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NEW PHARMACOTHERAPEUTICS FOR THE TREATMENT OF GLAUCOMA: TARGETING THE TRABECULAR MESHWORK

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New Pharmacotherapeutics for the Treatment of Glaucoma: Targeting the Trabecular Meshwork

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CONTENT SOURCE

This continuing medical education (CME)/continuing education (CE) activity captures content from a roundtable discussion.

ACTIVITY DESCRIPTION

The development and commercialization of two new topical glaucoma drugs has renewed interest in medical therapy. In late 2017, after a 2-decade gap in glaucoma pharmacology innovation, two drugs in novel classes were approved for IOP reduction in eyes with ocular hypertension or open-angle glaucoma. These drugs lower IOP through unique mechanisms of action not previously available with existing drug choices. This activity will provide education on the efficacy, safety, and mechanism of action of these two new drugs.

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:

- **Identify** the mechanisms of action as well as the efficacy and safety profiles of novel trabecular outflow medications
- **Demonstrate** proficiency in selecting appropriate therapies to achieve individualized patient-specific treatment goals
- **Advocate** for patients who would benefit from new drugs before they are incorporated into payors' formularies

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

2. Please rate how often you intend to apply advances in the management of glaucoma in the clinic (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. What is the mechanism of action of latanoprostene bunod?

a. Latanoprostene bunod lowers intraocular pressure (IOP) by inhibiting the norepinephrine transporter pathways.
b. Latanoprostene bunod lowers intraocular pressure by increasing uveoscleral and trabecular outflow through relaxation and increased permeability of cells in the trabecular meshwork (TM) and Schlemm canal.
c. Latanoprostene bunod increases matrix metalloproteinase-1 (MMP-1) expression, which reduces episcleral venous pressure.
d. Latanoprostene bunod increases rho-kinase production, which remodels the extracellular matrix and increases aqueous humor outflow through the uveoscleral pathway.

4. What is the mechanism of action of netarsudil?

a. Netarsudil is a nitric oxide-donating prostaglandin F2α analog that increases MMP-1, MMP-3, and MMP-9 expression in the ciliary muscle, which reduces episcleral venous pressure.
b. Netarsudil increases rho-kinase production, which remodels the extracellular matrix and increases aqueous humor outflow through the uveoscleral pathway.
c. Netarsudil increases uveoscleral and trabecular outflow through relaxation and increased permeability of cells in the TM and Schlemm canal.
d. Netarsudil inhibits both rho-kinase and norepinephrine transporter pathways, which increases trabecular outflow, reduces episcleral venous pressure, and reduces aqueous production.

5. What dose of latanoprostene bunod was the most effective at lowering IOP compared with latanoprost in the VOYAGER study?

a. Latanoprostene bunod 0.006%
b. Latanoprostene bunod 0.012%
c. Latanoprostene bunod 0.024%
d. Latanoprostene bunod 0.040%

6. In patients with lower baseline IOP, which agent(s) should be considered as a potential first-line therapy?

a. Latanoprostene bunod and/or netarsudil
b. Timolol
c. Dorzolamide
d. Oral carbonic anhydrase inhibitors

7. In the ROCKET studies, more than half of the patients in the netarsudil arm developed what side effect?

a. Allergic reaction to the active ingredient
b. Excessive tearing
c. Hyperemia
d. Burning/stinging upon instillation

8. The MERCURY studies on netarsudil/latanoprost showed a _____ reduction in IOP in 30% of patients.

a. 20%
b. 30%
c. 40%
d. 50%

9. Mr. Jones has uncontrolled open-angle glaucoma, despite having undergone subliminal laser therapy and being on a prostaglandin. He also complains of ocular surface issues, predominantly redness, and tearing. What agent might be a viable adjunctive therapy?

a. BAK-free latanoprost
b. Netarsudil/latanoprost
c. Latanoprostene bunod
d. All the above

10. Which of the new agents has an impact on the TM?

a. All glaucoma agents bypass the TM.
b. None of the agents work at the TM level.
c. Netarsudil works at the TM level.
d. Latanoprost works at the TM level.

11. Which medication has three separate mechanisms of action?

a. Netarsudil
b. Latanoprostene bunod
c. Latanoprost
d. Bimatoprost

12. Based on the phase 3 MERCURY-1 and MERCURY-2 trials, netarsudil had a greater pressure lowering effect than in ROCKET, up to _____?

a. 6.1 mm Hg
b. 7.1 mm Hg
c. 8.1 mm Hg
d. 9.1 mm Hg

New Pharmacotherapeutics for the Treatment of Glaucoma: Targeting the Trabecular Meshwork

For the first time in more than 20 years, ophthalmologists have new pharmacotherapeutics in their armamentarium for the treatment of glaucoma: latanoprostene bunod, netarsudil, netarsudil/latanoprost, and benzalkonium chloride (BAK)-free latanoprost. The approvals couldn't come at a better time; with the aging population, the National Eye Institute expects a 58% increase in glaucoma cases in the United States by 2030.[1] These new agents have unique mechanisms of action (MOAs) and are thought to decrease intraocular pressure (IOP) by directly impacting the trabecular meshwork (TM) and Schlemm canal with, possibly, disease-modifying effects. The following roundtable discussion brings together glaucoma specialists to discuss how they are using these new agents in the clinic, the potential side effects, and how to select the appropriate therapies to achieve individualized patient-specific treatment goals.

—Thomas Samuelson, MD, Moderator

NEW DRUG APPROVALS FOR GLAUCOMA

Q | THOMAS SAMUELSON, MD: There have been a number of new pharmacotherapeutics approved in the last few years including latanoprostene bunod (Bausch + Lomb), rho-kinase (ROCK) inhibitors such as netarsudil (Rhopressa, Aerie Pharmaceuticals) and combination netarsudil/latanoprost (Rocklatan, Aerie Pharmaceuticals) and BAK-free latanoprost (Xelpros, Sun Pharmaceutical Industries Ltd).[2-5] How has the addition of these agents affected the way you manage patients?

JASON BACHARACH, MD: It's great that we have more options. It's been well over 2 decades since we've had a new option for the pharmaceutical management of glaucoma. Latanoprostene bunod and netarsudil have unique and interesting MOAs. Netarsudil actually has three. First, it lowers IOP by inhibiting the ROCK and the norepinephrine transporter (NET) pathways. The ROCK inhibitor increases the trabecular outflow and reduces episcleral venous pressure while the NET inhibitor decreases aqueous production.[6-10] Latanoprostene bunod is a nitric oxide (NO)-donating prostaglandin F2 analog that seems to work in two ways. First, latanoprost acid increases metalloproteinase-1 (MMP-1), MMP-3, and MMP-9 expression in the ciliary muscle, which remodels the extracellular matrix and increases aqueous humor outflow through the uveoscleral pathway.[11,12] Second, the NO-donating moiety increases aqueous outflow through the TM, Schlemm canal, and distal scleral vessels by inducing cytoskeletal relaxation through the sGC-cGMP signaling pathway.[12]

ALBERT S. KHOURI, MD: Before these latest approvals, the last two medications for glaucoma treatment were prostaglandins and alpha agonists, which were approved in 1996.[13] For 20 years, we were working with different combinations of approved medications. Glaucoma specialists have been waiting for new class medications for a long time. In the past, all other medications worked on outflow and inflow, but outflow was mostly uveoscleral. Now, we have medications that work at the site where we believe the pathology is located, the TM, by enhancing outflow through the conventional pathway. Importantly, latanoprostene bunod and netarsudil are dosed only once per day, which is very favorable for patient adherence and side effects.[11]

CONSTANCE OKEKE, MD, MSCE: Having performed my own research on medication compliance in glaucoma patients, those conclusions forever changed my focus with glaucoma treatment. In clinical practice I am constantly looking for management strategies to minimize patient burden, enhance compliance and improve quality of life. What these new medications bring are not only novel MOA, but the essential triad of efficacy, tolerability, and simplicity that are the best formula to maximize on medication compliance.

