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TARGETING THE TRABECULAR MESHWORK: INCORPORATING NEW OUTFLOW DRUGS INTO GLAUCOMA CARE

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Targeting the Trabecular Meshwork: Incorporating New Outflow Drugs Into Glaucoma Care

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a round table discussion.

ACTIVITY DESCRIPTION

Glaucoma is seeing a resurgence in innovative therapeutic developments. The recent approval of two drugs in novel classes for IOP reduction in eyes with ocular hypertension or open-angle glaucoma utilizes 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 and how they compare to traditional glaucoma treatments.

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:

- **Describe** the mechanisms of action of novel therapeutics and classes of drugs
- **Compare** the efficacy of novel therapeutics with traditional prostaglandins
- **Understand** and explain the likelihood of achieving target intraocular pressure with monotherapy compared with combination regimens
- **Restate** the most common side effects of novel therapeutics
- **Identify** how to provide the best possible collaborative care when comanaging patients

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1. Please rate your confidence in your ability to apply updates in medical glaucoma therapy 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 apply the latest available medical glaucoma therapy 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. Describe the mechanism of action of netarsudil.

a. Netarsudil increases uveoscleral and trabecular outflow through relaxation and increased permeability of cells in the trabecular meshwork (TM) and Schlemm canal.
b. 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 (EVP).
c. Netarsudil inhibits both rho-kinase and norepinephrine transporter pathways, which increases trabecular outflow, reduces EVP, and reduces aqueous production.
d. Netarsudil increases rho-kinase production, which remodels the extracellular matrix and increases aqueous humor outflow through the uveoscleral pathway.

4. Describe the mechanism of action of latanoprostene bunod.

a. Latanoprostene bunod is a nitric oxide-donating prostaglandin analogue (PGA) that increases aqueous humor through both the TM and the uveoscleral pathway.
b. Latanoprostene bunod is a rho-kinase inhibitor that enhances the trabecular outflow and lowers EVP.
c. Latanoprostene bunod increases aqueous humor outflow through the uveoscleral pathway.
d. Latanoprostene bunod relaxes the TM by promoting the assembly of actin stress fibers and focal adhesions.

5. Mrs. Smith is a 74-year-old female with low-tension glaucoma, hypertension, and chronic obstructive pulmonary disease. She has tried multiple topical agents including several PGAs, brimonidine, and dorzolamide with minimal response, her intraocular pressure (IOP) remains in the mid to upper teens, her visual fields are progressing. What is the next step in her treatment?

a. Netarsudil as an adjunct treatment
b. Switch to netarsudil monotherapy
c. Selective laser trabeculoplasty (SLT)
d. Latanoprostene bunod

6. Mr. George is in his mid-50s with a baseline pressure of 40 mm Hg. You want to reduce his IOP by 40%. Which of these agents is unlikely to be used in the first-line setting?

a. Latanoprostene bunod
b. Combination aqueous suppressant
c. Netarsudil/latanoprost
d. Netarsudil

7. What is the most concerning side effect of netarsudil for young people?

a. Iris pigmentation
b. Corneal verticillata
c. Hyperemia and blurred vision
d. All of the above

8. Based on the phase 4 MOST trial data, adding netarsudil to a PGA resulted in IOP reductions of _____ mm Hg?

a. 4.2 mm Hg
b. 4.5 mm Hg
c. 5.3. mm Hg
d. 6.0 mm Hg

9. Based on phase 1/2 data, what percentage of patients with the bimatoprost sustained-release implant were able to go 2 years without rescue treatment?

a. About 25%
b. About 30%
c. About 15%
d. About 20%

10. Mr. Davis is a nonresponder to latanoprost. He has struggled with compliance to his medical glaucoma therapy, and underwent an SLT last year to reduce his IOP without medical therapy. His pressure is slowly starting to increase. What treatment option may be appropriate for him next?

a. Repeat the SLT
b. Netarsudil/latanoprost
c. Latanoprostene bunod
d. Netarsudil

11. Latanoprostene bunod works on which outflow systems?

a. Trabecular outflow
b. Uveoscleral outflow
c. Ciliary body outflow
d. Both trabecular and uveoscleral pathways are involved

12. In the JUPITER trial, a 1-year study of latanoprostene bunod, what was the percent reduction in IOP in patients with a baseline IOP of 15 to 21 mm Hg?

a. 25%
b. 10%
c. 50%
d. 33%

Targeting the Trabecular Meshwork: Incorporating New Outflow Drugs Into Glaucoma Care

Glaucoma is the leading cause of preventable blindness in the world.[1] Glaucoma is a chronic, lifelong condition with a significant treatment burden, accounting for 10 million physician visits annually in the United States alone.[2] Medical therapy is the first-line choice for most glaucoma physicians,[3] but its success is highly dependent on patient compliance and proper drop instillation.[4-6] Many patients continue to experience glaucoma progression even on multiple lines of therapy. For patients on maximal therapy with uncontrolled intraocular pressure (IOP), invasive surgical procedures are often required. In order to improve compliance and outcomes, more effective treatment options are needed. Until 2017, no new pharmacologic treatments had been approved in the United States in nearly 20 years. With the approval of two new compounds that may be disease modifying, as well as the development of sustained-release devices, physicians have more management options than ever before. The following roundtable brings together key opinion leaders in glaucoma treatment to discuss the latest treatment options and how to incorporate them into practice.

–Gagan Sawhney, MD, Moderator

THE ROLE OF THE TRABECULAR MESHWORK IN REGULATING IOP

Q | **GAGAN SAWHNEY, MD:** We are living in a renaissance in glaucoma treatment. The development and commercialization of two new novel glaucoma agents in 2017 have renewed the field's interest in medical therapy. Before 2017 with the FDA approval of latanoprostene bunod and netarsudil,[7,8] the last time we had a new glaucoma medication was 1996 with the approval of latanoprost.[9]

We know that oxidative stress is closely related to glaucoma development.[10] The aqueous contains antioxidants that are beneficial for ocular structures like the trabecular meshwork (TM).[11] When the aqueous outflow becomes dysfunctional, it reduces the number of antioxidants and leads to oxidative damage of the TM.

