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CASE PRESENTATIONS IN MEDICAL GLAUCOMA:

A REVIEW OF THERAPEUTIC ADVANCES

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Case Presentations in Medical Glaucoma:

A Review of Therapeutic Advances

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CONTENT SOURCE

This continuing medical education (CME)/continuing education (CE) activity captures content from a roundtable discussion that occurred on October 17, 2018.

ACTIVITY DESCRIPTION

Glaucoma is a leading cause of preventable blindness in the United States, and at least 3 million Americans have a form of this chronic disease. Somewhat asymptomatic, patients may lose more than 40% of their optic nerve fibers before noticing a loss of peripheral vision and seeking medical intervention. Given the rapid increase in the aging American population, as well as increases in groups at high risk for glaucoma (most of which have an age component), the burden of disease related to this condition becomes more significant each year.

TARGET AUDIENCE

This certified CME/CE activity is designed for optometrists managing glaucoma patients, glaucoma specialists, and general ophthalmologists involved in the management of glaucomatous disorders.

LEARNING OBJECTIVES

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

- **Discuss** the chemical structure and mechanism of action of topical glaucoma medications and evolving neuroprotective medications.
- **Explain** the anti-fibrotic activity in novel drug classes.
- **Evaluate** novel therapeutics and classes of drugs and their potential for enhanced patient compliance.

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

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

3. **ACCORDING TO COLLABORATIVE NORMAL-TENSION GLAUCOMA STUDY DATA, WHAT PERCENTAGE PRESSURE REDUCTION REDUCES PROGRESSION IN PATIENTS WITH NORMAL-TENSION GLAUCOMA?**
   a. 25%
   b. 30%
   c. 35%
   d. 40%

4. **IN PATIENTS WITH OCULAR SURFACE DISEASE ISSUES, TREATMENT OPTIONS MAY INCLUDE:**
   a. Laser trabeculoplasty
   b. Non-benzalkonium chloride preserved medications
   c. Preservative-free medications
   d. Medications requiring reduced frequency of dosing
   e. All of the above

5. **WHICH OF THE FOLLOWING DRUGS IS LEAST LIKELY TO ADVERSELY AFFECT OCULAR PERFUSION PRESSURE IN EYES WITH NORMAL-TENSION GLAUCOMA?**
   a. Netarsudil
   b. Timolol
   c. Dorzolamide/timolol
   d. Brimonidine/timolol

6. **A PATIENT WITH OCULAR SURFACE DISEASE AND LOW-PRESSURE GLAUCOMA WHO STRUGGLES WITH ADHERENCE TO MEDICAL THERAPY MAY BE AN IDEAL CANDIDATE FOR _____.**
   a. Carbonic anhydrase inhibitors
   b. Beta-blockers
   c. Standalone microinvasive glaucoma surgery
   d. Selective laser trabeculoplasty

7. **WHAT DID THE MERCURY AND ROCKET STUDIES SHOW REGARDING THE ADDITIVITY OF NETARSUDIL IN PATIENTS ALREADY USING A PROSTAGLANDIN ANALOGUE?**
   a. Netarsudil can have a detrimental effect on optic nerve head perfusion.
   b. Netarsudil demonstrated a consistent level of IOP lowering across various baseline IOPs.
   c. Netarsudil was less effective in eyes with pigmented trabecular meshwork.
   d. None of the above.

8. **WHICH GLAUCOMA MEDICATION REDUCES EPISCLERAL VENOUS PRESSURE?**
   a. Latanoprostene bunod
   b. Netarsudil
   c. Latanoprost
   d. Timolol

9. **WHICH OF THE FOLLOWING STATEMENTS IS TRUE?**
   a. Study data have shown corneal verticillata does not impact IOP measurement.
   b. Study data have shown corneal verticillata impacts IOP measurement.
   c. Study data have shown corneal verticillata is a common occurrence with all topical glaucoma medications.
   d. Study data have shown corneal verticillata is a rare occurrence in patients on prostaglandins.

10. **ADVANCING THERAPY SHOULD BE DETERMINED BY WHETHER _____ IS PROGRESSING OR STABLE.**
    a. Open-angle glaucoma
    b. Angle-closure glaucoma
    c. Steroid-induced glaucoma
    d. All of the above

11. **MRS. JONES PRESENTS WITH PSEUDOEXFOLIATION GLAUCOMA AND HAS PREVIOUSLY PROGRESSED WITH PRESSURES IN THE LOW 20S. MRS. JONES IS INTOLERANT OF MEDICATIONS AND HAS UNDERGONE GLAUCOMA SURGERY WHEN HER PRESSURE WAS HIGHER THAN 20 MM HG. WHAT MAY BE CONSIDERED AN APPROPRIATE COURSE OF TREATMENT IF SHE IS ABOVE TARGET PRESSURES?**
    a. Netarsudil
    b. Latanoprost
    c. Latanoprostene bunod
    d. All of the above
    e. None of the above

12. **_____ PLAYS A ROLE IN REGULATING IOP BY INCREASING AQUEOUS HUMOR OUTFLOW THROUGH THE CONVENTIONAL PATHWAY.**
    a. Netarsudil
    b. Latanoprost
    c. Latanoprostene bunod
    d. All of the above
    e. None of the above

Case Presentations in Medical Glaucoma:

A Review of Therapeutic Advances

Patients with glaucoma may lose more than 40% of their optic nerve fibers before noticing a loss of peripheral vision and seeking medical intervention.[1] Increased IOP is caused by chronic cellular contraction and increased extracellular matrix deposition within the trabecular meshwork (TM) of the conventional outflow pathway, resulting in reduced aqueous humor outflow, higher pressure, optic nerve damage, and, ultimately, vision loss.[2-4]

In today's real-world clinical settings, topical medical therapy is the first-line choice for the majority of physicians and patients. However, these treatment options are not perfect and must be adjusted to each patient's needs. Patients often require multiple medications to achieve adequate IOP control. Further, many patients continue to lose visual field despite IOP control at target pressures.[5]

Until recently, there were no commercially available treatments that relax the TM and lower episcleral venous pressure with minimal daily dosing. While commercially available medications either enhance uveoscleral outflow through the ciliary muscle or suppress the formation of aqueous humor, a novel class of drugs (Rho kinase, or ROCK, inhibitors) function by relaxing the TM, which may lead to improved aqueous outflow.[6,7] This, in turn, would lower IOP. Multiple studies have shown that for every 1 mm Hg drop in IOP, the risk of disease progression lowers by 10%.[8-11]

Neuroprotection in the field of glaucoma is defined as any treatment, independent of IOP reduction, which prevents retinal ganglion cell death.[12] Glutamate antagonists, ginkgo biloba extract, neurotrophic factors, antioxidants, calcium channel blockers, brimonidine, glaucoma medications with blood regulatory effect, and nitric oxide synthase inhibitors are among compounds with possible neuroprotective activity; however, results of clinical trials for these agents specific to neuroprotection have not been conclusive.[12-14]