MURRAY FINGERET, OD, FAAO: Before the introduction of the new medications, I would often wish for a primary agent that could lower the IOP more or if my patient was on a prostaglandin that was well tolerated and working well, I wished for an agent that would be a once-per-day drug and could achieve greater IOP reduction. With the introduction of the new agents, we have these, though at times, local side effects occur which we have to work around. Still we now have greater flexibility that allows us to manage our patients medically for extended periods.

LATANOPROSTENE BUNOD VS LATANOPROST

Q | DR. SAMUELSON: How does adding latanoprostene bunod change the equation for a patient who has only been on a traditional prostaglandin?

DR. BACHARACH: Latanoprostene bunod has been in evolution for many years. Nicox, a French company, partnered with Bausch + Lomb to try to improve upon the IOP reduction that latanoprost alone delivered.[14-17] They conducted clinical trials using NO-donating moiety, and they are continuing that approach in clinical trials right now with bimatoprost (NCT03657797). What's interesting is that it's not a fixed combination. NO is really a gas, and the only way to keep it soluble is to link it to another molecule. In this case, latanoprost was the molecule that it was linked to. It's broken down into the eye through esterases and hydroxylases.[18]

Latanoprost primarily works through uveoscleral outflow, but it also has a trabecular outflow effect, impacting the extracellular matrix.[15] However, the principal mechanism of the NO component is the TM outflow. The primary way to get nutrition to the TM is through the aqueous because there's no blood flow in the TM.[12] NO has the additional benefit of continuing to percolate aqueous through the TM outside of enhanced IOP reduction. It may enhance the health of the meshwork itself.

DR. FINGERET: What is intriguing about NO is that it may provide other properties to the TM and eye such as enhancing blood flow. Dr. Robert Furchgott received the Nobel Prize in Medicine for the discovery that NO was a signaling molecule liberated from endothelial cells to mediate smooth muscle cell relaxation. Impaired NO signaling could contribute to elevated IOP and enhanced optic nerve vulnerability. Whether a topical agent could influence blood flow at the optic nerve still needs to be determined, but the idea that an eyedrop could influence properties outside of IOP reduction is worth exploring.

Q | DR. SAMUELSON: What did the VOYAGER trials tell us about the effectiveness of the IOP lowering power of latanoprostene bunod compared with standard latanoprost?

DR. KHOURI: VOYAGER was a head-to-head trial of 413 patients comparing the efficacy and safety of latanoprost 0.005% versus four different doses of latanoprostene bunod (0.006%, n = 82; 0.012%, n = 85; 0.024% n = 83; and 0.040%, n = 81).[19] It was our chance to see how the NO-donating moiety would perform. Patients were dosed once a day for 28 days. The results were impressive. Although all doses resulted in significant IOP reductions from baseline, latanoprostene bunod 0.024% was the most effective dose, achieving a reduction in mean diurnal IOP of 9.0 mm Hg. To me, though, one of the key points of the study was that a single dose of latanoprostene bunod led to prolonged IOP reductions that lasted up to 40 hours.

In the phase 3 registration trials, latanoprostene bunod was significantly more effective than timolol (Timoptic, Bausch + Lomb), with more patients reaching a mean IOP less than or equal to 18 mm Hg and IOP reduction at least 25%. The pressure reductions were maintained with latanoprostene bunod for up to a year without loss of effect or tachyphylaxis.[14-16]

DR. SAMUELSON: It should be noted that the concentration of latanoprost is different in the two agents as well, that is when you compare standard latanoprost versus the concentration of latanoprost in the latanoprostene bunod molecule.

DR. BACHARACH: That's correct. The concentration is greater in the latanoprostene bunod moiety than it is in latanoprost. That's a great point to bring up because there were some thoughts that the increased concentration of latanoprost was giving that additive effect, and maybe it wasn't the NO. We know from the original latanoprost dose-response studies that increasing the concentration of latanoprost had no additional IOP affect.[20] In the VOYAGER study, the concentration of latanoprost was increased from to 0.04 to 0.025%, and it had no additional IOP-lowering benefit.[19] It doesn't seem to be the increased concentration of latanoprost that brings the added value. It's really the nitric oxide donating moiety.

Q | DR. SAMUELSON: Have you seen any changes in tolerability due to a higher concentration of latanoprost?

DR. KHOURI: In clinical practice, I think latanoprostene bunod is well-tolerated and in line with the phase 3 trials where the rate of hyperemia was low.[14-16] The discontinuation rate was extremely low in the registration trial at about 1.5%.[15] That's remarkable.

DR. SAMUELSON: That's been my experience as well that switching from a traditional prostaglandin to latanoprostene bunod hasn't led to changes in tolerability.

DR. FINGERET: I agree, I also have not seen any issues when switching from latanoprost to latanprostene buond. It is well tolerated, similar to latanoprost.

Q | DR. SAMUELSON: In the VOYAGER trial, the latanoprostene bunod consistently was lower than latanoprost by about a millimeter. Is that correct?

DR. BACHARACH: It was 1.25 mm for approximately 40% of the participants, but there were subsets of individuals who were hyperresponders. About 12% of participants achieved a 5 mm Hg or greater IOP reduction.[19] The challenge is we don't know how to identify those patients proactively. Is there a target population of people who will be hyperresponders? We haven't quite figured that out, but they're out there.

Q | DR. SAMUELSON: Are there patients for whom you particularly select latanoprostene bunod over other agents?

DR. FINGERET: I see this as a first-line drug for individuals requiring greater IOP reduction, such as those with optic nerve and visual field damage in which the target pressure is in the 35 to 40% range. One agent may get to this point where another prostaglandin may not, allowing the person to use just one drug.

DR. KHOURI: I tend to use medications that target the TM in exfoliation and pigment dispersion patients because we know that the TM is diseased in those cases. Those patients were excluded from all the clinical trials, so this is simply based on my experience as a clinician. I also like to prescribe TM-targeting medications like netarsudil and latanoprostene bunod in patients with Drance hemorrhages that often may have normal tension glaucoma because those work well in patients with lower baseline pressures. The JUPITER study, which was conducted in Japan with latanoprostene bunod, helped illustrate this.[17] Normal-tension glaucoma is common in the Japanese population. The majority of eyes in the JUPITER trial had a baseline IOP between 15 and 21 mm Hg, and mean IOP reductions of 22.0% and 19.5% were achieved by week 4 in study and treated fellow eyes, respectively. These reductions were maintained through week 52. Similarly, there is an ongoing trial with netarsudil in Japan to study its effects in that population with glaucoma.