Until recently, most of our medications worked on decreasing aqueous production or increasing uveoscleral outflow. Latanoprostene bunod and netarsudil, however, lower IOP through novel mechanisms of action not available in any other drug choice.[12]

Netarsudil can actually help rejuvenate the TM by inhibiting the rho-kinase (ROCK) and norepinephrine transporter (NET) pathways, which enhances the trabecular outflow and lowers episcleral venous pressure (EVP).[13,14] Latanoprostene bunod, on the other hand, is a nitric oxide (NO)-donating prostaglandin analogue that increases aqueous humor through both the TM and the uveoscleral pathway.[15,16]

Q | **What are your thoughts on these medications in relation to the TM and oxidative damage?**

JACOB BRUBAKER, MD: With netarsudil, we talk so much about how it relaxes the TM by inducing loss of actin stress fibers and focal adhesions.[17] However, it's also interesting to think about how it also reduces transforming growth factor-ß2 and some of the oxidative stress processes.[18] We don't have long-term histological data yet, but the idea of relaxing the TM and maybe rejuvenating it is the Holy Grail of glaucoma treatment. You're treating the actual disease state of the eye. This is something that needs to be investigated further, but it gives me confidence that in addition to reducing IOP, I could be remodeling the TM long-term.

DR. SAWHNEY: The aqueous contains antioxidants that are good for the eye. When I think of our traditional medications like timolol that reduce aqueous production, we could still be damaging the TM by promoting oxidative stress, even though we're lowering IOP.[19] That's one reason I like the netarsudil family of products; it stops that vicious cycle of damage.

ROCK inhibitors remodel the TM and gets fluid flowing through collector channels. As a result, has anyone found that ROCK inhibitors improve goniotomy outcomes?

OLUWATOSIN U. SMITH, MD: There are no studies to help us look at that directly. However, there are studies that show us that Schlemm canal and the collector channels have collapsed in patients with advanced glaucoma.[20] If your TM is dysfunctional, you're not getting as much aqueous through your conventional outflow system. If we can preserve that function early on in the disease process, we can then do a trabecular bypass or stripping procedure to maximize outflow in that direction and acheive better effects. It will be interesting to see how we can better study this process as more patients use ROCK inhibitors before proceeding to surgery.

NOVEL MEDICATIONS CURRENTLY ON THE MARKET

Netarsudil

Q | DR. SAWHNEY: Netarsudil has a dual mechanism of action. Not only does it impact the TM to prevent contraction of those actin and mycin stress fibers, relaxing the tissue allowing for aqueous outflow, it also lowers EVP by dilating the episcleral veins.[13] How does the EVP come into play in managing this disease?

DR. BRUBAKER: Netarsudil is both a ROCK inhibitor and a NET inhibitor. I think that's why we could see improved outcomes with goniotomy after netarsudil therapy; it reduces EVP, allowing us to further lower IOP. I've started patients on netarsudil after a 360-degree gonioscopy-assisted transluminal trabeculotomy (GATT), and they still respond. I think that is a testament that the NET inhibition component of netarsudil is leading to EVP reduction.

DR. SAWHNEY: EVP plays a significant role in patients with low-tension glaucoma. How does netarsudil impact low-tension patients? Are you changing your treatment paradigm with this new medication based on decreased EVP?

DR. SMITH: We should always think about the mechanism of action of medications when treating patients with glaucoma. When we combine drops with different mechanisms, we can create synergy and enhanced IOP reduction. It's always difficult to lower pressure in patients who already have low IOP.[21,22] Netarsudil meets an important clinical need in its ability to drive that low pressure even lower through its unique mechanism of action. It's one of the first drugs I think of using when I have a patient with low-tension disease.

DR. SAWHNEY: I completely agree. I used to start my low-tension patients on a prostaglandin followed by an alpha agonist. Now, I'm often starting patients with a ROCK inhibitor such as netarsudil. I am noticing that with netarsudil I can achieve IOPs in the single digits or very low teens. We can achieve these low IOPs with netarsudil because of its effect on EVP. Where does netarsudil or latanoprostene bunod fit within the treatment paradigm? Is it a first-line or second-line agent?

DR. SMITH: My use of netarsudil often depends on how the patient presents. For example, many of my patients with low-tension glaucoma are usually on multiple medications to attain their low target pressures. I now take them off everything to get a new baseline, and then I put them on netarsudil to see if that gets us closer to the pressure goal before I start adding more medications. Latanoprostene bunod, a NO donating prostaglandin, can also be used first-line.

DR. BRUBAKER: We also have to take insurance into consideration. I have trouble getting netarsudil covered as a first-line agent. Because of this, I still use prostaglandins in the first-line setting. Netarsudil becomes my second-line agent in patients with low-tension glaucoma who don't have success with a prostaglandin; it's easier to get insurance approval. I agree that it may be ideal to use netarsudil in the first-line setting for low-tension glaucoma patients, but it's difficult to do in a real-world situation.

DR. GADDIE: I agree; insurance often drives my prescribing decisions. I would love to use netarsudil or latanoprostene bunod as first-line therapy, but insurance makes it challenging to do so.

Netarsudil Versus Other Agents: Literature Review

DR. SAWHNEY: Netarsudil and latanoprost were compared head-to-head in a 4-week phase 2 trial.[23] Patients were randomized to one-daily netarsudil or once-daily latanoprost, with a primary endpoint of IOP reduction at week 4. Results showed that latanoprost was more efficacious at high pressures, whereas netarsudil was able to lower pressures equally, both at higher pressures and lower pressures, by 5.7 mm Hg.

Netarsudil also went head-to-head against timolol in the phase 3 ROCKET trials (ROCKET-1, ROCKET-2, and ROCKET-4).[24,25] All three trials were similarly designed, with patients randomized to netarsudil 0.02% dosed once or twice daily or to twice daily timolol 0.05%, and all three trials had the same endpoint of noninferiority of netarsudil versus timolol. IOP was measured three times a day at 8 AM, 10 AM, and 4 PM at baseline and following 2 weeks and 3 months of treatment. The ROCKET trials added further evidence that netarsudil consistently lowers IOP at both high- and low-pressure points, with netarsudil lowering IOP by 3.3 to 5.0 mm Hg at month 3 in both ROCKET-1 and ROCKET-2. ROCKET-4 found that netarsudil was noninferior to timolol in an analysis of eyes with an IOP of less than 25 mm Hg at baseline.

Q | How do these data translate to the clinic?

DR. BRUBAKER: In the ROCKET trials, we noticed that timolol had a greater impact with higher starting pressures. Netarsudil, on the other hand, did better in patients starting with lower pressures at baseline. Mechanistically, this goes back to the EVP lowering affect. Netarsudil seems to give you a consistent numerical pressure reduction regardless of the starting pressure. Contrast this with timolol or prostaglandins, which typically results in a percentage IOP reduction. The higher the starting pressure, the larger the delta. This is great, if the starting pressure is high, but if you are trying to get into the low teens from the upper teens, it makes these agents less effective.

If a patient comes in with a pressure in the 30s or 40s, I'm not reaching for netarsudil as a first-line option. I'm usually prescribing prostaglandins and aqueous suppressants. However, if someone comes in with normal-tension pressures in the mid to upper teens, that's when a ROCK inhibitor is an ideal treatment option.

