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INDIVIDUALIZED MANAGEMENT OF PATIENTS WITH GLAUCOMA:

HOW THERAPEUTIC ADVANCES WILL IMPROVE PATIENT CARE

PART 1

Thomas Samuelson, MD, Moderator

Murray Fingeret, OD, FAAO

Douglas Rhee, MD

James C. Tsai, MD, MBA

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Individualized Management of Patients With Glaucoma:

How Therapeutic Advances Will Improve Patient Care PART 1

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FACULTY

THOMAS SAMUELSON, MD, MODERATOR
Minnesota Eye Consultants
Bloomington, Minnesota

MURRAY FINGERET, OD, FAAO
Chief of Optometry
Department of Veterans Administration
New York Harbor Health Care System
Brooklyn, New York
Clinical Professor
SUNY College of Optometry
New York, New York

DOUGLAS RHEE, MD
Case Western Reserve University
Department Chair
University Hospitals
Department of Ophthalmology
and Visual Sciences
Cleveland, Ohio

JAMES C. TSAI, MD, MBA
President
New York Eye and Ear Infirmary
of Mount Sinai
Delafield-Rodgers Professor and System Chair
Department of Ophthalmology
Icahn School of Medicine at Mount Sinai
New York, New York

CONTENT SOURCE

This continuing medical education (CME)/continuing education (CE) activity captures content from a roundtable discussion that occurred on April 23, 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 the chronic disease.[1] Somewhat asymptomatic, patients may lose more than 40% of their optic nerve fibers before noticing a loss of peripheral vision and seeking medical intervention.[2] 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 antifibrotic activity in novel drug classes
- **Evaluate** novel therapeutics and classes of drugs and their potential for enhanced patient compliance

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

2. **PLEASE RATE HOW OFTEN YOU INTEND TO APPLY ADVANCES IN GLAUCOMA MANAGEMENT IN THE CLINIC. (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NEVER AND 5 BEING ALWAYS.)**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

3. **WHAT PERCENTAGE OF PATIENTS ARE NONCOMPLIANT WITH GLAUCOMA THERAPY?**
   a. 30%
   b. 40%
   c. 50%
   d. 60%

4. **WHAT IS THE CURRENT STANDARD FIRST-LINE THERAPY FOR GLAUCOMA TREATMENT?**
   a. Laser trabeculoplasty
   b. Prostaglandins
   c. Beta-blockers
   d. Carbonic anhydrase inhibitors

5. **ACCORDING TO THE PANELISTS, WHICH PROSTAGLANDIN IS THE LEAST EXPENSIVE AND THE MOST WELL-TOLERATED?**
   a. Bimatoprost
   b. Latanoprostene bunod
   c. Latanoprost
   d. Travoprost

6. **WHAT IS THE MOST COMMON REASON PATIENTS MAY BE HESITANT TO USE ALTERNATIVE TREATMENT OPTIONS SUCH AS A SUSTAINED-DELIVERY SYSTEM?**
   a. Perceived invasiveness of the procedure
   b. Cost
   c. Risk of complications
   d. Unproven effectiveness

7. **IS NETARSUDIL A DISEASE-MODIFYING AGENT?**
   a. Yes
   b. No
   c. Evidence suggests it is not, but it's inconclusive
   d. There's not enough evidence to say either way

8. **IS LATANOPROSTENE BUNOD SUPERIOR TO TIMOLOL AND LATANOPROST?**
   a. Yes; APOLLO, LUNAR, and VOYAGER all concluded latanoprostene bunod was superior.
   b. No; real-world evidence has only shown minimal benefit
   c. The data are inconclusive, and physicians need more time to evaluate
   d. It's only superior in previously untreated eyes

9. **WHAT IS THE DEFINITION OF MAXIMUM THERAPY FOR GLAUCOMA TREATMENT?**
   a. Two bottles and laser trabeculoplasty
   b. Five medications
   c. Four medications
   d. Two bottles, three medications