DR. OKEKE: I intentionally use medications that relax the TM in younger patients. Theoretically, it is possible that over time these medications could be disease modifying by changing the structure of the fibers within the TM and inner wall of Schlemm canal. I also use it in patients with recently diagnosed glaucoma where I often get a robust response. I believe that when there is a robust response that their TM outflow system is still viable, and by chronically utilizing these TM-targeting medications I'm actually helping them over time. I also use it in patients who have had microinvasive glaucoma surgery (MIGS), believing here that there is a symbiotic effect that helps maintain the TM and outflow system.

LATANOPROST BUNOD VS TIMOLOL

Q | DR. SAMUELSON: How did latanoprostene bunod compare to timolol in the phase 3 trials?

DR. BACHARACH: There were two studies, APOLLO and LUNAR, which mirrored each other.[14-16] Both were designed to compared the safety and efficacy of 3 months of latanoprostene bunod with 3 months of timolol. Patients were randomly assigned 2:1 to a 3-month regimen of latanoprostene bunod 0.024% every evening (qPM) or one drop of timolol 0.5% twice daily (BID). Both trials had very specific endpoints. IOP was assessed at screening and at 8 AM, 12 PM, and 4 PM at baseline. Patients were required to have an IOP of at least 26 mm Hg at one or more timepoints, at least 24 mm Hg at at least one timepoint, and 22 or greater mm Hg at one timepoint in the same eye, and an IOP of 36 or less mm Hg at all three baseline timepoints in both eyes. The eye with the highest IOP became the study eye.

Mean IOP was found to be significantly lower in the latanoprostene bunod group versus the timolol group in all measured timepoints but one. Results from both studies showed that latanoprostene bunod reduced IOP by 7.5 to 9.1 mm Hg during 3 months of treatment.

Q | DR. SAMUELSON: Do you think that clinicians should migrate toward drugs that have a mechanism that might enhance outflow versus aqueous suppression?

DR. KHOURI: Yes, I do. With MIGS being a mainstay for glaucoma treatment, we're trying to bypass the layer of most resistance to aqueous outflow. It makes sense, clinically, to rejuvenate and maintain an active outflow pathway. Maintaining flow through the conventional outflow could have disease-modifying characteristics.

DR. OKEKE: I think that it makes sense to want to enhance what is naturally supposed to happen; aqueous production and continuous outflow. Though aqueous suppressants have helped us lower IOP and slow down the progression of glaucoma, what they may be doing to the outflow system long term may be detrimental. In time I believe there will be an even more clear advantage to the use of drugs that target the TM and enhance the outflow system.

DR. SAMUELSON: I agree; I like the idea of maintaining the canal. We're now trying to resurrect the canal whether it be surgically with some of our canal-based procedures or drugs that improve coefficients of outflow. We can do it surgically, we can do it medically, and we can combine the two and hopefully modify the disease over time.

DR. FINGERET: I agree, reducing aqueous production goes against normal physiology as compared to enhancing the already established outflow mechanism. I would much rather use a TM drug, if it is well tolerated. And with timolol, there are many other issues such as its inability to reduce the IOP during the nocturnal hours, its systemic side effect profile and that tolerance often develops. One positive attribute of timolol is it being cost effective.

ROCK INHIBITORS IN CLINICAL PRACTICE

Q | DR. SAMUELSON: Netarsudil, a ROCK inhibitor, was recently approved for open-angle glaucoma based on the ROCKET trials, which found that netarsudil reduced IOP by up to 5 mm Hg.[21, 22] What do we know about netarsudil in the clinic thus far?

DR. BACHARACH: Many companies have tried to commercialize ROCK inhibitors, but struggled to find that perfect balance between efficacy and clinically acceptable tolerability. Netarsudil is really interesting. Although the exact MOA is unclear, it's believed that netarsudil lowers IOP by increasing trabecular outflow, decreasing aqueous production, and reducing episcleral venous pressure. Netarsudil was compared to timolol in the ROCKET-1, ROCKET-2, and ROCKET-4.[21,22] Once-daily dosing of netarsudil was effective and well tolerated overall, although hyperemia occurred in about half of the patients. Netarsudil was noninferior to timolol in the per-protocol population with maximum baseline IOP less than 25 mm Hg in ROCKET-1 and ROCKET-2 and noninferior to timolol in patients with baseline IOP less than 27 mm Hg and less than 30 mm Hg in ROCKET-4.[21,22]

In addition, results of a phase 2 study in which I was a co-author found that netarsudil was only less effective than latanoprost by 1 mm Hg in patients with unmedicated IOPs of 22 to 35 mm Hg when we looked at the total group of patients.[23] Like the ROCKET trials, hyperemia was the most frequently reported adverse event,

occurring in a little more than half of patients on netarsudil. The drug has uniqueness that may be clinically important clinical to a subset of individuals.

Q | DR. SAMUELSON: How have you been incorporating netarsudil into your practice?

DR. OKEKE: I add netarsudil to patients who are already on a prostaglandin and who need additional IOP reduction. Its once-daily dosing is appealing, as is its different MOA. Data from the phase 3 MERCURY-1 and MERCURY-2 trials were just released. Netarsudil had a greater pressure lowering effect in these trials than in ROCKET, up to 6.1 mm Hg.[24,25] Based on these data, netarsudil is a strong adjunct, but could also be considered in the first-line setting for certain cases.

Netarsudil is also a great agent to use on patients post-MIGS if I don't want them on a prostaglandin. Sometimes I'm surprised at how robust the pressure lowering is in those circumstances. That said, the side-effect profile can be a deterrence, with hyperemia being the most common adverse event, although it's mostly mild. I have seen hyperemia improve in some patients with time, which was confirmed in the trial by Dr. Bacharach and colleagues; the frequency of hyperemia decreased over the 28-day study period.[23] I see the hyperemia as something to be concerned about, but not a strong deterrent to using the medication. I've also found that many patients don't notice the hyperemia unless I point it out.

DR. FINGERET: I find it to be an excellent additive medication when a person is taking a prostaglandin and needs further IOP reduction. Its once per dosage schedule is better than the other second-line agents and its ability to lower IOP even when starting with IOP in the mid-teens is another important attribute. Still hyperemia does occur and needs to be managed.

Q | DR. SAMUELSON: Let's dive into this drug's unique MOA a little further. We know netarsudil has favorable effects at the TM level. How does the episcleral venous component factor into the situation?

DR. KHOURI: Netarsudil works at the level of the TM by inhibiting ROCK. It's been shown to also lower episcleral venous pressure by about 10%.[26] That partly explains the level of hyperemia that we see with ROCK inhibitors—it's how they work, and partly why they work so well in patients with lower baseline pressures. In contrast, with latanoprost and timolol, for example, the pressure reduction was better when the patient started with higher baseline pressure.[22] But those mediations were not as effective when the baseline pressure was lower. With netarsudil, the episcleral venous pressure reduction component plays a key factor in making those medications more effective at lower baseline pressures.