DR. SMITH: In the phase 2 studies,[23] in previously unmedicated patients, the low IOP subgroup was found to be noninferior to latanoprost. We know that the IOP lowering capability of prostaglandins is less at lower pressures. At certain pressures, both drugs are comparable in their action and so that leaves me open to prescribing either one of those drugs.

DR. SAWHNEY: Let's dig into the ROCKET data a bit more. ROCKET-1, ROCKET-2, and ROCKET-4 looked at netarsudil once-daily dosing.[24,25] The data pool showed that netarsudil achieved up to a 5-point reduction in IOP and was noninferior to timolol. How do these data compare to your experience in the clinic? Are you seeing this 5-point reduction? Is it more, is it less?

DR. GADDIE: I may have a slightly different perspective, given I'm not in a surgical glaucoma practice where patients are on three or four medications and waiting for an interventional surgery. My patients are typically on one or two medicines, and we need to add an additional medical therapy. In most cases, I found that patients achieve 4 to 6 mm Hg of additional lowering with netarsudil. However, there are some patients who paradoxically achieve no effect, even if they were just on a prostaglandin, and we added netarsudil. For the most part, I think the real-world experience with netarsudil lives up to the clinical data, but some patients are nonresponders.

DR. SAWHNEY: When I first started prescribing netarsudil, most of my patients had moderate to severe disease and were on three medications, on average. When I added netarsudil, those patients achieved a 6-point reduction, which was consistent regardless of how many medications they were on.

I've also had patients who I'd consider super hyper-responders on ROCK inhibitors, with significant pressure reductions to 8 or 9 mm Hg. These patients have IOP reductions greater than what the studies show for netarsudil. This pressure-lowering impact is not uncommon for this new class of agents. For example, 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). Although 40% of patients achieved an average of 1.25 mm Hg IOP reduction on latanoprostene bunod versus latanoprost, 12% of patients achieved a 5 mm Hg or greater IOP reduction.[26] Has anyone else experienced this in the clinic?

DR. GADDIE: I have experienced that. Some patients had IOPs in the double digits on prostaglandins, which we lowered to 9 mm Hg when switched to combination netarsudil/latanoprost.

DR. SMITH: I agree. I have seen hyper-responders but I've also seen patients who respond moderately or not at all. Every now and then I see a patient with a higher pressure on a ROCK inhibitor. I can't really explain that. In the instances that the patient has significant response and they are on multiple medications, I try to back off some of them and see how I can simplify their regimen.

DR. SAWHNEY: With these new classes of mediations, we are now in a position of scaling back other glaucoma medications once the patient has achieved their target pressure. When my patient hits their target, I always ask myself what drops can be stopped to simplify their regimen? We know that compliance improves when a patient is on fewer drops.[27,28] That's one of the benefits of these new mediations; we're getting pressure reductions we haven't seen before and can actually take patients off other medications.

The 12-week MOST study evaluated the efficacy, tolerability, and safety of netarsudil in 260 patients in a real-world setting as a monotherapy (n = 91) and as an adjunct to a prostaglandin (n = 151).[29] Adding netarsudil to a prostaglandin resulted in IOP reductions of 4.3 and 4.5 mm Hg. There were no treatment-related serious adverse events, and the most common side effects included hyperemia (20%) and blurred vision (7%).

In my opinion, when you add on timolol, followed by brimonidine, and followed by dorzolamide, the effect of each subsequent drop diminishes because you can only decrease so much; you can only act at the ciliary body so much. But now we have a medication that focuses on an entirely new path for that TM. It relaxes and rejuvenates that tissue, and acheives pressure reduction that's independent of these other drops. That's why you see that consistent response.

DR. BRUBAKER: I agree. It's interesting to look at the MOST study and see that regardless of the medication you add to netarsudil, it's going to have the same impact. That speaks to its completely different mechanism of action. We have our aqueous suppressants, we have our prostaglandins, and now we have an agent that potentially rejuvenates the TM. The MOST study data are helpful for our real-world experiences because we're not always seeing treatment-naïve patients or patients on single-agent therapy.[29] We're often seeing patients on two or three mediations. These data give us confidence that we can achieve a good response by adding netarsudil regardless of what we've tried before.

Managing Netarsudil Side Effects

DR. SAWHNEY: Although netarsudil works well, we do need to think about the side effect profile. Netarsudil had a significantly higher rate of hyperemia than timolol across all three ROCKET trials, incurring in a little more than half of patients. Hyperemia only occurred in 4 to 11% of patients on timolol.[24,25] However, the hyperemia rate was less in the MOST trial, occurring in only 20% of patients.[29] Netarsudil also had higher rates of corneal verticillata and conjunctival hemorrhages than timolol. Although corneal verticillata and hemorrhages occurred in 15 and 9% of netarsudil patients, respectively, in ROCKET-1 and ROCKET-2, rates were higher in ROCKET-4, at 24 and 16% respectively.[24, 25] The MOST trial saw fewer instances of corneal hemorrhage as well, at only about 7%.[29]

When I first started prescribing netarsudil, my discontinuation rate was high because I didn't prepare patients for hyperemia. Then patients would develop it, assume something was wrong, and stop using the drug. Now, when I prescribe netarsudil or netarsudil/latanoprost, I explain to patients that the medication works very well but they may experience some mild ocular redness. I ensure them that nothing is wrong, just to stay on the drop, come back, and we'll evaluate their pressure. When they come back and see that their IOP is well controlled, they are more accepting of the hyperemia.My discontinuation rate went from 30 to 15% with that new approach.

Q | **Hyperemia is an important issue to patients, and having that conversation is critical. In addition to properly managing patient**

expectations, how do you manage hyperemia for both netarsudil and netarsudil/latanoprost?

DR. SMITH: The MOST study has helped us understand how patients and physicians perceive medication tolerance. For example, 89% of patients in MOST had perceived tolerance to the medicine, but only 70 to 80% of doctors thought the patient acceptance was good to excellent.[29] Most patients that have hyperemia tend to be mild; the percentage of people who have moderate to severe hyperemia is a lot less.

I tend to have conversations with my patients about how they perceive the redness. Most patients believe the drug is helping and find the hyperemia tolerable. If a patient has really severe hyperemia, I will switch them. We need to keep patients on these drugs for an extended period of time. We must be mindful to make sure they are on a regimen they will follow.

DR. BRUBAKER: I leave the decision up to the patient and ask them directly if the redness is tolerable. Many times, they've been fighting with multiple medications trying to get their IOP under control. Once they see how well netarsudil works, they are often willing to tolerate side effects they wouldn't be able to with a less efficacious agent.