The ROCK pathway is involved in various cellular functions through phosphorylation of their specific substrates.[15] The activation of the ROCK pathway results in TM contraction, and the inhibition of this pathway would lead to relaxation of TM with subsequent increase in outflow facility and, thereby, decrease IOP.[6,7] A review of the role of the ROCK pathway in the pathogenesis and treatment of glaucoma noted that both in vitro and in vivo studies have shown ROCK inhibitors are expressed in the cells of the outflow pathway, and that ROCK was expressed more abundantly in the TM than in the ciliary muscle.[15] Although Goldhagen et al found RhoA, ROCK1, and ROCK2 all distributed in the human aqueous outflow pathway, they could not find any significant expression difference of ROCK between normal and glaucomatous eyes,[16] which Wang et al believe may be explained because medications used to manage glaucoma may affect the expression of ROCK within the outflow pathway.[15] Furthermore, the ROCK pathway is involved in optic nerve neuroprotection. In the optic nerve head, RhoA expression is increased significantly in human glaucoma eyes when compared to human normal subjects.[15,16] In their review, Wang et al cited both in vivo and in vitro studies that suggest ROCK inhibitors may increase ocular blood flow, and noted "there is increasing evidence suggesting the protective effects of RhoA/ROCK-inhibition on adult retinas."[15] In vivo and in vitro studies have shown inactivation of ROCK increases retinal ganglion cell axon regeneration, indicating neuroprotection.[17,18] This class of drugs also is being investigated in combination with prostaglandins in an attempt to provide greater pressure reduction.[19] The first ROCK inhibitor, netarsudil, was approved in 2017.

Another novel entity, latanoprostene bunod, also was approved in 2017. This compound metabolized into two moieties: the first, latanoprost acid, is a prostaglandin F2a analogue, while the second, butanediol mononitrate, releases nitric oxide (NO).[20-23] NO is an endogenous signaling molecule generated by a family of enzymes called the NO synthases.[21] There is evidence to suggest that NO plays a role in regulating IOP by increasing aqueous humor outflow through the conventional pathway.[21,24] The exact method of action and how NO regulates IOP is unknown.[24]

The following roundtable convenes thought leaders in glaucoma to discuss the management of real-world complicated cases when first-line treatment fails.

CASE 1: NORMAL-TENSION GLAUCOMA

TONY REALINI, MD, MPH: Our first case is of a healthy 77-year-old man who is retired and hikes daily. He has no major systemic health issues or high blood pressure, and he is not on blood pressure medication. He was recently diagnosed with normal-tension glaucoma (NTG). He is phakic with excellent VA (20/25). His IOP was 16 mm Hg at diagnosis and fluctuated between 14 mm Hg and 17 mm Hg pretreatment. His visual fields and OCT showed inferior retinal nerve fiber layer (RNFL) loss with superior visual field loss in the left eye, while the right eye was less affected (Figure 1).

On the basis of his IOPs, visual fields, and optic nerve findings, I made the diagnosis of NTG. I initiated treatment with generic latanoprost, which reduced his pressure from 16 mm Hg to 14 mm Hg. While his IOP did not change significantly at the first on-treatment assessment, my practice is to recheck IOP at least once more before declaring treatment failure. This is due to spontaneous IOP variability in the range of 4 mm Hg to 5 mm Hg within a typical day,[25] which can mask or mimic a true therapeutic effect. I want to avoid inadvertently declaring someone a prostaglandin nonresponder and depriving them of a highly effective and safe drug that can be dosed once daily at a low cost in generic form.

What should his target pressure be? My approach to NTG reflects the findings of the Collaborative Normal-Tension Glaucoma Study (CNTGS), which demonstrated a substantial reduction in the risk of progression with a 30% reduction in IOP.[26] Do you treat NTG on the basis of the CNTGS recommendations? Do you aim for a 30% pressure reduction in these patients?

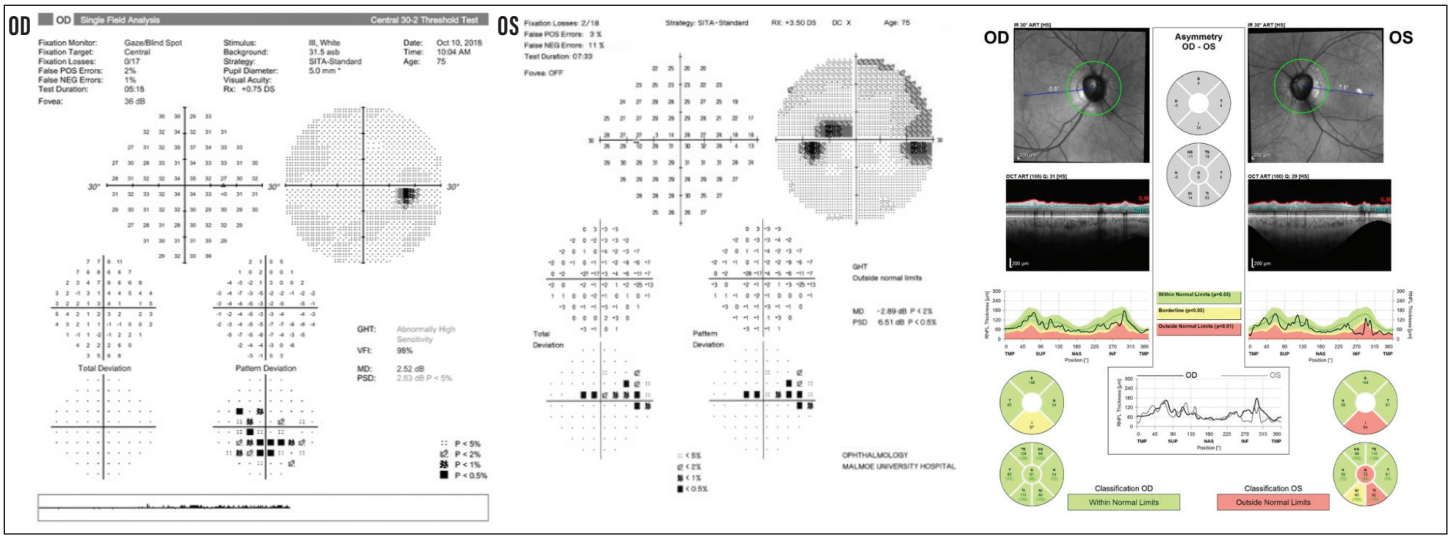

Figure 1. Visual fields and OCT in a 77-year-old man with NTG.

RUTH D. WILLIAMS, MD: One of the challenges with NTG is that we often do not have multiple baseline IOPs to guide our pressure targets. It is possible that the IOPs fluctuate in this patient, but there is no way to know. Therefore, I strive for a 30% reduction from the documented baseline IOP.

JONATHAN S. MYERS, MD: A 30% pressure reduction is a great goal. However, it is often difficult medically, even with a laser treatment, to achieve that. CNTGS included patients at high risk for progression in terms of history of progression, paracentral defects, and disc hemorrhages.[26] For patients who are not at a high risk of progression, I will allow for a 20% pressure reduction. That is my bottom line—trying to balance tolerability of therapy versus disease risk.