DR. BACHARACH: In the ROCKET and MERCURY trials, it wasn't that ROCK inhibitors worked less well at higher pressures.[21,22,24,25] When you actually looked at the data, the ROCK inhibitors worked about the same percentage-wise no matter the starting pressure. That's incredibly unique. Most classes of medicines work about 0.5 mm less well for every millimeter of lower starting pressure.

Q | DR. SAMUELSON: Some clinicians mistakenly compare ROCK inhibitors to prostaglandins in terms of side effects, perhaps because they are both dosed every night at bedtime (qHS). Do any of the adverse effects seen with ROCK inhibitors overlap with the adverse effects from prostaglandins? Patient's won't experience eyelash growth, periorbital lid changes, or iris color change with ROCK inhibitors, correct?[27]

DR. BACHARACH: That's correct. One of the benefits of combination netarsudil/latanoprost is you can dose them together. Most of the hyperemia seen with netarsudil occurs a couple of hours after dosing, which is one of the reasons netarsudil is dosed before bed; it hides the hyperemia. When you look at the MERCURY data compared to the ROCKET data, combining netarsudil and latanoprost in the same bottle didn't worsen the hyperemia that much.[21,22,24,25] Most of the hyperemia experienced was a trace to mild.

Q | DR. SAMUELSON: When we talk to patients about the hyperemia experienced with netarsudil compared to the hyperemia experienced with brimonidine, for example, do you draw a distinction between them? To me, they are very different. Do you agree?

DR. OKEKE: Yes, they are very different. With netarsudil, the mechanism of hyperemia is episcleral vessel vasodilation that's occurring. With brimonidine, the hyperemia seems to be related to allergy with conjunctival or follicular conjunctivitis that can occur while on the medication.[28-30] It's a much lighter, milder kind of hyperemia, but one that results in the patient stopping the drop. When I talk to patients about netarsudil, I explain that it's typically tolerated well, but that hyperemia can be expected. I also explain that the hyperemia improves over time. It's important to be upfront with patients so they know what to expect. Most patients will be able to tolerate the hyperemia.

I don't talk as much about some of the other potential side effects of netarsudil, like the corneal verticillata, because it doesn't impact the patient visually; it's something that we see on the exam. I also don't bring up conjunctival hemorrhages because it happens so infrequently.[31,32]

Q | DR. SAMUELSON: I've seen conjunctival hemorrhages, and I've seen frank subconjunctival hemorrhages that are larger more diffuse. In general, when I see a red eye from an alpha agonist like brimonidine, I know it's the beginning of the end of that drop because it's often frank allergy. But that's not necessarily true with hyperemia from ROCK inhibition. Has anyone else experienced this?

DR. KHOURI: Yes, I've experienced this as well. When patients have hyperemia from netarsudil, it's typically mild. Only a small minority of patients experience moderate or severe hyperemia. In ROCKET-4, when we looked at the data from repeat visits, the hyperemia wasn't

present every single time the patient came in.[21] I've observed this in clinical practice as well; the hyperemia toggles back and forth. Talking to patients about hyperemia is important because it's part of how the medication works. It also prevents you from getting a phone call from the patient asking about it when they first use the medication. Once they know that the hyperemia will come and go, that it will fluctuate, but that it will mostly be mild, patients are more accepting of it and tolerate the medication better.

DR. BACHARACH: I agree with both of my colleagues. Like Dr. Okeke mentioned, the verticillata seen with netarsudil is visually insignificant; we're not going to take the patient off netarsudil because of it. For the hyperemia, you have to discuss it with the patient in advance. They will call and ask about it if you don't, and it's not fair to them for it to be a surprise. Unlike brimonidine, the hyperemia seen with netarsudil is not an allergic response. With brimonidine the redness is the result of a true allergy to the medicine. You have to scratch it from your repertoire and all the derivatives of it for that patient. With netarsudil, I tell my patients to hang in there if they experience a red eye; it most likely will dissipate. That said, if they experience a beet red eye, it is not the right drug from them.

DR. FINGERET: I agree with the comments from my colleagues. Hyperemia associated with brimonidine and netarsudil are different. Brimonidine is an allergy that will advance with continuing use. This is not typically the case with netarsudil with many improving over time but there are a few patients who present with deep hyperemia that does not change and the medication needs to be stopped.

Q | DR. SAMUELSON: I do exactly what you all do. I also explain why I like netarsudil—it's well tolerated systemically and it works on a critical part of the outflow system. I also explain that it will cause some redness and that not everyone will tolerate it. That said, it's worth a try because it comes with many benefits. I think explaining to the patient the different MOA helps them through some of the rougher stretches of hyperemia because they know it's a special drug that works in a special way. What is your failure rate? What percentage of patients discontinue netarsudil because of hyperemia?

DR. OKEKE: About 10 to 15% of my patients won't be able to tolerate the level of redness. However, I am always surprised that when the medication is working well, many will change their level of tolerance towards acceptance.

DR. KHOURI: Not all the patient populations are the same. When netarsudil first launched, I was using it as a third (or sometimes even a fourth) medication. Those eyes already were hyperemic; they were already on multiple medications, including a prostaglandin. Most people didn't complain about the hyperemia when I added netarsudil. Now that we've started using netarsudil as a second medication the chance that patients will have hyperemia and will contact the physician about it is higher than if we were incorporating it later.

Q | DR. SAMUELSON: Will you stop a drug when you add netarsudil or do you simply add it?

DR. KHOURI: Early on, I wasn't stopping other drugs because netarsudil was the only medication that was working at the TM level. Everything else decreases aqueous production or bypasses the TM. In terms of complementary mechanism of action, it made sense to continue with the other medications and add netarsudil. It's difficult for the third or fourth medication to dent the IOP, but we did see some patients who had a significant IOP drop when we added netarsudil as a third or a fourth medication. When you use it on top of a prostaglandin, there is a greater chance the hyperemia will be significant.

NOVEL FIXED COMBINATIONS IN CLINICAL PRACTICE

Q | DR. SAMUELSON: With the approval of netarsudil/latanoprost, we now have a fixed combination of a prostaglandin and ROCK inhibitor that showed a 40% drop in IOP in nearly a third of patients in clinical trials.[24,25] That's pretty profound. What's been your experience with fixed combination netarsudil/latanoprost?

DR. BACHARACH: The phase 3 studies reiterated what Lewis et al published in the phase 2 trial.[33] The numbers blew our minds; people reached IOPs below 14 mm Hg in both studies with a once-a-day drop.[24,25] This is a significant improvement to our therapeutic armamentarium.

DR. OKEKE: I was involved in the MERCURY trial, and we had one patient who just made the cut-off of 36 mm Hg. After the trial was unmasked, we discovered that his pressures dropped to 12 and 13 mm Hg. At that time, I was flabbergasted; it was almost miraculous. It's exciting to know that the TM is still viable and that there can be a robust reaction to this class of medication.

