___ 11-15
___ 15-20
___ 20+

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

Training of Fellows ___ Yes ___ No

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Explain how novel therapeutics differ in their methods of action from other topical medications.	_____	_____	_____
Evaluate the safety and efficacy of latanoprostene bunod for ocular hypertension and primary open-angle glaucoma.	_____	_____	_____
Describe how a healthy eye manages IOP in contrast with an unhealthy eye.	_____	_____	_____

POSTTEST QUESTIONS

1. PLEASE RATE YOUR CONFIDENCE IN YOUR ABILITY TO APPLY UPDATES IN GLAUCOMA TREATMENT IN THE CLINIC BASED ON THIS ACTIVITY (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NOT AT ALL CONFIDENT AND 5 BEING EXTREMELY CONFIDENT).

a. 1
b. 2
c. 3
d. 4
e. 5

2. PLEASE RATE HOW OFTEN YOU INTEND TO APPLY ADVANCED GLAUCOMA TREATMENT TO "REAL-WORLD" PATIENT MANAGEMENT (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NEVER AND 5 BEING ALWAYS).

a. 1
b. 2
c. 3
d. 4
e. 5

3. PROSTAGLANDIN ANALOGUES (PGAs) REMAIN THE STANDARD FIRST-LINE TREATMENT OVER SELECTIVE LASER TRABECULOPLASTY (SLT) BECAUSE _____.

a. PGAs are more effective than SLT.
b. PGAs are easier to get approved by insurance companies.
c. Patients are fearful of surgery and more comfortable with pharmacotherapy.
d. Patient compliance is better with PGAs than SLT.

4. WHAT PERCENTAGE OF PATIENTS WITH GLAUCOMA HAVE MILD TO MODERATE DRY EYE DISEASE?

a. 33%
b. 30%
c. 26%
d. 24%

5. NITRIC OXIDE LOWERS IOP BY _____.

a. Decreasing aqueous production.
b. Relaxing the trabecular meshwork.
c. Reducing episcleral venous pressure.
d. Inhibiting the norepinephrine transporter pathway.

6. IN VOYAGER, RESEARCHERS REPORTED ONCE-DAILY LATANOPROSTENE BUNOD LOWERED IOP BY UP TO _____ MORE THAN ONCE-DAILY LATANOPROST.

a. 0.5 mm Hg
b. 1 mm Hg
c. 1.5 mm Hg
d. 2 mm Hg

7. THE APOLLO STUDY FOUND LATANOPROSTENE BUNOD LEADS TO HYPEREMIA IN _____ OF PATIENTS.

a. 3%
b. 4%
c. 5%
d. 6%

8. WHICH STATEMENT BEST DESCRIBES NETARSUDIL?

a. Netarsudil works best as a single agent and not combined with a PGA.
b. Netarsudil only has a single mechanism of action.
c. Netarsudil can lower IOP by 3 to 4 mm Hg.
d. Netarsudil does not cause conjunctival hyperemia.

9. TYPICALLY, PATIENTS WITH EARLY PARACENTRAL VISION LOSS AND OPEN-ANGLE GLAUCOMA EXHIBIT WHICH OF THE FOLLOWING FEATURES?

a. High blood pressure
b. Untreated IOP > 30 mm Hg
c. Untreated IOP ~ 21 mm Hg
d. Male gender

10. ACCORDING TO THE PANELISTS, PATIENTS WHO ARE SUFFERING FROM HYPEREMIA SHOULD BE SWITCHED FROM A BRANDED PGA TO _____.

a. Netarsudil.
b. Latanoprostene bunod.
c. Generic latanoprost.
d. Brimonidine.

11. A RECENTLY PUBLISHED META-ANALYSIS FOUND THAT _____ AND TOPICAL MEDICATION DEMONSTRATED SIMILAR SUCCESS RATES IN IOP REDUCTION FOR PATIENTS WITH OPEN-ANGLE GLAUCOMA.

a. Microincisional glaucoma surgery
b. Argon laser trabeculoplasty
c. SLT
d. Incisional surgery

12. _____ IS CONSIDERED A VALUABLE MARKER BY THE PANELISTS FOR PREDICTING PATIENT RESPONSE TO PGAs.

a. Baseline IOP
b. Corneal hysteresis
c. Presence of dry eye disease
d. Patient age

ACTIVITY EVALUATION/SATISFACTION MEASURES

Your responses to the questions below will help us evaluate this CME/CE activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____

This activity improved my competence in managing patients with this disease/condition/symptom. _____ Yes _____ No

I plan to make changes to my practice based on this activity. _____ Yes _____ No

Please identify any barriers to change (check all that apply):

_____ Cost

_____ Lack of administrative support

_____ Lack of time to assess/counsel patients

_____ Reimbursement/insurance issues

_____ Patient compliance issues

_____ Other. Please specify: _____

_____ Lack of consensus or professional guidelines

_____ Lack of experience

_____ Lack of opportunity (patients)

_____ Lack of resources (equipment)

_____ No barriers

The design of the program was effective for the content conveyed. ___ Yes ___ No

The content supported the identified learning objectives. ___ Yes ___ No

The content was free of commercial bias. ___ Yes ___ No

The content was relative to your practice. ___ Yes ___ No

The faculty was effective. ___ Yes ___ No

You were satisfied overall with the activity. ___ Yes ___ No

Would you recommend this program to your colleagues? ___ Yes ___ No

Please check the Core Competencies (as defined by the ACCME) that were enhanced through your participation in this activity:

_____ Patient Care

_____ Practice-Based Learning and Improvement

_____ Professionalism

_____ Medical Knowledge

_____ Interpersonal and Communication Skills

_____ System-Based Practice

Additional comments:

_____

_____ I certify that I have participated in this entire activity.

This information will help evaluate this CME/CE activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

_____

COLLABORATIVE | EYE