DR. REALINI: If you dissect the CNTGS study, patients were enrolled if they had a qualifying field, nerve findings, and normal pressures.[26] Only those with a sight-threatening visual field defect were randomized at the time of study entry. The rest were observed without treatment until progression was observed. Overall, 85 of 230 eyes (37%) remained stable on no treatment after study entry and were never randomized. Of those who were randomized to the observation arm, 65% never progressed after randomization. Overall, the vast majority of untreated subjects did not progress with up to 7 years of follow-up.

A key lesson from the CNTGS is that progression of NTG is an uncommon event. On this basis, I often take a conservative approach. In patients without a sight-threatening field defect, I often offer the option of close observation rather than initial treatment. What are the panel's thoughts on this approach?

ALBERT S. KHOURI, MD: I agree, NTG is a diagnosis of exclusion. It can be asymmetric, like it is in your patient here, and advancing therapy is determined by whether the disease is progressing or stable. The right eye in this patient has a preserved RNFL distribution, and the visual field looks intact. If this patient is progressing at a slow rate, a watch-and-wait approach will not negatively impact their quality of life. The CNTGS gave us guidelines, but it is often challenging to achieve a 30% pressure reduction from a baseline in the teens without significant side effects or without incisional surgery in many patients.

DR. MYERS: I agree that a low-risk patient without progression can be monitored closely, although in my practice progressive field loss in NTG is frequent. We all see patients with tilted, myopic, or anomalous nerves that can be difficult to distinguish from NTG. In this case, I would urge this patient to be treated because paracentral defects in the left eye are concerning.

DR. REALINI: Would you treat both eyes?

DR. MYERS: That would be a discussion with the patient, depending on their preferences. I would probably treat both eyes because where one eye goes the other tends to follow.

DR. WILLIAMS: I would treat the left eye and possibly both eyes depending on patient preferences. Another important point is how to monitor this patient whether or not treatment is initiated. I favor the 10-2 Humphrey visual field to monitor a paracentral scotoma because it gives more detailed information about the defect.

DR. REALINI: Would you also follow the 24-2 visual field?

DR. WILLIAMS: Yes. My patients with a paracentral scotoma do both, but not on the same day. NTG patients tend to be open to doing multiple visual fields and generally do not mind them as much as other patients.

DR. KHOURI: I typically follow patients with paracentral scotomas with a 10-2 visual field. I also stress that to my residents. The spatial separation of the tested points on a 24-2 field can often miss smaller scotomas closer to fixation. In this patient, the left eye findings are troubling. The right eye may display abnormalities on the 10-2 as well.

A ganglion cell thickness map of the posterior pole may also help guide our treatment for the right eye particularly if loss is detected.

DR. REALINI: The patient I have presented today did have a fixation-threatening field defect in the left eye, so I did recommend treatment. Although the total deviation plot in his right eye remains full (Figure 1), I treated both eyes because this is typically a bilateral, although often asymmetric, disease. We achieved a modest reduction in IOP with prostaglandin analogue (PGA) monotherapy, which left us 3 mm Hg short of his target IOP. What is your next treatment approach?

DR. KHOURI: Beta-blockers would not be my first choice for an adjunctive agent in this patient for multiple reasons. We have to consider beta-blocker side effect profile, particularly lower heart rate,[27] blood pressure, and exercise intolerance,[28] along with the concern of nocturnal hypotension[9] and the possible effects on optic nerve head perfusion.[30] Currently, we have better adjunctive agents than beta-blockers for many patients with NTG.

DR. REALINI: The reality is beta-blockers do not add well to PGAs.[31,32] Another issue with beta-blockers is their potential effects on hemodynamics. Beta-blockers and adrenergic agonists were excluded from the CNTGS because of their potential detrimental effects on optic nerve head perfusion.

We could add a carbonic anhydrase inhibitor, which most likely works best with a PGA out of all our options.[33-35] We could also add netarsudil, switch to latanoprostene bunod, or we could go straight to a fixed combination. There is also selective laser trabeculoplasty (SLT), which is effective in eyes with low baseline IOP.[36-38] Reducing his IOP by 3 mm Hg will be difficult because we are approaching the limit of episcleral venous pressure.

DR. MYERS: It is interesting that SLT is not more fully embraced by the ophthalmic community or by our patients. SLT is often a great choice for patients with low- or high-tension glaucoma. If the patient does not choose SLT, what do we think about the relative merits of netarsudil versus the other choices in this case?

DR. WILLIAMS: NTG is a sweet spot for the addition of netarsudil to a PGA. As we know from the ROCKET studies,[39-41] netarsudil worked effectively at multiple IOP levels. Based on my experience over the last 6 months in treating NTG, netarsudil is a great choice for lowering pressures that are already fairly low.

DR. KHOURI: The MERCURY and ROCKET analyses examined the additivity of netarsudil in patients who were already on a PGA.[42] It demonstrated a consistent level of IOP lowering across various baseline IOPs over the follow-up period. Safety data in ROCKET 4 were also consistent with previous phase 3 data on netarsudil, and the most common adverse event was hyperemia, which was reported in 48% of patients. Netarsudil is a once-daily medication, which is a big advantage.

DR. REALINI: The MERCURY studies, which evaluated fixed-combination netarsudil/latanoprost, support that approach.[42,43] I also like the fact that netarsudil may have some ability to lower episcleral venous pressure.[44] It potentially has three different mechanisms of action, which is why I selected it for this patient. Over the next few visits, his target pressure was achieved and maintained.

CASE 2: PSEUDOEXFOLIATION AND SLT

DR. REALINI: Our next case is a 68-year-old woman with moderate pseudoexfoliation in her right eye. Her IOP was 29 mm Hg before treatment. I set her target pressure to 18 mm Hg, which is approximately a 35% reduction. Currently, her pressure is 22 mm Hg on a generic PGA and the generic fixed-combination dorzolamide hydrochloride/timolol.

This eye has undergone SLT twice. The first SLT lasted 1.5 years and worked well. The second SLT lowered her pressure dramatically for about 3 months, but she was back to baseline by month 6. We have tried generic brimonidine, but within about 4 months she developed the classic blepharoconjunctivitis, which limits its use in many patients. She does have early cataracts, but she is still 20/20, which is relevant because she is starting to move beyond the spectrum of medications and laser. It is attractive to think about microinvasive glaucoma surgery (MIGS), but our hands are tied here—we are limited to those MIGS procedures that are approved for standalone use.[45,46]

Her OCT and visual fields demonstrate that she has fairly early disease, with both superior and inferior RNFL loss and an inferior field defect in the right eye (Figure 2). Her left eye is unaffected so far. How do we treat this patient?

DR. MYERS: She now has run the gamut of traditionally available therapy, short of surgery, both with the laser trabeculoplasty and the combination. She is on a PGA—a single monotherapy in addition to the combination. We could keep her with two bottles and switch her to latanoprostene bunod. Her pressure is 22 mm Hg, and we are aiming for 18 mm Hg. Based on the literature, is a pressure of 18 mm Hg a realistic expectation for latanoprostene bunod in this patient?