DR. FINGERET: I have been pleasantly surprised at the level of IOP reduction in many of my patients who have used this agent. It allows, at times, taking medications away, which is something I was not used to doing.

Q | DR. SAMUELSON: Is there a more potent single drop than combination latanoprost/netarsudil?

DR. KHOURI: Combination latanoprost/netarsudil is one of the most robust pressure-reducing agents we currently have. In APOLLO, latanoprostene bunod had a 9.1 mm Hg IOP reduction at its peak effect timepoint.[16] But what's unique about latanoprost/netarsudil is its ability to achieve a 40% IOP reduction in 30% of patients. Those are levels we rarely talk about with other pharmacologic agents for glaucoma (40% reduction). There's some similarity with MIGS, too. You have patients where you bypass the TM (by various surgical means), and you achieve a large reduction in pressure. That probably reflects a healthy and preserved

downstream outflow system. When we bypass the TM with some pharmacologic agents, we're seeing similar responses.

Q | DR. SAMUELSON: Do you find that combination netarsudil/latanoprost has similar tolerability to netarsudil alone?

DR. BACHARACH: Yes. Other than a mild bump in hyperemia, there were no additional ocular adverse events reported.[24]

DR. FINGERET: Yes, I agree that the combination of netarsudil and latanoprost has a side effect profile similar to when using the two agents individually.

Q | DR. SAMUELSON: Are there any systemic concerns with ROCK inhibitors?

DR. OKEKE: There haven't been any systemic issues in the trials that were done comparing ROCK inhibitors to timolol. The researchers looked at different side-effect profiles and vital signs and didn't find any systemic decrease as compared to ones they found with timolol.[21,22] We also haven't seen negative effects during pregnancy, but that should be further explored. In the meantime, I'd recommend netarsudil in patients who are not pregnant.

DR. KHOURI: In MERCURY, about one in five patients had hyperemia when they were included in the clinical trials, which could make those hyperemia rates seem a little higher than what they would have been if those patients were excluded from the studies.[24,25] In terms of systemic safety, I think that the safety profile is very favorable with ROCK inhibitors. There's also data on endothelial cell counts that were stable throughout the studies. There's some reports from Japan that have looked at ROCK inhibitors in patients with pseudophakic bullous keratopathy and some modulation of the endothelium there.[34,35] It's not approved for that indication in the United States, but that could be an area of study in the future.

DR. SAMUELSON: I caution clinicians against dismissing ROCK inhibitors because of the tendency for hyperemia. A certain percentage of patients may get more redness than they are willing to put up with, but there are many upsides to this class of drugs. I think it's a mistake to give up on these agents because of a small subset of patients.

DR. KHOURI: I agree; it's a disservice to patients to dismiss such potent medications based on mild, sporadic hyperemia. We know it's going to fluctuate; it's not going to worsen overtime. There's not a single medication that we have that is going to be tolerated by every patient. Clinicians need to go through the process with the patient, explain the adverse effects, and give it a good chance prior to dismissing it outright.

DR. SAMUELSON: Patients need to know it's not an allergy, it's not an infection, it's not inflammatory. It's just part of the way the drug works. I think they do find that reassuring.

BAK-FREE LATANOPROST

Q | DR. SAMUELSON: Another new addition to the glaucoma pharmacotherapeutics is BAK-free latanoprost. The manufacturer, Sun Pharmaceuticals, took an interesting approach by going direct to patients, bypassing insurers. Has that been a success in anyone's practice?

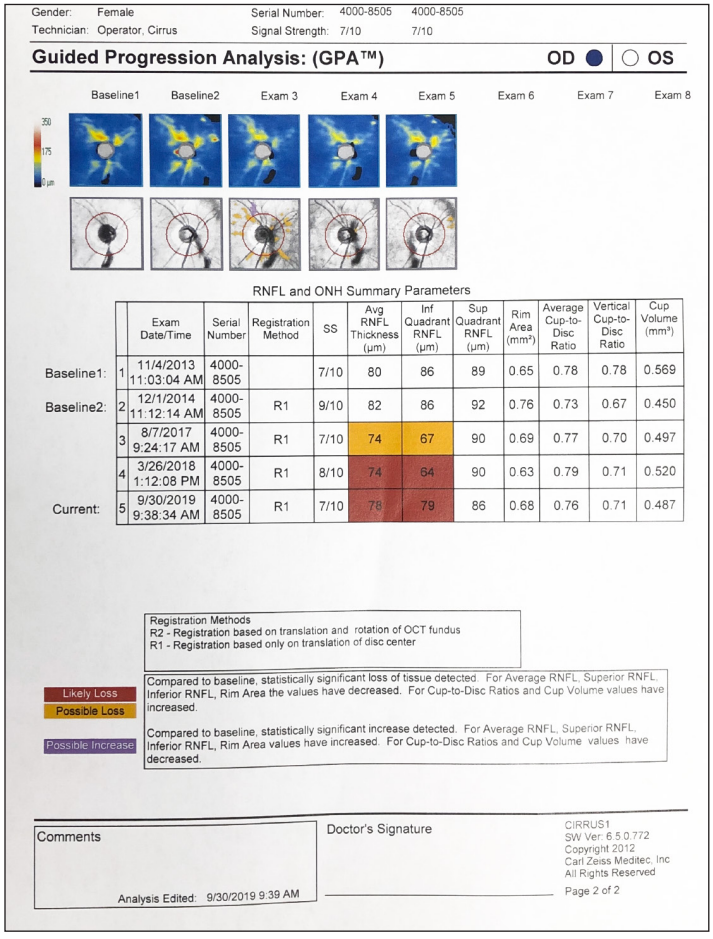
DR. BACHARACH: Glaucomatologists have become experts in pharmacoeconomics and how to get our patients these great new tools. There is a subset of individuals, particularly people that don't have Medicare Part D, who enjoy the ability to have reduced out-of-pocket expenditures by using either specialty pharmacies or nontraditional avenues, such as couponing, to get medications. The manufactures of all of the new agents discussed in this manuscript are perfect examples of companies embracing these tools in an attempt to contain medication costs for patients.

DR. OKEKE: I've noticed access differences between new and existing classes of medicines. For example, latanoprostene bunod stayed in the prostaglandin class, meaning you have to use other prostaglandins before you can use latanoprostene bunod. I've been able to get netarsudil much faster for my patients because it's a new class of medicine. My use of BAK-free latanoprost has been limited, but I find it very useful and effective in my patients with BAK allergies. It can work really well, and I have seen patients experience a much better side-effect profile when they switch.[36,37]

DR. FINGERET: In regard to the BAK-free latanoprost, I don't see this as a significant advance because it does have a preservative, just not BAK. Travatan Z has been with us for years and now we have another prostaglandin in this group. The bigger story is its distribution being in a cash pay model, which is very different. Novartis is doing a similar thing with Travatan Z, also now using the cash pay model. The BAK-free latanoprost requires the use of mail order pharmacies which may be a burden for patients not use to this. Novartis is partnering with local pharmacies which may improve its chances of its cash pay model working. This is a fascinating development which points to the strange ways our health system works.