DR. SAWHNEY: I've noticed the hyperemia with netarsudil doesn't worsen over time. For example, if you start developing a follicular reaction with brimonidine, it becomes worse, then redder and eventually more intolerable overtime.[30] Then, paradoxically, it could cause the pressure rise because of congested episcleral vessels. Hyperemia also worsens over time with prostaglandins.[31] For netarsudil, most cases are mild and don't progress in my patient population.

DR. GADDIE: The hyperemia from netarsudil seems to improve over time in my patients. However, a side effect I see that continues to limit the drug is the small amount of blurred vision patients experience. It's usually a line or two of vision, and that does bother patients. Most of my patients tolerate the hyperemia if the drug is effective.

Q | DR. SAWHNEY: In the MOST trial, blurred vision occurred in 9% of patients on netarsudil monotherapy and in 6% of patients on netarsudil as an adjunct.[29] Another side effect with netarsudil is subconjunctival hemorrhages. Most of the time these are small petechial perilimbal hemorrhages, but every now and then a patient will have a diffuse subconjunctival hemorrhage. In those cases, I reassure the patient that it will resolve on its own, even with continued use of the medication.

Corneal verticillata was another adverse event reported in the trial. Have you noticed this in your patients, and, if so, how do you manage it?

DR. SMITH: I have seen cases of corneal verticillata in my patients. In the ROCKET trials, corneal verticillata was seen in 15 to 24% of patients.[24,25] I see it in slightly more than the 20% described, depending on how long they've been on netarsudil. It's difficult to explain what verticillata is to a patient, so I don't have a discussion with the patient about it specifically before prescribing the drop; I just keep an eye out for it. However, if I notice it is starting to form on follow-up visits, then I discuss it. We then decide how to proceed, depending on how bad it is.

DR. SAWHNEY: The longer my patients are on netarsudil, the more often I see corneal verticillata. It doesn't affect visual acuity, but it's something I see and note. The longer they've been on it the drug, the more likely I see it. If you stop the medication, it does resolve with time.

DR. GADDIE: I see it in my patients as well. Interestingly, I've never had a patient with both blurred vision and verticillata. I don't treat the verticillata. The patient doesn't know it's there, and it doesn't impact my management of their disease.

DR. BRUBAKER: I agree. I don't think it's worth discussing with patients, as it doesn't change their management and they won't see or notice it.

DR. SAWHNEY: I agree with these approaches. One thing I like about the netarsudil family of agents is you don't see as many systemic adverse events. For example, with timolol, you always think about how it will impact the elderly and patients' cardiac or pulmonary disease.[32] I don't worry about the hypotensive effects of an alpha agonist with netarsudil like I do with brimonidine.[33] I've even had patients on prostaglandins with odd systemic manifestations that completely resolve when they stop the prostaglandin. I have not yet seen that with netarsudil.

DR. SMITH: I agree that most of the adverse events or side effects with netarsudil are local. That is something to consider when you're treating glaucoma in people with other systemic comorbid conditions.

DR. SAWHNEY: Netarsudil is also my agent of choice for patients with a history of uveitis or young patients who may not tolerate the cosmetic side effects of a prostaglandin.[34,35] If someone has a history of uveitis or cystoid macular edema, I'll typically start off with netarsudil before I go to a prostaglandin. How do these scenarios factor into your decision making?

DR. SMITH: Young people tend to be more concerned about hyperemia than older people. That said, if netarsudil is efficacious and the hyperemia is mild, then that's the clear option over a prostaglandin in this case, given its cosmetic side effects.

DR. BRUBAKER: If young patients can tolerate the hyperemia, then netarsudil is a great option. Young patients are able to use sponsored coupons, whereas our older patients on Medicare usually can't. The coupons make the price more reasonable as well, which can be very helpful.

Using Netarsudil/Latanoprost in the Clinic

Q | DR. SAWHNEY: Combination netarsudil/latanoprost was approved in 2019. The once-daily agent combines the mechanism of action from each drug to help sustain IOP control. Netarsudil increases the TM outflow and lowers EVP, while the prostaglandin latanoprost promotes uveoscleral outflow.[36] How do you use netarsudil/latanoprost in your practice?

DR. SMITH: Regimen simplification is key. If I have the of opportunity to move a patient from a single agent to a combination drug to further reduce their IOP or move away from a certain class of medicine, I will. In this case, the combination is synergistic because they act at different locations.

I may start patients on netarsudil/latanoprost as first-line therapy if they have baseline high pressure and will need more than one medication. However, if I started them on latanoprost, or if I had a patient who needs further pressure reduction with once-daily dosing, then I will switch them to netarsudil/latanoprost.

DR. SAWHNEY: I completely agree. I am very comfortable with prescribing the netarsudil line of products. Once netarsudil/latanoprost became available, I felt very comfortable switching patients to the combination agent or even starting them on the combination agent. I used to wonder if I should start patients on netarsudil and see how they tolerate the hyperemia before switching them over. But I've found that the hyperemia rate is low, cases are mild, and most people tolerate it, especially with counseling. Therefore, I find myself switching to netarsudil/latanoprost.

DR. GADDIE: I do like the convenience of once-daily dosing. That's the beauty of netarsudil/latanoprost, you have every mechanism of action known in glaucoma medication in a once-daily drop. I also find the tolerability to be slightly better from the netarsudil component when it's combined into one bottle.

DR. BRUBAKER: I have a few patients who were previously nonresponsive to latanoprost. If I see that in their history, I'm hesitant to switch them to an agent that now has latanoprost plus netarsudil. I'm switching the vast majority of my patients to netarsudil/latanoprost in most other instances.

Q | DR. SAWHNEY: Data from the phase 3 MERCURY-1 and MERCURY-2 trials show that netarsudil had a greater IOP lowering effect than in the ROCKET trials, up to 6.1 mm Hg.[37,38] Dr. Brubaker, you were a study investigator. How do the MERCURY trials impact practice?

DR. BRUBAKER: The MERCURY trials were a continuation of the ROCKET trials. In MERCURY 1, 718 patients were randomized 1:1:1 to netarsudil/latanoprost, netarsudil monotherapy, or latanoprost monotherapy.[16] Primary endpoints were mean IOP at 8 AM, 10 AM, and 4 PM at week 2, week 6, and month 3. Sixty percent of patients in the netarsudil/latanoprost arm had a mean diurnal IOP of 16 mm Hg or lower, demonstrating statistical superiority over both its individual components. MERCURY 2 (n = 750) evaluated IOP at 90 days in three arms: netarsudil/latanoprost, netarsudil monotherapy, or latanoprost monotherapy.[17] Results were similar to MERCURY 1, with the combination showing greater IOP-lowering activity compared with either monotherapy. Netarsudil/latanoprost lowered IOP by an additional 1.5 to 3.3 mm Hg when compared with the other arms. Fifty-six percent of patients in the combination arm achieved a mean diurnal IOP less than 16 mm Hg, and side effects are mild. MERCURY 2 only had a 10% discontinuation rate, with the most common side effect being mild hyperemia. No systemic side effects were reported.