DR. REALINI: The VOYAGER study compared latanoprostene bunod to latanoprost and showed a 28-day advantage for latanoprostene bunod of about a 1.23 mm Hg on average.[47] In general, half of the patients will achieve less than that, and half will achieve more. It is not unreasonable to try it and hope that she is in the half who will respond better than average.

DR. KHOURI: Clinical trial data do not always translate into daily practice. We know from our clinical experience over the past several months, not just clinical trial data, that netarsudil efficacy can be superior to timolol in many patients. I have seen that in patients that I now call "hyperresponders" to netasurdil. In this particular case we are discussing, given that the next step will be surgery, I do not think it is unreasonable to prescribe latanoprostene bunod and reevaluate for the response.

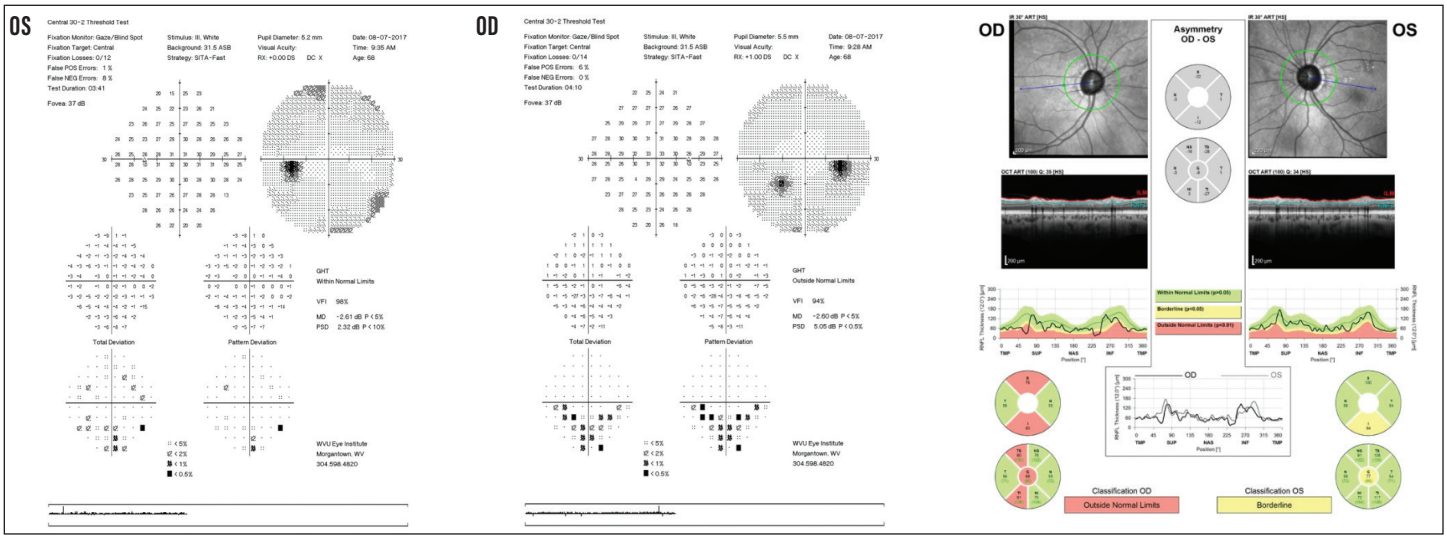

Figure 2. Visual fields and OCT in a 68-year-old woman with moderate pseudoexfoliation glaucoma.

DR. WILLIAMS: We are still learning how netarsudil and latanoprostene bunod perform in patients who have had SLT or who are on several medications, and we do not have data for these real-life situations. It behooves us to try these medications on these patients before sending them to surgery.

DR. REALINI: Another treatment option for this patient is standalone MIGS. We could do either incisional goniotomy with a Trabectome (NeoMedix) or excisional goniotomy with a Kahook Dual Blade (New World Medical). We could also put in a XEN Gel Stent (Allergan). If we did not want to progress to surgery in this patient, is it reasonable to watch and wait to see if her pressure increases? She started with a pressure of 29 mm Hg and now has a pressure of 22 mm Hg. Her visual field does not have a central fixation-threatening defect.

DR. WILLIAMS: Her pressure is likely to increase over time. It would not be terribly unreasonable to watch and wait, but you will likely need to intervene at some point because she has pseudoexfoliation.

DR. KHOURI: I agree. Exfoliation patients tend to have a more aggressive disease course often with fluctuating and spiking IOPs that can lead to damage in shorter periods of time. When exfoliation patients start to progress, they tend to progress faster than primary open-angle glaucoma (POAG) patients. I would be extra cautious with exfoliation patients, and I would be more likely to intervene at an IOP in the lower 20s like in this patient.

DR. REALINI: I believe that pseudoexfoliation is primarily a TM problem. I wanted to add something that was going to work at the site of the problem. I was concerned that latanoprostene bunod might not lower her pressure enough given that she is already on a PGA, so I added netarsudil. Netarsudil has several mechanisms of action, and it could potentially be additive to any regimen. Her pressure came down to 19 mm Hg, but her target pressure was 18 mm Hg. At this point, I acknowledged to myself and to the patient that my target IOP was simply an educated guestimate, and the risk of achieving the additional 1 mm Hg was unlikely to be worthwhile. We accepted the IOP of 19 mm Hg, and I did not operate. She developed some mild corneal verticillata that were not clinically significant. She is doing fine so far.

DR. MYERS: Who has seen corneal verticillata in patients on netarsudil?

DR. WILLIAMS: I have seen quite a few cases, and the verticillata are typically mild, though they were dramatic in one patient. I have never had a patient report visual effects from verticillata, and they have not limited my view.

DR. REALINI: Do you include it in your description of safety issues when you prescribe the drug? I do not because I am convinced that it is not clinically relevant. I do not want to have to have a long conversation with a patient about something that very likely does not matter.

DR. WILLIAMS: I do tell patients it is there when I see it because I am documenting it in their chart, because I generally inform patients when I put a new finding in the medical record. I explain that it is a common and predictable change in their cornea, and it is not causing a problem. That usually ends the conversation.

DR. REALINI: Corneal verticillata do not impact IOP measurement,[48] and they are highly unlikely to affect precataract surgery biometry or intraoperative visibility, based on experience with verticillata of other causes, such as amiodarone therapy.

DR. KHOURI: In my experience, the occurrence of corneal verticillata has been much lower than what was noted in ROCKET 4.[49] I have to qualify that statement by saying that we have been using netasurdil for several months only and our observations may change with longer follow-up.

DR. REALINI: Dr. Khouri, you have published some data suggesting that a failed SLT is not necessarily predictive of a failed next SLT.[50,51] Assuming we try netarsudil and latanoprostene bunod and we do not get her pressure down, would you consider lasering her one more time?

DR. KHOURI: Yes, a repeat SLT can be very effective. The second SLT can lead to better IOP reductions than the first treatment in some patients. One should not hesitate to repeat an SLT even when the first treatment effect does not meet efficacy goals. However, when we looked at third repeat SLT data, third SLTs tended not to be effective. The IOP reductions were mild and short lived. Although in some patients with pigmented TM (like pigmentary and exfoliation patients) SLT can be more effective when repeated more than once. One could attempt it, but the likelihood that it would work will be small.