CASE 1: OPEN-ANGLE GLAUCOMA AND OCULAR SURFACE DISEASE

DR. KHOURI: Our first case is a 62-year-old diabetic patient with primary open-angle glaucoma. He has significant ocular surface disease and has struggled with the use of previous medications, which has negatively impacted compliance. The patient has punctal plugs and is on topical cyclosporine and artificial tears. He was on latanoprost for his glaucoma and has pressures in the high teens with previously stable structure and function testing. However, over the past 2 years, his pressures have increased. His acuity is well-preserved, but his pressures are now 23 and 22 mm Hg. He has a relative afferent pupillary defect in the right eye. His OCT RNFL analysis shows progression (Figure 1). The ocular surface is in poor shape with fluorescein uptake on the cornea. His discs are glaucomatous, and his central corneal thickness is slightly below average. What are the options for this patient? What are your next steps?


Gender: Female Serial Number: 4000-8505 4000-8505
Technician: Operator, Cirrus Signal Strength: 7/10 7/10

Guided Progression Analysis: (GPA™) OD ● ○ OS

Baseline1 Baseline2 Exam 3 Exam 4 Exam 5 Exam 6 Exam 7 Exam 8

RNFL and ONH Summary Parameters

		Exam Date/Time	Serial Number	Registration Method	SS	Avg RNFL Thickness (µm)	Inf Quadrant RNFL (µm)	Sup Quadrant RNFL (µm)	Rim Area (mm²)	Average Cup-to-Disc Ratio	Vertical Cup-to-Disc Ratio	Cup Volume (mm³)
Baseline1:	1	11/4/2013 11:03:04 AM	4000-8505		7/10	80	86	89	0.65	0.78	0.78	0.569
Baseline2:	2	12/1/2014 11:12:14 AM	4000-8505	R1	9/10	82	86	92	0.76	0.73	0.67	0.450
	3	8/7/2017 9:24:17 AM	4000-8505	R1	7/10	74	67	90	0.69	0.77	0.70	0.497
	4	3/26/2018 1:12:08 PM	4000-8505	R1	8/10	74	64	90	0.63	0.79	0.71	0.520
Current:	5	9/30/2019 9:38:34 AM	4000-8505	R1	7/10	78	79	86	0.68	0.76	0.71	0.487

Registration Methods
R2 - Registration based on translation and rotation of OCT fundus
R1 - Registration based only on translation of disc center

Likely Loss / Possible Loss: Compared to baseline, statistically significant loss of tissue detected. For Average RNFL, Superior RNFL, Inferior RNFL, Rim Area the values have decreased. For Cup-to-Disc Ratios and Cup Volume values have increased.

Possible Increase: Compared to baseline, statistically significant increase detected. For Average RNFL, Superior RNFL, Inferior RNFL, Rim Area values have increased. For Cup-to-Disc Ratios and Cup Volume values have decreased.

Comments
Analysis Edited: 9/30/2019 9:39 AM

Doctor's Signature

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Page 2 of 2

Figure 1. The patient's OCT retinal nerve fiber layer analysis shows progression.

DR. OKEKE: We need to address his ocular surface and reduce his pressure without adding more drops since compliance is clearly an issue. I'd consider selective laser trabeculoplasty (SLT). If he has had SLT already, I would look to see if the SLT was effective. If you must add medication, I'd consider combination netarsudil/latanoprost or latanoprostene bunod since he is only taking latanoprost currently. I'd also have a low threshold to consider a MIGS stand-alone procedure in this patient.

DR. BACHARACH: I would also try SLT in this patient. The LiGHT study showed that SLT was a viable alternative in terms of patient's acceptance.[38] SLT wouldn't preclude using one of the new agents as an adjunct to streamline the amount of drops placed on the corneal surface, considering the ocular surface disease.

DR. SAMUELSON: I agree; I would take this patient off latanoprost and recommend SLT. Sometimes we use SLT as an initial treatment, and sometimes we do an SLT to replace current treatment. In this case, since we're doing an SLT to replace current treatment, I'd add back latanoprostene bunod if the SLT alone didn't provide enough pressure reduction.

DR. FINGERET: As mentioned by others, we need to get the ocular surface disease under control, which will need to include more than the use of tears and cyclosporine. Then, SLT would be indicated. Having a nonpreserved glaucoma agent would be useful if further IOP reduction is needed, though the only nonpreserved agent I am aware of is timolol or timolol-dorzolamide. Non-BAK additive medications such as those preserved with Purite or Sofia Z may also be considered to further lower the IOP.

DR. OKEKE: It's possible the patient has a BAK allergy. BAK-free latanoprost could be an option in this case if they needed additional pressure lowering after the SLT.

DR. KHOURI: I performed an SLT, and the pressure reduced to the high teens. I was concerned about progression and felt that a pressure of 18 mm Hg was too high for this patient. I discontinued the latanoprost, switched him to combination netarsudil/latanoprost, and his pressures reduced. He currently has pressures in the 12 to 14 mm Hg range and is tolerating the combination netarsudil/latanoprost well.

DR. OKEKE: How did his ocular surface do?

DR. KHOURI: His ocular surface is still dry and uses preservative-free tears, but he's tolerating the glaucoma medication well. Access to medications often determines which product you choose. Once a patient fails a prostaglandin it's sometimes a little easier to get coverage for netarsudil-latanoprost or latanoprostene bunod.

DR. BACHARACH: We can't let apathy get in our way. One of the most commonly used combinations in the United States is generic timolol and generic latanoprost. Quite honestly, they're not great from an efficacy standpoint, in an additivity nature. They're the path of least resistance for clinicians, but we have to push for these newer agents for our patients.

CASE 2: RISING IOP POST-SLT TREATMENT

DR. BACHARACH: Our second case is a 67-year-old Hispanic male. He has a medical history of chronic obstructive pulmonary disease and hypertension, but no known drug allergies. His family history includes maternal aunt who is blind from glaucoma. He takes an oral beta blocker and a steroid inhaler as needed. On slit lamp examination, he had moderate cataract, 1+ nuclear sclerosis. He has an IOP of 23 mm Hg in his right eye and 26 mm Hg on his left, with corneal pachymetry of 505 µ and 500 µ. Gonioscopically, he was wide open in the ciliary body with normal pigmentation. He had a normal retinal exam and cupping worse in the left eye than right eye.

Figure 2 shows asymmetry in cupping, with the right eye approximately 0.7 and the left eye 0.8 to 0.85 with an enclosed to the rim inferiorly. The OCT corroborates the asymmetry, with the left eye having abnormal temporal, superior, nasal, inferior, temporal (TSNIT) and ganglion cell count (GCC) values, and the right eye having essentially a normal OCT with one borderline reading in TSNIT.