10. **WHAT GLAUCOMA MEDICATIONS ARE CONSIDERED EFFECTIVE FOR OVERNIGHT USE (24-HOUR EFFICACY)? (SELECT ALL THAT APPLY.)**
    a. Latanoprost
    b. Brimonidine
    c. Timolol
    d. Bimatoprost
    e. Dorzolamide

11. **THERE ARE SUSTAINED-RELEASE DEVICES IN DEVELOPMENT THAT LAST FOR HOW LONG?**
    a. 9 to 12 months
    b. 6 to 9 months
    c. 3 to 6 months
    d. More than 1 year

12. **ALL OF THE FOLLOWING ARE NOVEL GLAUCOMA THERAPIES EXCEPT:**
    a. Netarsudil
    b. Sustained-delivery systems
    c. Punctal plugs
    d. Latanoprostene

Individualized Management of Patients With Glaucoma:

How Therapeutic Advances Will Improve Patient Care PART 1

Glaucoma is a leading cause of preventable blindness in the United States.[1] Often asymptomatic, patients may lose more than 40% of their optic nerve fibers before noticing a loss of peripheral vision and seeking medical intervention.[2] In today's real-life clinical settings, medical/topical therapy is the first-line choice for the majority of physicians. Yet these treatment options are not perfect, nor are they a "one size fits all" approach. Patients are typically on multiple medications before successfully controlling their IOP, which leads to many challenges such as compliance issues and medication cost.

The good news is there are novel agents and combination treatments in the pipeline that may be more effective than current therapies, and disease-modifying therapy may not be as far afield as we once thought. The following roundtable discusses the mechanism of action for topical glaucoma treatments and evaluates novel therapies and classes of drugs for enhanced patient compliance.

—Thomas Samuelson, MD, Moderator

FIRST-LINE GLAUCOMA TREATMENT

Q | THOMAS SAMUELSON, MD: What are your initial treatment steps for a treatment-naïve glaucoma patient? How often do you use pharmaceutical therapy, and how much do you use laser therapy as an initial treatment?

DOUGLAS RHEE, MD: I explain that the overall goal of glaucoma management is to lower their IOP. For every 1 mm Hg drop in IOP, the risk of disease progression drops by 10%.[3] I then review the different IOP-lowering options available such as topical medications, laser trabeculoplasty, and incisional surgery. Topical prostaglandin medications are currently the standard first-line treatment,[4] and my approach is no different. In my practice, we use laser as a first-line treatment in fewer than 5% of patients.

JAMES C. TSAI, MD, MBA: I agree with Dr. Rhee. I would say our initial percentage for patients undergoing laser therapy in the first-line setting is 5% to 10%.

DR. SAMUELSON: Why do you think laser hasn't taken more of a foothold as an initial therapy, despite its safety and similar efficacy to prostaglandins?

DR. TSAI: I'm not sure why first-line laser therapy hasn't taken off. The safety and efficacy of laser therapy has been widely researched.[5,6] As far back as 1995, the Glaucoma Laser Trial showed that patients who had argon laser trabeculoplasty as a first-line therapy had better long-term outcomes than patients who started on topical medications.[7] Today, selective laser trabeculoplasty lowers IOP by about 20% initially, but the efficacy is reduced after 3 to 4 years.

I think patients view laser treatment as invasive and permanent and view medications as the easier option. They may initially like the fact that there's a reversibility with medications that they don't see with the laser treatment.

That said, patients don't seem to realize how challenging it is to take daily eye drops. Poor compliance is a huge issue—studies have shown up to 60% of patients with glaucoma are noncompliant.[8-12] The reasons for this are multifold. Patients are forgetful. They don't have support at home. They don't feel sick and may not fully understand the nature and severity of their disease.