CASE 3: PSEUDOEXFOLIATION GLAUCOMA

DR. MYERS: Our next patient is an 81-year-old man with pseudoexfoliative glaucoma. Thirteen years ago, I performed a laser trabeculoplasty on this patient. Subsequently, he had a combination phacoemulsification/trabeculectomy and a tube shunt in the left eye. He has been intolerant of a few medications over the years, but he tolerates branded latanoprost. His vision is good, but he has some cupping. His pressure is 20 mm Hg with latanoprostene bunod, which we switched to because his IOP started to increase. He has moderate nasal loss in both eyes. His OCT shows definite damage inferiorly, but it is not severe, although there is relative thinning superiorly (Figure 3).

Are we content with a pressure of 20 mm Hg in this patient, given that he is 81-years-old and healthy overall? Should we wait for field loss before advancing therapy?

DR. KHOURI: Exfoliation glaucoma is a relentless disease that can progress at a fast pace, which is what happened here. The left eye seems to be the worse eye. Since the patient has progressed in the past at a pressure in the low 20s, I would intervene to lower pressure further and reduce the risks of progression.

I would prescribe netarsudil because of its alternate mechanisms of action. If one site of pathology is believed to be the TM in exfoliation eyes, then netarsudil could be a reasonable choice. Of course, we have no data or guidance from clinical trials on netarsudil effect (or any other medication for that matter) in eyes with a tube shunt, but I am inclined to use it as a therapeutic trial anyway.

DR. MYERS: The Early Manifest Glaucoma Trial illustrated that pseudoexfoliation is a risk factor for progression.[8,52,53] This patient is intolerant of medications, and we have performed surgery when his pressure was higher than 20 mm Hg. I substituted netarsudil and was pleasantly surprised to see that the pressure was lower after several visits, with a consistent pressure of 17 mm Hg. Of course, it is unclear exactly what his pressure would have been if he had also continued latanoprostene bunod or latanoprost with the netarsudil, but he is improving on a single bottle.

DR. REALINI: My experience has shown that a pressure in the mid to high teens is adequate for most patients with pseudoexfoliation and pigmentary glaucoma. They are not like patients with NTG or POAG who progress at virtually any pressure along the spectrum.

DR. WILLIAMS: It can be challenging to determine a target pressure in complex patients. We still must follow these patients with visual fields, OCTs, and exams to determine if their disease is stable and our target pressure is appropriate.

DR. KHOURI: Considering that this patient was intolerant to many other medications, how did he fare with the side effects of netarsudil?

DR. MYERS: He has done well on it. I had warned him about conjunctival hyperemia, but his eyes are quiet.

DR. WILLIAMS: I have also had success with netarsudil on two patients who could not tolerate other medications, including preservative-free drops, though I was surprised since many patients have side effects from netarsudil.

DR. KHOURI: When you examine netarsudil clinical trial data,[44,54] you note that although the percentage of patients with hyperemia tended to be high, the majority of patients had a fluctuating level of hyperemia that was graded as mild on most visits by investigators.

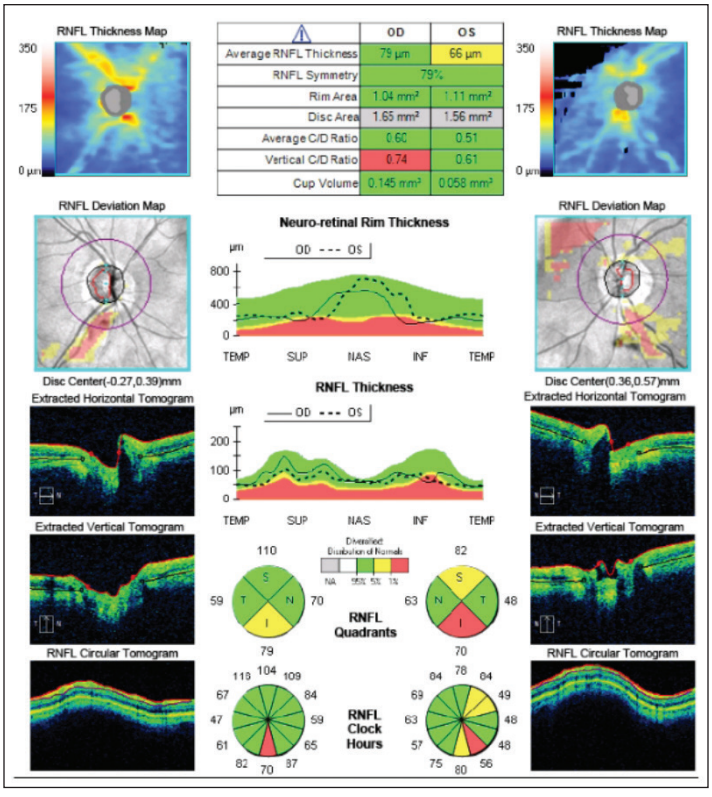

Figure 3. OCT in an 81-year-old man with pseudoexfoliative glaucoma.

This actually is in line with what we have observed in clinical practice. The hyperemia tends to wax and wane in most patients, and for the most part, is mild. That said, it is important to discuss the possible occurrence of hyperemia with patients, specifically when you start the medication, so patients will know what to expect. Once informed most patients will tend to tolerate it well. I have had very few discontinuations from hyperemia so far.

DR. WILLIAMS: Many of my patients do very well on netarsudil and do not mind the hyperemia. There is a small subset of patients who will have a fairly aggressive hyperemic effect, so we do need to prepare them. When I am putting a patient on netarsudil, I explain that red eye is common and that it may diminish with time.

DR. REALINI: I do the same. I do not tend to bring up verticillata or conjunctival hemorrhages when I am prescribing netarsudil, but I do discuss the hyperemia because patients will notice it if it occurs.

DR. MYERS: I have seen tiny petechial hemorrhages, and my patients do not tend to notice them. I have had a couple patients with more than one larger subconjunctival hemorrhage that might be drug-related. Some patients have subconjunctival hemorrhages without netarsudil, so it is hard to judge if it is related unless it is recurrent.

CASE 4: POST-REFRACTIVE SURGERY AND SYSTEMIC HYPOTENSION

DR. WILLIAMS: Our next case is a 58-year-old woman with systemic hypotension. She has previously had LASIK, and her corneas are thin. I take a meticulous blood pressure history in suspected NTG patients; her typical blood pressure is 90/60. She says she is cold all the time. She denies migraines, Raynaud's disease, or sleep apnea, but she does have Lyme disease and a thin body habitus. She takes hydroxychloroquine, which makes her a challenging patient to follow.

The IOPs are 14 mm Hg and 15 mm Hg while taking bimatoprost bilaterally once a day and dorzolamide bilaterally three times daily, down from a baseline IOP of 19 mm Hg in both eyes. The visual fields demonstrate a superior arcuate scotoma and inferior nasal defect in both eyes. The scotoma in the left eye encroaches on the central 10°. The OCT shows bimodal thinning in both eyes consistent with her visual fields.