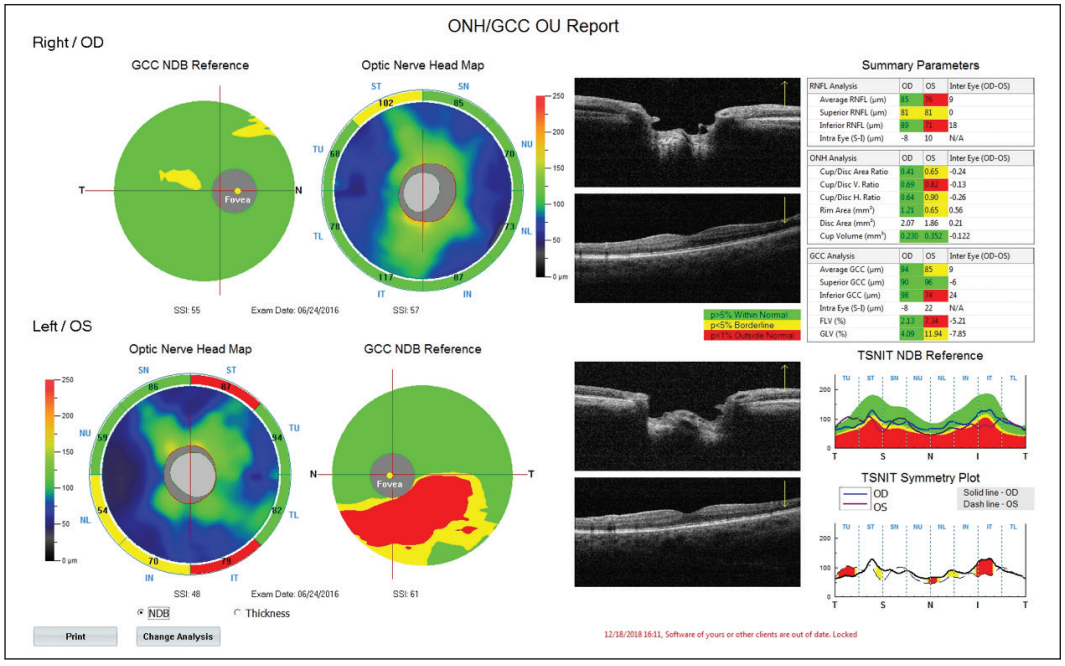

Figure 2. The OCT-TSNIT and GCC of a 67-year-old Hispanic male with a medical history of chronic, obstructive pulmonary disease and hypertension. He has asymmetry in cupping. The left eye has abnormal TSNIT and GCC values, and the right eye has normal OCT with one borderline reading in TSNIT.

His visual fields make sense from a structure/function relationshipThe right eye was essentially non-glaucomatous and the left eye has a superior visual field defect that is in line with the inferior rim in that eye (Figure 3).

In 2016, I set a target pressure of a 30% reduction, which would be 16 mm Hg in the right and 18 mm Hg in the left. SLT brought the pressure down into that range, with pressures fluctuating between 16 mm Hg and 18 mm Hg over the following couple of years. The pressures started to escalate into the mid-20s a couple of years later, and the left eye developed a new Drance hemorrhage in the area that was thinning. I then set a new maximum IOP to the mid-teens. How can we achieve that in this patient?

DR. KHOURI: The patient is Hispanic, meaning he is at higher risk for thin central corneal thickness.[39] You need to get aggressive in pressure reduction. The SLT worked once, and may be worth repeating. There is plenty of evidence showing that repeat SLT works.[40-43] Medications that target the trabecular meshwork tend to work well at lower pressures. I'd consider adding either latanoprostene bunod or combination netarsudil/latanoprost in this case.

DR. FINGERET: I would also consider having the SLT repeated but also consider utilizing latanoprostene bunod or netarsudi or netarsudil/latanoprost.

DR. OKEKE: I noted the patient had a cataract of 1+ nuclear sclerosis. He could be a candidate for a MIGS combo with a cataract if that cataract is visually significant. If it's not, then I'd also repeat the SLT because we know it has the potential to work again. Given that he has a family history of someone going blind from glaucoma, I'd also start him on latanoprostene bunod.

DR. BACHARACH: I started the patient on latanoprostene bunod because in early 2018, when I was making these decisions, there was no combination netarsudil/latanoprost. I did not repeat the SLT because although it can be efficacious, the duration of efficacy isn't as long as the initial treatment. I was able to get the patient down to the 16 to 17 mm Hg range with a latanoprostene bunod. One of my colleagues had been experimenting by adding netarsudil to latanoprostene bunod, with the thought that both mechanisms of action include improvement in trabecular outflow. With the possibility that this could help reduce pressures further, I tried that combination in this patient. It worked very well, and continues to work well to this day. He's maintained pressures in the low teens, between 13 and 14 mm Hg, on two drops at bedtime.

DR. SAMUELSON: I like the way you've managed this case. I think it demonstrates the flexibility and the power that we have with our new drugs. You've added basically one drop a day, and you've significantly improved his pressure profile. Other individuals might do better with just a single drop, and maybe for that individual, you use combination netarsudil/latanoprost. There's definitely room for both netarsudil/latanoprost and netarsudil in the treatment of glaucoma.

Thank you all for your input on new medications for the treatment of glaucoma. It's an exciting time for our field, and it was a pleasure working with you. ■

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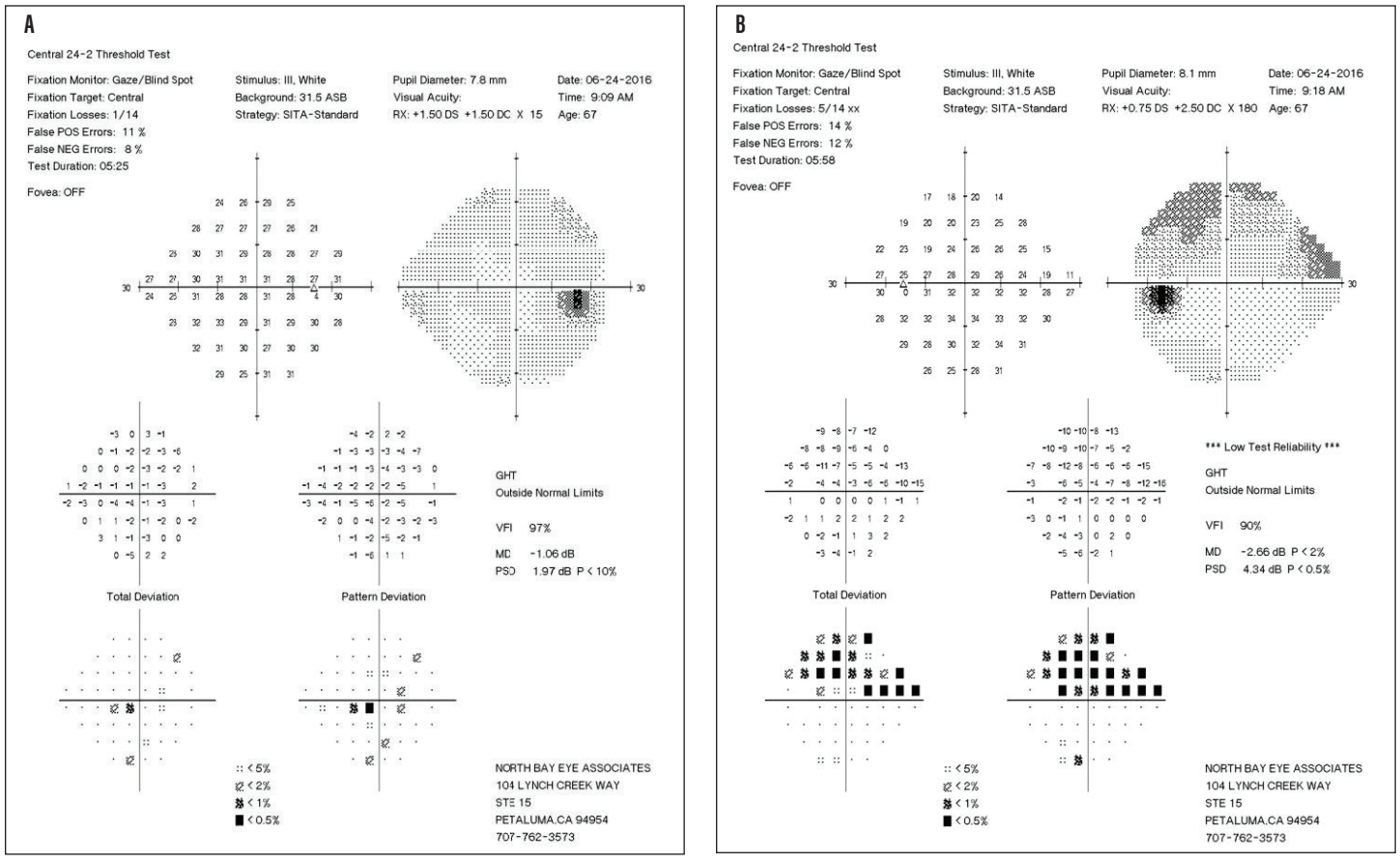