Pooled efficacy and safety data showed that 30% of patients on the combination had a 40% IOP reduction from baseline, compared with only 6% and 8% of patients on netarsudil or latanoprost monotherapy, respectively.[36] This is the first drug in the United States that's been approved as a combination with a prostaglandin. We've previously seen trials that attempted to do that with timolol, and they all failed. But now we actually have a product that is combining a prostaglandin with another agent, and it's a success.

DR. SAWHNEY: The netarsudil/latanoprost combination was two to three times more likely to achieve pressures of 14 mm Hg or below with a single agent. That's very important for slowing optic neuropathy and visual field loss. Dr. Brubaker, can you update the group on the MERCURY 3 trial?

DR. BRUBAKER: The MERCURY 3 trial is ongoing in Europe. They just finished enrollment. We don't have data yet, but they are comparing netarsudil/latanoprost to combination bimatoprost/timolol. It will be interesting to see how netarsudil/latanoprost compares to another combination product.

Latanoprostene bunod

DR. SAWHNEY: What's interesting about latanoprostene bunod is that you have latanoprostene, which releases that latanoprost, and then you have the bunod, which gives an NO component that acts at a very high level through a cyclic GMP cascade to inhibit ROCK.[39,40] That's where you get the relaxation of the TM and improved aqueous outflow.[41,42]

VOYAGER, which compared latanoprost 0.005% versus four different doses of latanoprostene bunod, established the 0.024% latanoprostene bunod dosing. Typically, they saw a 9-point reduction with latanoprostene bunod compared with a 7.8-point reduction with latanoprostene. They also reported 69% of patients achieved pressures of less than 18 mm Hg. In my practice, if I'm not getting the pressure reduction I need with another agent, oftentimes I'll switch them to latanoprostene bunod to see if that achieves additional IOP reduction.

Q | How are you using latanoprostene bunod in your practice?

DR. SMITH: One thing I think about when I use latanoprostene bunod 0.024% is that 42% of patients had an additional decrease of 2 mm Hg compared to just latanoprost in the VOYAGER study. If I have a patient who needs a couple of extra points of pressure reduction, I'll use latanoprostene bunod.

DR. SAWHNEY: I agree. Switching them to latanoprostene bunod to get a couple of additional points can really help as opposed to adding on a whole new class of medication.

DR. GADDIE: Latanoprostene bunod is also very tolerable. Except for a slight stinging sensation, patients haven't experienced hyperemia. From a safety standpoint, it's appealing.

DR. BRUBAKER: I agree. Latanoprostene bunod gives me an opportunity to switch within class and have the side effect profile be very similar, but hopefully get that extra pressure reduction that we need.

DR. SAWHNEY: APOLLO and LUNAR were two pivotal phase 3 randomized, multicenter, double-masked, parallel-group studies that compared once-daily latanoprostene bunod to twice-daily timolol in 840 patients.[43,44] Both studies demonstrated superior IOP reductions with latanoprostene bunod versus timolol at 17 of 18 time points. Typically, the IOP reduction was around 8 to 9 mm Hg from baseline. How do these data impact your practice?

DR. SMITH: When they pooled the data from those two studies, you had an IOP reduction range from 7.5 mm Hg all the way to 9.1 mm Hg. That's quite a big reduction. It could be appealing to start a patient on latanoprostene bunod initially. There was an additional 9-month safety extension on the APOLLO study.

DR. SAWHNEY: I agree. These new medications allow us to aggressively treat glaucoma with significantly IOP reduction in the first-line setting. We know from the Advanced Glaucoma Intervention Study and the Collaborative Initial Glaucoma Treatment Study that aggressive and early IOP lowering can help prevent progressive visual field loss.[45,46] If you can achieve significant pressure reduction with monotherapy, you've helped your patient because compliance goes up and their disease stays stable. That's one of the benefits of latanoprostene bunod, and both APOLLO and LUNAR illustrate this.

These data were further confirmed in the phase 3 JUPITER trial. JUPITER was a single arm, multicenter, 1-year study of latanoprostene bunod in Japanese patients with open-angle glaucoma and an IOP range of 15 to 30 mm Hg. Interestingly, 75% of patients had pressures of less than 21 mm Hg, and they still had really good IOP reduction of about 26%.[47] When they only looked at patients in that 15 to 21 mm Hg range, IOP reduction was still around 25%. To me, this drives home the message that latanoprostene bunod works at both low and high pressures. This could be a good agent to use in the first-line setting for patients with low-tension glaucoma.

Q | What do you make of these data?

DR. BRUBAKER: It's a strong study and gives us confidence as we're treating low-tension patients and specifically low-tension patients of Japanese descent.

DR. SMITH: What strikes me is that the IOP reduction was consistent over 12 months. Not only did latanoprostene bunod reduce IOP, it maintained that reduction for a period of time. Treating patients with low-tension glaucoma can be a struggle with pressures rising even with multiple drops. Latanoprostene bunod seems to be beneficial in this patient group.

DR. SAWHNEY: You don't have a weaning effect or tachyphylaxis. It really keeps that pressure consistent and stable long-term. The side effect profile for latanoprostene bunod is similar to latanoprost alone. I don't see an increased rate of hyperemia.

DR. SMITH: I agree. Side effects are very similar to what you would find with latanoprost. I haven't had a patient come in with unexpected adverse events.

SUSTAINED-RELEASE DEVICES

Q | DR. SAWHNEY: How do these new agents compare to novel implantable medications? For example, the bimatoprost sustained-release intracameral implant is now approved by the FDA and has been launched.[48] For me, when I think about the bimatoprost device, I thought I might be limited by the FDA indication, which is a single injection, but that's not been the case. In my practice, I'm finding it useful for a wide variety of patients (compliance, ocular surface disease, cost, etc.). I will continue using netarsudil and latanoprostene bunod when appropriate because of their multiple mechanism of actions and great efficacy. How do you plan on using bimatoprost sustained-release in the clinic?

DR. BRUBAKER: While designed to last 4 to 6 months, surprisingly in phase 1/2 data, nearly 25% of patients were able to maintain pressure control out to 2 years with a single implant. This is not that dissimilar to other treatment options such as selective laser trabeculoplasty (SLT). While not perfect, I think the bimatoprost device opens up a lot of options. I think this treatment is particularly attractive to patients with ocular surface issues. Additionally, it could be helpful if you did a minimally invasive surgical procedure and were trying to get the patient off that last eyedrop. This is the first step forward into the world of implantable medications. Hopefully it opens up the flood gates.

DR. SAWHNEY: It could also be helpful in patients who are having issues with compliance. A sustained-release implantable device takes compliance out of their hands. I think it will be individualized to each patient.