This patient is on latanoprost and dorzolamide in both eyes, and her pressures are still 14 mm Hg and 15 mm Hg. She is intolerant to beta-blockers, which make her light headed, and this is not surprising given her low blood pressure.

What is an appropriate target for this patient? Are there are adherence issues? In this patient, probably not, but it is something I am always considering.

Finally, we know that nighttime IOPs tend to be higher and nighttime blood pressures tend to be lower, which can contribute to progression due to lower ocular perfusion pressure.[55] What is her nighttime IOP and blood pressure?

DR. MYERS: The nighttime IOP is a great question in patients with NTG. I have not seen data on that, but I have been impressed with the diurnal curve pressure I have seen with netarsudil. It is a relatively flat curve, especially considering that it is a once-daily drug. We will have to wait for overnight IOP data with netarsudil.

DR. KHOURI: When it comes to documenting a patient's blood pressure, I often communicate with their primary doctor or cardiologist about possible drug interactions especially with antihypertensive medications including beta-blockers. Although we, as ophthalmologists, are more acutely aware of the impact of systemic hypotension on some glaucoma patients, many of our colleagues in medicine are not. They may be more focused on mainly reducing blood pressure to prevent end organ damage. We must communicate well with our colleagues in other specialties about the possible deleterious effects of hypotension on ocular perfusion especially in patients with glaucoma who may be more vulnerable due to existing nerve damage.

DR. REALINI: I agree, but it is very hard to do. Where the communication breaks down for me is that we have no solid data to suggest a clinical benefit to withdrawing or changing blood pressure mediations in patients with glaucoma. We have epidemiologic studies showing clinical associations between perfusion pressure and the likelihood of developing glaucoma or the likelihood of glaucoma progression.[56-59] It is hard to get nonophthalmology clinicians to potentially compromise their management of the patient's systemic hypertension to help us achieve a theoretical benefit on our end.

DR. WILLIAMS: It is true that these conversations are difficult. When you tell a cardiologist that low blood pressure is bad for glaucoma management, they do not want to hear it. It is difficult to prove, and it is the opposite of what they have been taught. In this case, I added netarsudil once a day, which resulted in a consistent IOP of 9 mm Hg or 10 mm Hg. She is very happy.

DR. KHOURI: There seems to be a theme here with these cases; these patients are "hyperresponders" to netarsudil.

DR. MYERS: Netarsudil is the first medicine that does not show greater response at higher pressures. Instead, it shows an even response across many pressures that have been studied, which means a relatively greater effect at relatively lower pressures. I do not fully understand the reason for that or why netarsudil is different from other medicines we have used.

DR. REALINI: This may be related to its effects on episcleral venous pressure and/or the fact that it works at the TM. It may be lowering the floor established by episcleral venous pressure. If we can move that target, then we may achieve greater IOP reductions, even in people with relatively lower baseline pressures.

DR. WILLIAMS: That makes sense. Netarsudil does seem to be particularly effective in treating NTG.

DR. KHOURI: Netarsudil with its unique mechanisms of action may be a good adjunctive agent for patients on other medications who are not at their target pressures and who are hovering in the high teens or low 20s. Many of the current adjunctive agents share the same mechanism of action so they may not be as additive.

CASE 5: PRIMARY OPEN-ANGLE GLAUCOMA

DR. WILLIAMS: Our next case is a 73-year-old woman who was diagnosed with POAG in 2013. She was referred when her ophthalmologist noted recurring disc hemorrhages in her left eye. Her baseline pressures at the time of diagnosis were 27 mm Hg and 26 mm Hg. She has a family history of glaucoma, has had an SLT in her left eye, and phacoemulsification with the iStent Trabecular Micro-Bypass (Glaukos) in both eyes. She had follicular conjunctivitis in response to brinzolamide/brimonidine

Her current medications include latanoprost and dorzolamide/timolol in both eyes, and her pressures are consistently in the mid-teens. Her OCT shows deep inferior thinning in the right eye and superior and inferior thinning in the left eye (Figure 4). The OCTs are consistent with her visual fields, which show a paracentral scotoma in the left eye. Her pressures of 15 mm Hg and 16 mm Hg were a good target pressure given the baseline IOP of 27 mm Hg. I have not documented progression on her visual field, but she has a paracentral scotoma in her left eye and recurring disc hemorrhages at a pressure of 15 mm Hg. What should we do with this patient?

DR. REALINI: I am unsure what a disc hemorrhage tells me. I do not know if it is a sign of progression or a consequence thereof. Which comes first? The disc hemorrhage or the progression? My concern when I see patients like this, who have disc hemorrhages and paracentral visual field loss, is whether this is even pressure-dependent?

In CNTGS, the risk factors for progression were not IOP-related, they were vascular: migraine, disc hemorrhage, and female gender.[26] In a post-hoc analysis of the CNTGS data,[60] among those who had vasculopathic issues, including disc hemorrhage, cerebrovascular disease, or cardiovascular disease, there was little or no benefit to IOP-lowering therapy. I understand that we get nervous when we see disc hemorrhages, but I have a hard time aggressively lowering someone's pressure on the basis of a disc hemorrhage alone.

DR. MYERS: I agree, and I often do not advance therapy with disc hemorrhage. However, Weinreb et al examined a subset of the DIG study, which retrospectively studied two groups of patients who had a disc hemorrhage with progressive OCT thinning.[61]

In one group of 18 eyes, further pressure reduction was pursued, and in the other group of 18 eyes, therapy was not advanced. In the more aggressively treated group, the rate of OCT RNFL thinning was substantially reduced with intensification of treatment in the quadrant without disc hemorrhage.[61]

DR. REALINI: There is also a very real possibility of a selection bias here. We learned from the Ocular Hypertension Treatment Study that we are not very skilled at picking up disc hemorrhages.[9,62] Approximately 85% of the disc hemorrhages that were seen by the Optic Disc Reading Center were missed by the clinician. Disc hemorrhages may be happening just as frequently in our stable patients as in our nonstable patients—we may just be more robust in our optic nerve exams in those in whom we suspect progression.

DR. WILLIAMS: This patient has a paracentral scotoma in the left eye. In a patient with a paracentral scotoma and a disc hemorrhage, would you watch and wait or try to lower the pressure a bit more?

DR. REALINI: That is a very small paracentral defect. I might observe this without further treatment. There is no clinical study that suggests a benefit to further IOP reduction at this point.

DR. WILLIAMS: I added netarsudil to this patient, and her pressure dropped to 13 mm Hg and 11 mm Hg. This illustrates that netarsudil, when added to polytherapy, can sometimes lower IOP even further.

CASE 6: PARACENTRAL SCOTOMA

DR. KHOURI: This is a 68-year-old woman with 20/20 central vision. Her IOP was in the low 20s, but it now hovers in the mid- to high-teens with a PGA. Her OCT from 2017 is within normal limits. There are some borderline changes temporal to the disc, but the RNFL is well preserved overall. There seems to be some progression between the 2017 and 2018 OCT, and now the papillomacular bundle changes have become more apparent (Figure 5).