Figure 3. Visual fields of a 67-year-old Hispanic male with a medical history of chronic, obstructive pulmonary disease and hypertension. The right eye is non-glaucomatous (A), and the left eye has a superior visual field defect (B).

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NEW PHARMACOTHERAPEUTICS FOR THE TREATMENT OF GLAUCOMA: TARGETING THE TRABECULAR MESHWORK

Release Date: Jan. 5, 2020
CME Expiration Date: January 2021
COPE Expiration Date: Dec. 15, 2022

INSTRUCTIONS FOR CREDIT

To receive credit, you must complete the attached Post Test/Activity Evaluation/Satisfaction Measures Form and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, please click https://evolvemeded.com/online-courses/1918-supplement. If you are experiencing problems with the online test, please email us at info@evolvemeded.com. Certificates are issued electronically; please be certain to provide your email address below.

Please type or print clearly, or we will be unable to issue your certificate.

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

Phone (required) _____ ❑ Email (required) _____

Address _____

City _____ State _____ Zip _____

License Number _____

OE Tracker Number _____

DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ 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 educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
___ 51+

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

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Identify the mechanisms of action as well as the efficacy and safety profiles of novel trabecular outflow medications	_____	_____	_____
Demonstrate proficiency in selecting appropriate therapies to achieve individualized patient-specific treatment goals	_____	_____	_____
Advocate for patients who would benefit from new drugs before they are incorporated into payors' formularies	_____	_____	_____

POSTTEST QUESTIONS

1. Based on this activity, please rate your confidence in your ability to apply updates in the treatment of glaucoma 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. Based on this activity, please rate how often you intend to apply advances in the management of glaucoma in the clinic (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. What is the mechanism of action of latanoprostene bunod?

a. Latanoprostene bunod lowers IOP by inhibiting the norepinephrine transporter pathways.
b. Latanoprostene bunod lowers intraocular pressure (IOP) by increasing uveoscleral and trabecular outflow through relaxation and increased permeability of cells in the trabecular meshwork (TM) and Schlemm canal.
c. Latanoprostene bunod increases matrix metalloproteinase-1 (MMP-1) expression, which reduces episcleral venous pressure.
d. Latanoprostene bunod increases rho-kinase production, which remodels the extracellular matrix and increases aqueous humor outflow through the uveoscleral pathway.

4. What is the mechanism of action of netarsudil?

a. Netarsudil is a nitric oxide-donating prostaglandin F2 analog that increases MMP-1, MMP-3, and MMP-9 expression in the ciliary muscle, which reduces episcleral venous pressure.
b. Netarsudil increases rho-kinase production, which remodels the extracellular matrix and increases aqueous humor outflow through the uveoscleral pathway.
c. Netarsudil increases uveoscleral and trabecular outflow through relaxation and increased permeability of cells in the TM and Schlemm canal.
d. Netarsudil inhibits both rho-kinase and norepinephrine transporter pathways, which increases trabecular outflow, reduces episcleral venous pressure, and reduces aqueous production.

5. What dose of latanoprostene bunod was the most effective at lowering IOP compared with latanoprost in the VOYAGER study?

a. Latanoprostene bunod 0.006%
b. Latanoprostene bunod 0.012%
c. Latanoprostene bunod 0.024%
d. Latanoprostene bunod 0.040%

6. In patients with lower baseline IOPs, which agent(s) should be considered as a potential first-line therapy?

a. Latanoprostene bunod and/or netarsudil
b. Timolol
c. Dorzolamide
d. Oral carbonic anhydrase inhibitors

7. In the ROCKET studies, more than half of the patients in the netarsudil arm developed what side effect?

a. Allergic reaction to the active ingredient
b. Excessive tearing
c. Hyperemia
d. Burning/stinging upon instillation

8. The MERCURY studies on netarsudil/latanoprost showed a _____ reduction in IOP in 30% of patients.

a. 20%
b. 30%
c. 40%
d. 50%

9. Mr. Jones has uncontrolled open-angle glaucoma, despite having undergone subliminal laser therapy and being on a prostaglandin. He also complains of ocular surface issues, predominantly redness and tearing. What agent might be a viable adjunctive therapy?

a. BAK-free latanoprost
b. Netarsudil/latanoprost
c. Latanoprostene bunod
d. All the above

10. Which of the new agents has an impact on the TM?

a. All glaucoma agents bypass the TM.
b. None of the agents work at the TM level.
c. Netarsudil works at the TM level.
d. Latanoprost works at the TM level.

11. Which medication has three separate mechanisms of action?

a. Netarsudil
b. Latanoprostene bunod
c. Latanoprost
d. Bimatoprost

12. Based on the phase 3 MERCURY-1 and MERCURY-2 trials, netarsudil had a greater pressure lowering effect than in ROCKET, up to _____?

a. 6.1 mm Hg
b. 7.1 mm Hg
c. 8.1 mm Hg
d. 9.1 mm Hg

ACTIVITY EVALUATION

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 consensus or professional guidelines
_____ Lack of administrative support
_____ Lack of experience
_____ Lack of time to assess/counsel patients
_____ Lack of opportunity (patients)
_____ Reimbursement/insurance issues
_____ Lack of resources (equipment)
_____ Patient compliance issues
_____ No barriers
Other. Please specify: _____
_____
_____

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 Accreditation Council for Graduate Medical Education) 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 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.

_____