DR. SMITH: Over time, we'll figure out where these devices best fit in the way we practice. It may be in patients with ocular surface disease or in a person who needs an additional IOP reduction after SLT. Perhaps you switch them to an implant and reduce their medication burden. Sometimes it may make sense after a MIGS procedure where you need a supplement to lower IOP. You can add an implant to try to make the patient medication free, hoping they'll be one of the 25% who have an extended efficacy from the medicine. It would require us to look at individual patients to see what their needs are and what the best combination of available therapy will be to balance treatments to prevent of vision loss from glaucoma with ways of enhancing treatment related quality of life.

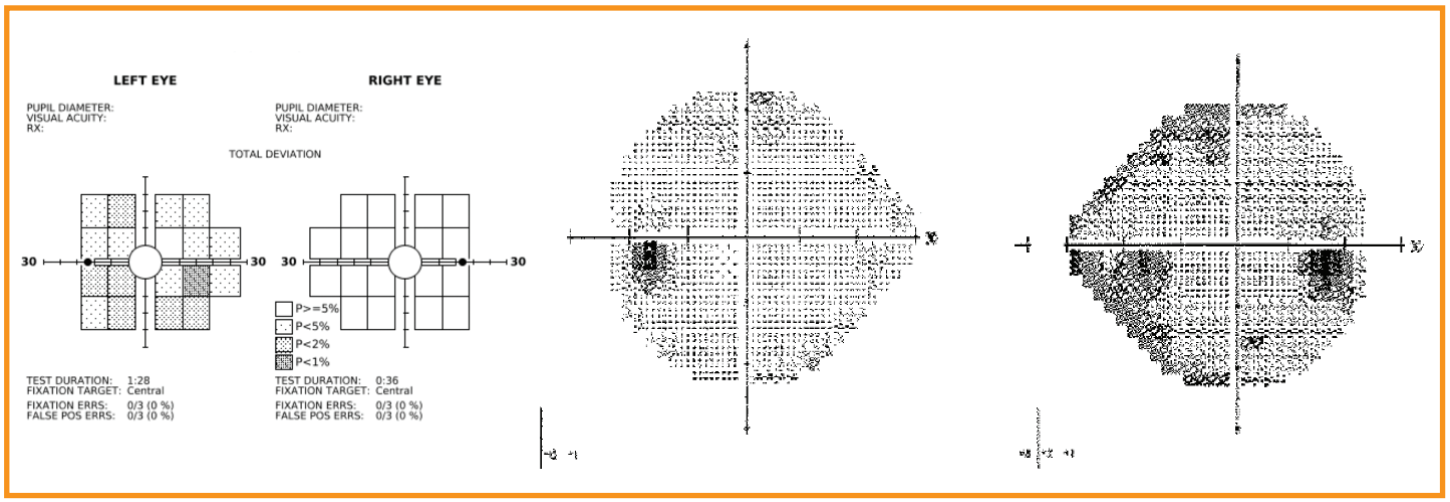

Figure 1. Case 2: FDT screening and visual field imaging.

DR. SAWHNEY: The more tools we have, the better we can manage our patients' glaucoma. You have to individualize the therapy to the patient. It's exciting, because we have far more options than we did 10 to 15 years ago.

CASE 1: INADEQUATE IOP CONTROL WITH PROSTAGLANDINS

DR. SMITH: Our first case is a 65-year-old woman diagnosed with glaucoma in 2014. Her IOP was 33 mm Hg in her right eye and 23 mm Hg in her left eye at diagnosis. She has a history of high blood pressure. She had a GATT in her left eye and a trabeculectomy in her right eye. Her IOP was previously controlled post-GATT, but her IOP became elevated over time. She did not respond to pilocarpine, and bimatoprost was effective but not covered by her insurance. Latanoprost was approved, but the IOP control was inadequate in the left eye. Her target IOP is mid to low teens in each eye. Our solution was combination treatment with dorzolamide/timolol and latanoprost. IOP was 9 mm Hg in her right eye and 20 mm Hg in her left. Her current medication regimen in the left eye was combination treatment with dorzolamide/timolol and latanoprost and no medications in the right eye. I opted to switch her left eye from latanoprost to netarsudil/latanoprost and continued dorzolamide/timolol. She's essentially on four medicines but in two different bottles. The actual number of drops per day was three. She came back with an IOP of 12 mm Hg and achieved a 40% reduction in IOP on her left eye.

DR. SAWHNEY: I would have done the same thing. Netarsudil has helped me hold off surgery for many patients. It works in the setting of post-GATT. It works despite how many medications the patient is already on, and you'll still see that 30 to 40% reduction.

DR. BRUBAKER: This goes back to what we were talking about earlier. Netarsudil may be rejuvenating the TM in addition to lowering the EVP; that's where we see the efficacy. At times, I struggle to take patients off a drop and see what happens, because that means they have to come back to the clinic for additional monitoring. It's just another visit.

DR. SAWHNEY: Yes, especially in the COVID-19 era. Sometimes times I try to reduce medications if the patient has gone below their target pressures, but we have to be careful about how quickly we bring patients back to the office.

CASE 2: NORMAL-TENSION GLAUCOMA

DR. BRUBAKER: Our next case is a 75-year-old male with low-tension glaucoma who presented in March 2020, right before COVID-19 shut down our offices. He was originally diagnosed with glaucoma in 1985 and referred to me for progression of his visual field in his left eye, despite good pressure. He's allergic to brimonidine and has had phacoemulsification in both eyes. He's currently taking timolol and latanoprost. His vision is 20/30 (right eye) and 20/40 (left eye), but his eye pressure is 13 and 14 mm Hg, right and left eyes, respectively.

We were able to do an frequency doubling technology screening (Figure 1), which showed some damage in his left eye. I was able to get his visual field record from the referring physician, but it was from 2016 (Figure 1). We decided to switch him to combination netarsudil/latanoprost, stop latanoprost, and continue with timolol. We couldn't see him until 3 months later, due to COVID-19 closures. When he returned, he presented with some mild hyperemia, and his pressure reduced to 9 mm Hg (right eye) and 11 mm Hg (left eye). He was pretty happy with his pressure, and we are still working to get a more recent visual field from his referring doctor. He is scheduled for a follow up with me in 6 months. This case gives me a lot of confidence. We didn't have to do a trabeculotomy in the middle of a pandemic. Instead, he gets to go home, take his drops, and see me in 6 months.