I obtained a 24-2 visual field, which showed paracentral scotoma in the left eye. I referred this patient to a neuroophthalmology colleague who investigated for other

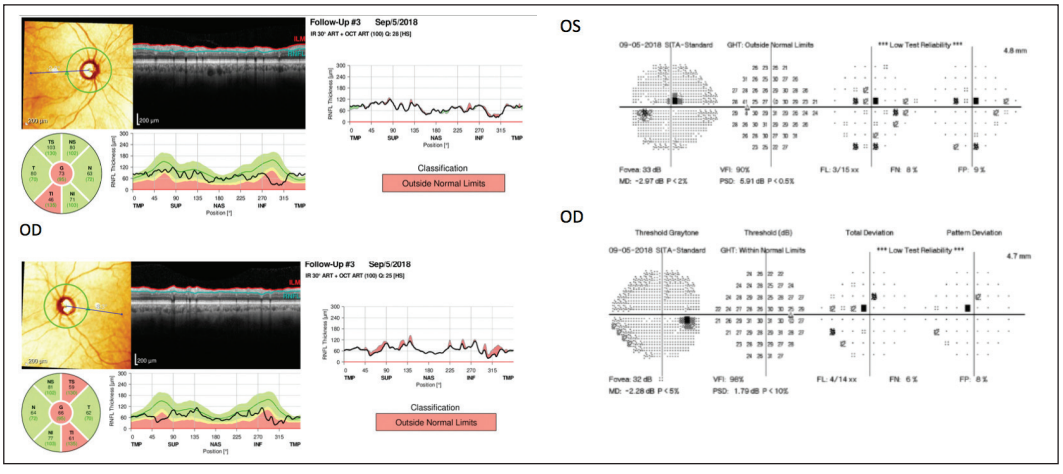

Figure 4. Visual field tests and OCT in a 58-year-old woman with NTG and systemic hypotension.

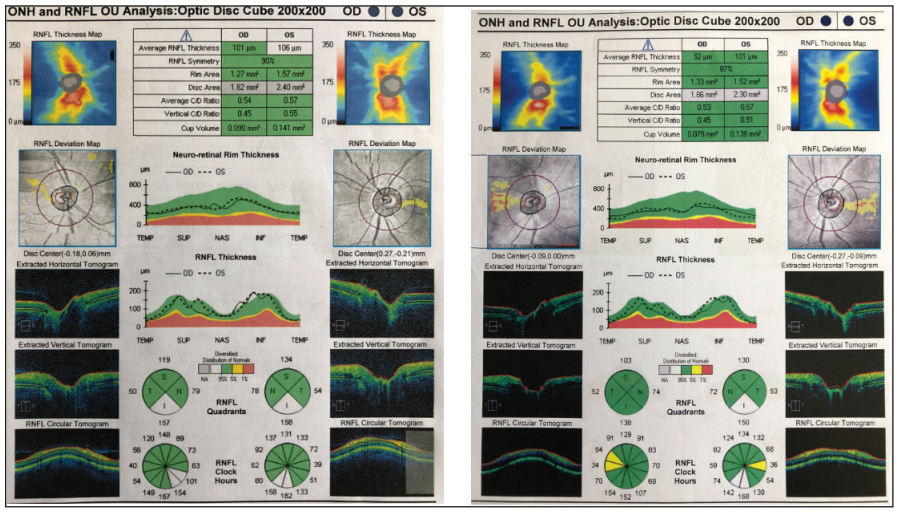

Figure 5. Structural loss with a lower IOP. From 2017 (left) to 2018 (right), the papillomacular bundle changes become more apparent.

CASE 7: OCULAR SURFACE DISEASE

DR. KHOURI: Our next case is a 59-year-old woman with ocular surface disease who was diagnosed with glaucoma a few years ago. She is a paralegal who is constantly on the computer. Her vision fluctuates, as is the case in many patients with ocular surface disease. Her baseline pressure was 27 mm Hg, and we set her target range in the mid-teens. She was started on a PGA as a first-line medication, and her pressure dropped to the low 20s. We then tried a fixed-combination dorzolamide/timolol, and she did not tolerate it well. She described a stinging sensation that made the medicine intolerable, which is not unusual in patients with ocular surface disease. Because of her busy lifestyle, she also struggled with keeping up with the PGA regimen.

Her exam shows some meibomian gland dysfunction; her tear break-up time is diminished. She has epithelial fluorescein uptake on her lower cornea. Given her significant ocular surface disease, how would you advance therapy in this patient in order to reach her target pressure?

DR. WILLIAMS: One challenge with a second agent in this patient is she is already having trouble taking the first agent.

DR. REALINI: This is the ideal patient for SLT. Starting with an IOP above 20 mm Hg, she may achieve adequate IOP control with SLT alone and will not need medications. We have relatively little data on primary SLT, but I have found that it can be incredibly effective.[66]

DR. KHOURI: Of course, SLT can be an excellent choice as a primary therapy in patients with ocular surface disease. In most patients SLT is equivalent to a single agent. Unfortunately, many patients will still require topical therapy after SLT to achieve their IOP goal. Ocular surface disease is not rare at all in glaucoma patients on topical therapy; we all have patients with significant ocular surface disease who need to be treated with topical medications. In patients with adherence issues, it is also not ideal to have to prescribe a second agent. However, if we must, I favor once-daily medications; more-frequent dosing is not realistic in patients who struggle to adhere.

DR. WILLIAMS: Latanoprost has some of the highest concentrations of benzalkonium chloride (BAK), and people tolerate it nicely.

DR. MYERS: Often it is the drug and not the BAK. Although some people clearly have issues with BAK specifically, it is often not the driving force behind some of the tolerance challenges.

KEY LEARNING POINTS

DR. WILLIAMS: Netarsudil is effective at a range of pressure levels, which makes it useful in many clinical situations. Hyperemia is a concern, but in many patients it is well tolerated.

etiologies of her neuropathy, and an MRI of the brain and orbits was obtained, which were negative.

DR. REALINI: In this case, the significant mismatch between the ganglion cell loss and the RNFL loss does not add up. How are the axons doing so well when the ganglion cells are dead or dying?

DR. MYERS: I agree. I do not usually see this much of a mismatch in patients with ganglion cell and RNFL loss at the same time.

DR. REALINI: We do not have long-term data on the clinical relevance of ganglion cell loss. It is difficult to create an action plan without evidence.

DR. KHOURI: Our knowledge about posterior pole ganglion cell loss as one of the earliest pathologic processes in glaucoma continues to evolve. It is particularly difficult to ignore posterior pole changes when they are associated with a visual field defect. That is why we perform posterior pole scans in glaucoma. For this patient, I added a second agent, brimonidine, and she was intolerant to it. I wanted to avoid a beta-blocker and then prescribed netarsudil, and she had an excellent IOP response. I prefer to give patients once-daily agents. Her IOP is now hovering in the low teens which is a better target for someone who seems to be progressing at lower IOPs.

DR. WILLIAMS: I have used netarsudil as primary therapy in two young female patients who are concerned about long-term orbitopathy from PGAs,[63] which they only know about because I tell them. I think that is a conversation we probably have not had enough with our younger patients.