DR. SAWHNEY: This case highlights the effectiveness of netarsudil in lowering IOP in normotensive glaucoma patients. I believe we can

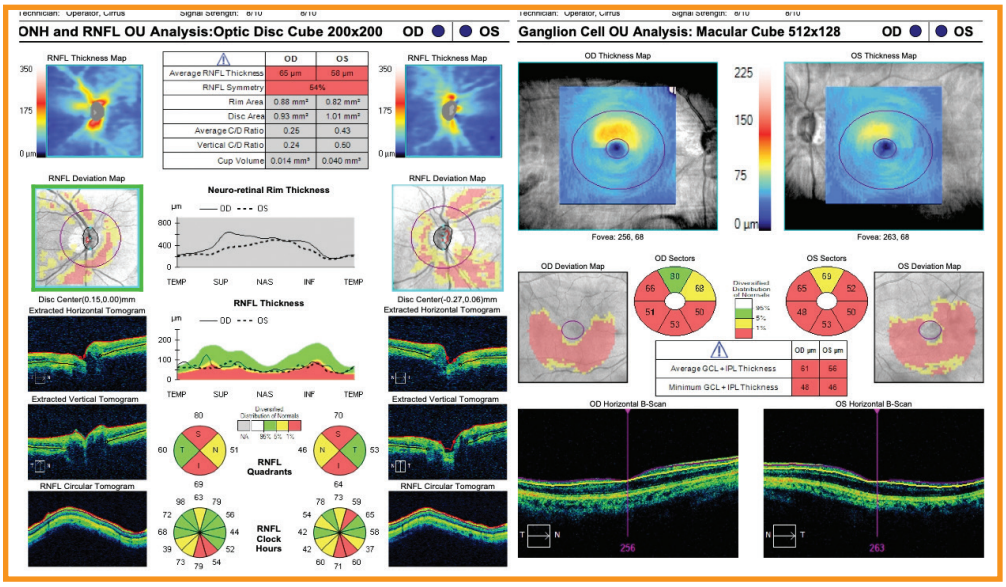

Figure 2. Case 3: Imaging.

achieve very low IOP targets because not only does netarsudil lower IOP by promoting outflow through the TM, it also lowers EVP.

CASE 3: DIFFICULTY WITH FOLLOW-UP

DR. GADDIE: Our next case is a 63-year-old male who works in the Middle East for an oil company and is only home once or twice a year. As you can imagine, it's difficult to manage this patient from afar. He first presented in June 2017 with pressures of 20 and 30 mm Hg in his right and left eye, respectively. Gonioscopy was normal. Pachymetry is slightly thinner in the right eye, and the hysteresis in his left eye was pretty low. His imaging shows very small optic nerves and a diminished nerve fiber layer (Figure 2). There's some interesting ganglion cell geography there as well. His visual field shows some defects, but they don't look classically glaucomatous (Figure 3). We started him on travoprost in August 2017 and lowered his pressures to 10 and 13 mm Hg. Six months later, his IOP increased to 14 and 16 mm Hg. He decided the eye drops weren't working for his lifestyle and asked for an SLT. The SLT lowered his IOP to 12 and 15 mm Hg. After a year of no drops post-SLT, the pressure in his left eye is starting to creep back up. We switched him to latanoprostene bunod and his pressure lowered to 15 mm Hg in that left eye, which is about a 50% reduction from baseline.

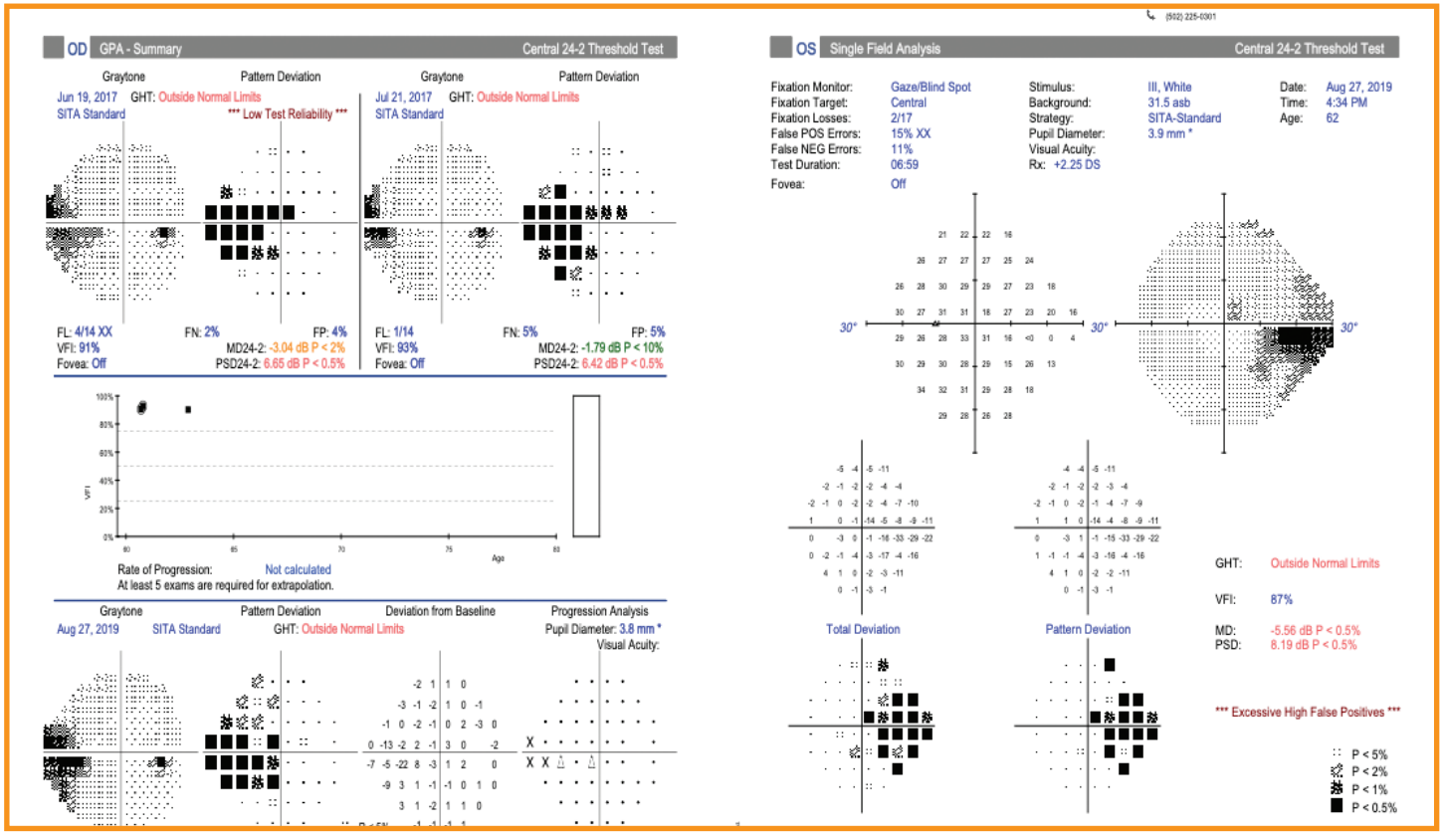

Figure 3. Case 3: Visual field imaging.

DR. SAWHNEY: Do you think there is an added benefit of adding these medications posttreatment?

DR. GADDIE: There's certainly a lot of speculation. I'd like to believe it does. Some have speculated that because SLT works in the TM, medications that work in the meshwork may not be as effective post SLT. I haven't noticed that in most of my patients.

DR. BRUBAKER: Theoretically, it should help, especially netarsudil with changes in EVP. If you're able to get through the TM and get that functioning better through the SLT, the EVP affect should help reduce pressure further.

CASE 4: PROGRESSING VISUAL FIELDS

DR. SAWHNEY: Our final case is a man with severe low-tension glaucoma, given his advanced optic nerve cupping and severe visual field loss. His starting pressure was 17 mm Hg. He was referred to be because of progressive visual field loss. The patient was starting to develop some periorbital fat atrophy with topical prostaglandins. Also, he had a history of heart failure, which may have been contributing to some further optic nerve damage. The patient was prescribed brimonidine in the past, which resulted in a follicular reaction. We wanted a pressure of around 10 mm Hg or less. We stopped the prostaglandin and switched the patient to netarsudil. With just netarsudil alone, we were able to achieve an IOP of 8 mm Hg. This highlights the utility of netarsudil in that low-tension setting by working on multiple mechanisms. We were able to hold off surgery.

DR. BRUBAKER: These agents are a great option for patients with low-tension glaucoma who just need a little reduction. It saves them from surgery.

DR. SMITH: We all try to defer trabeculectomies in patients due to the adverse events, even though we know how well it lowers IOP. These agents help us get closer to target IOP levels without having to do surgery.

DR. SAWHNEY: I agree. It's a great time to be a glaucoma specialist. Thank you for your insights. ■

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TARGETING THE TRABECULAR MESHWORK: INCORPORATING NEW OUTFLOW DRUGS INTO GLAUCOMA CARE

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___ > 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
Describe the mechanisms of action of novel therapeutics and classes of drugs	_____	_____	_____
Compare the efficacy of novel therapeutics with traditional prostaglandins	_____	_____	_____
Understand and explain the likelihood of achieving target intraocular pressure with monotherapy compared with combination regimens	_____	_____	_____
Restate the most common side effects of novel therapeutics	_____	_____	_____
Identify how to provide the best possible collaborative care when comanaging patients	_____	_____	_____

POSTTEST QUESTIONS

1. Based on this activity, please rate your confidence in your ability to apply updates in medical glaucoma therapy 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. Based on this activity, please rate how often you plan to apply the latest available medical glaucoma therapy 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. Describe the mechanism of action of netarsudil.

a. Netarsudil increases uveoscleral and trabecular outflow through relaxation and increased permeability of cells in the trabecular meshwork (TM) and Schlemm canal.
b. 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 (EVP).
c. Netarsudil inhibits both rho-kinase and norepinephrine transporter pathways, which increases trabecular outflow, reduces EVP, and reduces aqueous production.
d. Netarsudil increases rho-kinase production, which remodels the extracellular matrix and increases aqueous humor outflow through the uveoscleral pathway.

4. Describe the mechanism of action of latanoprostene bunod.

a. Latanoprostene bunod is a nitric oxide-donating prostaglandin analogue (PGA) that increases aqueous humor through both the TM and the uveoscleral pathway.
b. Latanoprostene bunod is a rho-kinase inhibitor that enhances the trabecular outflow and lowers EVP.
c. Latanoprostene bunod increases aqueous humor outflow through the uveoscleral pathway.
d. Latanoprostene bunod relaxes the TM by promoting the assembly of actin stress fibers and focal adhesions.

5. Mrs. Smith is a 74-year-old female with low-tension glaucoma, hypertension, and Chronic obstructive pulmonary disease. She has tried multiple topical agents including several PGAs, brimonidine, and dorzolamide with minimal response, her intraocular pressure (IOP) remains in the mid to upper teens, her visual fields are progressing. What is the next step in her treatment?

a. Netarsudil as an adjunct treatment
b. Switch to netarsudil monotherapy
c. Selective laser trabeculoplasty (SLT)
d. Latanoprostene bunod

6. Mr. George is in his mid-50s with a baseline pressure of 40 mm Hg. You want to reduce his IOP by 40%. Which of these agents is unlikely to be used in the first-line setting?

a. Latanoprostene bunod
b. Combination aqueous suppressant
c. Netarsudil/latanoprost
d. Netarsudil

7. What is the most concerning side effect of netarsudil for young people?

a. Iris pigmentation
b. Corneal verticillata
c. Hyperemia and blurred vision
d. All of the above

8. Based on the phase 4 MOST trial data, adding netarsudil to a PGA resulted in IOP reductions of _____ mm Hg?

a. 4.2 mm Hg
b. 4.5 mm Hg
c. 5.3. mm Hg
d. 6.0 mm Hg

9. Based on phase 1/2 data, what percentage of patients with the bimatoprost sustained-release implant were able to go 2 years without rescue treatment?

a. About 25%
b. About 30%
c. About 15%
d. About 20%

10. Mr. Davis is a nonresponder to latanoprost. He has struggled with compliance to his medical glaucoma therapy, and underwent an SLT last year to reduce his IOP without medical therapy. His pressure is slowly starting to increase. What treatment option may be appropriate for him next?

a. Repeat the SLT
b. Netarsudil/latanoprost
c. Latanoprostene bunod
d. Netarsudil

11. Latanoprostene bunod works on which outflow systems?

a. Trabecular outflow
b. Uveoscleral outflow
c. Ciliary body outflow
d. Both trabecular and uveoscleral pathways are involved

12. In the JUPITER trial, a 1-year study of latanoprostene bunod, what was the percent reduction in IOP in patients with a baseline IOP of 15 to 21 mm Hg?

a. 25%
b. 10%
c. 50%
d. 33%

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this CME 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

Probability of changing practice behavior based on this activity: _____ High _____ Low _____No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

Change in pharmaceutical therapy _____

Change in nonpharmaceutical therapy _____

Change in diagnostic testing _____

Choice of treatment/management approach _____

Change in current practice for referral _____

Change in differential diagnosis _____

My practice has been reinforced _____

I do not plan to implement any new changes in practice ___

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

_____ Medical Knowledge

_____ Practice-Based Learning and Improvement

_____ Interpersonal and Communication Skills

_____ Professionalism

_____ System-Based Practice

Additional comments:

_____

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

This information will help evaluate this CME 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.

_____