DR. MYERS: I discuss iris color change[64] and eyelashes[65] but the orbitopathy can be notable as well, and it is much harder to have the conversation after issues arise.

DR. REALINI: We now have two new drugs with unique mechanisms of action that target the TM, which is the tissue that is primarily affected by POAG and is responsible for IOP elevations. We do not have a clear idea yet exactly where they fit into our treatment regimen, but it is always good to have new tools in our armamentarium. I am glad that we have these new drugs to offer to our patients.

DR. KHOURI: More than 2 decades after PGAs, we finally have new glaucoma medications with unique mechanisms of action. Netarsudil in clinical trials was not inferior to timolol, but in clinical practice many patients exhibit responses greater than what we expect from timolol.

Second, patients have struggled with adherence to adjunctive medications, but that was mostly when our adjunctive agents had twice-daily dosing. Patients' acceptance of medications is significantly improved with once-daily medications.

DR. MYERS: Patients really appreciate once-daily dosing, and I appreciate good efficacy across a broad range of pressures.

Thank you for your participation in this roundtable. ■

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CASE PRESENTATIONS IN MEDICAL GLAUCOMA: A REVIEW OF THERAPEUTIC ADVANCES

Release Date: November 2018
CME Expiration Date: November 30, 2019
COPE Expiration Date: November 18, 2021

INSTRUCTIONS FOR CME/CE CREDIT

To obtain *AMA PRA Category 1 Credit™* for this activity, you must read the activity in its entirety and complete the Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit http://evolvemeded.com/online-courses/1808-supp2/.

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If you are experiencing problems with the online test, please email us at support@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 ❑ non-MD 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 activity)
___ 0
___ 1-5
___ 6-10
___ 11-15
___ 16-20

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

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

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

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Discuss the chemical structure and mechanism of action of topical glaucoma medications and evolving neuroprotective medications.	_____	_____	_____
Explain the anti-fibrotic activity in novel drug classes.	_____	_____	_____
Evaluate novel therapeutics and classes of drugs and their potential for enhanced patient compliance.	_____	_____	_____

POSTTEST QUESTIONS

1. **PLEASE RATE YOUR CONFIDENCE IN YOUR ABILITY TO APPLY UPDATES IN GLAUCOMA MANAGEMENT IN THE CLINIC AFTER REVIEWING THIS ACTIVITY (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NOT AT ALL CONFIDENT AND 5 BEING EXTREMELY CONFIDENT).**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

2. **PLEASE RATE HOW OFTEN YOU INTEND TO APPLY ADVANCES IN GLAUCOMA MANAGEMENT IN THE CLINIC AFTER REVIEWING 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

3. **ACCORDING TO COLLABORATIVE NORMAL-TENSION GLAUCOMA STUDY DATA, WHAT PERCENTAGE PRESSURE REDUCTION REDUCES PROGRESSION IN PATIENTS WITH NORMAL-TENSION GLAUCOMA?**
   a. 25%
   b. 30%
   c. 35%
   d. 40%

4. **IN PATIENTS WITH OCULAR SURFACE DISEASE ISSUES, TREATMENT OPTIONS MAY INCLUDE:**
   a. Laser trabeculoplasty
   b. Non-benzalkonium chloride preserved medications
   c. Preservative-free medications
   d. Medications requiring reduced frequency of dosing
   e. All of the above

5. **WHICH OF THE FOLLOWING DRUGS IS LEAST LIKELY TO ADVERSELY AFFECT OCULAR PERFUSION PRESSURE IN EYES WITH NORMAL-TENSION GLAUCOMA?**
   a. Netarsudil
   b. Timolol
   c. Dorzolamide/Timolol
   d. Brimonidine/Timolol

6. **A PATIENT WITH OCULAR SURFACE DISEASE AND LOW-PRESSURE GLAUCOMA WHO STRUGGLES WITH ADHERENCE TO MEDICAL THERAPY MAY BE AN IDEAL CANDIDATE FOR _____.**
   a. Carbonic anhydrase inhibitors
   b. Beta-blockers
   c. Standalone microinvasive glaucoma surgery
   d. Selective laser trabeculoplasty

7. **WHAT DID THE MERCURY AND ROCKET STUDIES SHOW REGARDING THE ADDITIVITY OF NETARSUDIL IN PATIENTS ALREADY USING A PROSTAGLANDIN ANALOGUE?**
   a. Netarsudil can have a detrimental effect on optic nerve head perfusion.
   b. Netarsudil demonstrated a consistent level of IOP lowering across various baseline IOPs.
   c. Netarsudil was less effective in eyes with pigmented trabecular meshwork.
   d. None of the above.

8. **WHICH GLAUCOMA MEDICATION REDUCES EPISCLERAL VENOUS PRESSURE??**
   a. Latanoprostene bunod
   b. Netarsudil
   c. Latanoprost
   d. Timolol

9. **WHICH OF THE FOLLOWING STATEMENTS IS TRUE?**
   a. Study data have shown corneal verticillata does not impact IOP measurement.
   b. Study data have shown corneal verticillata impacts IOP measurement.
   c. Study data have shown corneal verticillata is a common occurrence with all topical glaucoma medications.
   d. Study data have shown corneal verticillata is a rare occurrence in patients on prostaglandins.

10. **ADVANCING THERAPY SHOULD BE DETERMINED BY WHETHER _____ IS PROGRESSING OR STABLE.**
    a. Open-angle glaucoma
    b. Angle-closure glaucoma
    c. Steroid-induced glaucoma
    d. All of the above

11. **MRS. JONES PRESENTS WITH PSEUDOEXFOLIATION GLAUCOMA AND HAS PREVIOUSLY PROGRESSED WITH PRESSURES IN THE LOW 20S. MRS. JONES IS INTOLERANT OF MEDICATIONS AND HAS UNDERGONE GLAUCOMA SURGERY WHEN HER PRESSURE WAS HIGHER THAN 20 MM HG. WHAT MAY BE CONSIDERED AN APPROPRIATE COURSE OF TREATMENT IF SHE IS ABOVE TARGET PRESSURES?**
    a. Netarsudil
    b. Latanoprost
    c. Latanoprostene bunod
    d. All of the above
    e. None of the above

12. **_____ PLAYS A ROLE IN REGULATING IOP BY INCREASING AQUEOUS HUMOR OUTFLOW THROUGH THE CONVENTIONAL PATHWAY.**
    a. Netarsudil
    b. Latanoprosts
    c. Latanoprostene bunod
    d. All of the above
    e. None of the above

ACTIVITY EVALUATION/SATISFACTION MEASURES

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

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

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

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

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

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

_____ Cost

_____ Lack of administrative support

_____ Lack of time to assess/counsel patients

_____ Reimbursement/insurance issues

_____ Patient compliance issues

_____ Other. Please specify: _____

_____ Lack of consensus or professional guidelines

_____ Lack of experience

_____ Lack of opportunity (patients)

_____ Lack of resources (equipment)

_____ No barriers

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

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

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

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

The faculty was effective. ___ Yes ___ No

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

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

Please check the Core Competencies (as defined by the 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 CME/CE activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

_____