MURRAY FINGERET, OD, FAAO: A prostaglandin is my first-line agent as well. I tend to start with a generic latanoprost because of formulary considerations, and then move to other agents as needed if there are problems. To Dr. Rhee's point, I will recommend laser treatment early on if a patient has difficulty instilling his or her drops. I practice in a veteran's hospital, and many of my patients are elderly. There have been occasions where the patient can't use drops because of dexterity. We also run into people who are forgetful and don't have support at home.

DR. SAMUELSON: Does anyone differentiate between the different molecules within the prostaglandin class?

DR. RHEE: Yes, I do, but it's usually not because of the molecule itself but the other aspects. Generic latanoprost is the least expensive option and is very well-tolerated. Travoprost is alternatively preserved, and talfuprost is preservative-free. Bimatoprost is an alternative to any of the others. My experience with latanoprostene bunod is still fairly limited.

All the prostaglandin molecules are agonists to the prostaglandin FP receptor.[13-15] The FP receptor has activity in both ciliary body smooth muscle cells as well as trabecular meshwork. Activation of the FP receptor causes an alteration in the matrix metalloproteinase enzymes to tissue inhibitors of matrix metalloprostinases towards greater extracellular matrix turnover, ie decreasing extracellular matrix. The vast majority of the enhanced outflow following prostaglandin dosing is through the uveoscleral outflow system.

DR. TSAI: I go with generic latanoprost unless there is a particular reason not to. One of the challenges for those of us who treat glaucoma is keeping track of all the different copays, the different schedules, and the changes in drug pricing. I've found that it's much easier to start with a generic agent, because I just don't know what the copays will be across a varied group of patients.

NOVEL DRUG-DELIVERY SYSTEMS

Q | DR. SAMUELSON: How will sustained-delivery devices change the glaucoma treatment landscape? Will some patients or treating physicians prefer an injectable sustained-delivery option compared to topical therapy? And if so, where do you see laser fitting in—why wouldn't they choose to initiate treatment with a laser first?

DR. FINGERET: That's an interesting question. I believe that selective laser trabeculoplasty isn't used in the first-line setting because most believe that it's not as effective as a prostaglandin. We often want that extra IOP reduction in the first-line setting. Still it has an important role as a primary agent when there are concerns about adherence, which include patient factors such as difficulty in instilling medications or forgetfulness.

Knight and Lawrence[16] reviewed novel drug-delivery systems for glaucoma and found that nanoparticle-based formulations, drug-eluting contact lenses, punctum inserts, and bioadhesive matrices are all viable options that not only improve drug delivery but overcome some patient compliance issues. I'm not sure patients will take us up on the more invasive treatment options, however. A punctal plug, ring, or contact lens may be tried initially since they are reversible to some extent and less invasive. It may be difficult for a patient to consent to an eye injection as compared to an eye drop because of the perceived invasiveness of the procedure. If we can develop drug-delivery systems that are less invasive, those treatments may be more readily received. Sustained-delivery options in the future are going to present an option for patients, but I doubt they will easily displace eye drops as a first-line approach.

There are currently a host of agents in the pipeline, from contact lenses and the bimatoprost ring that sit either on the corneal surface or in the cul-de-sac that have the potential to provide therapy for several months. A punctal plug is also in development that will reside in the punctum, and also hopefully provide up to 90 days of therapy. There are some inserts in development that look like small pellets that contain medication and are injected into the anterior chamber. These may provide up to 6 months of relief. In addition, a stent containing a reservoir of medication is in development that is inserted into the trabeculum and may lower IOP for an extended period of time. The holy grail will be a drug-delivery device that is connected to an implanted IOP monitoring device so that the medication can be titrated and released based upon the patient's IOP at that point in time.

DR. RHEE: I agree that sustained-delivery options all have potential use for first-line therapy but the invasiveness makes patients nervous. It may not make us nervous, but it makes the patient nervous. Regardless, I'm excited about the different possibilities because we need more than one tool in our armamentarium.

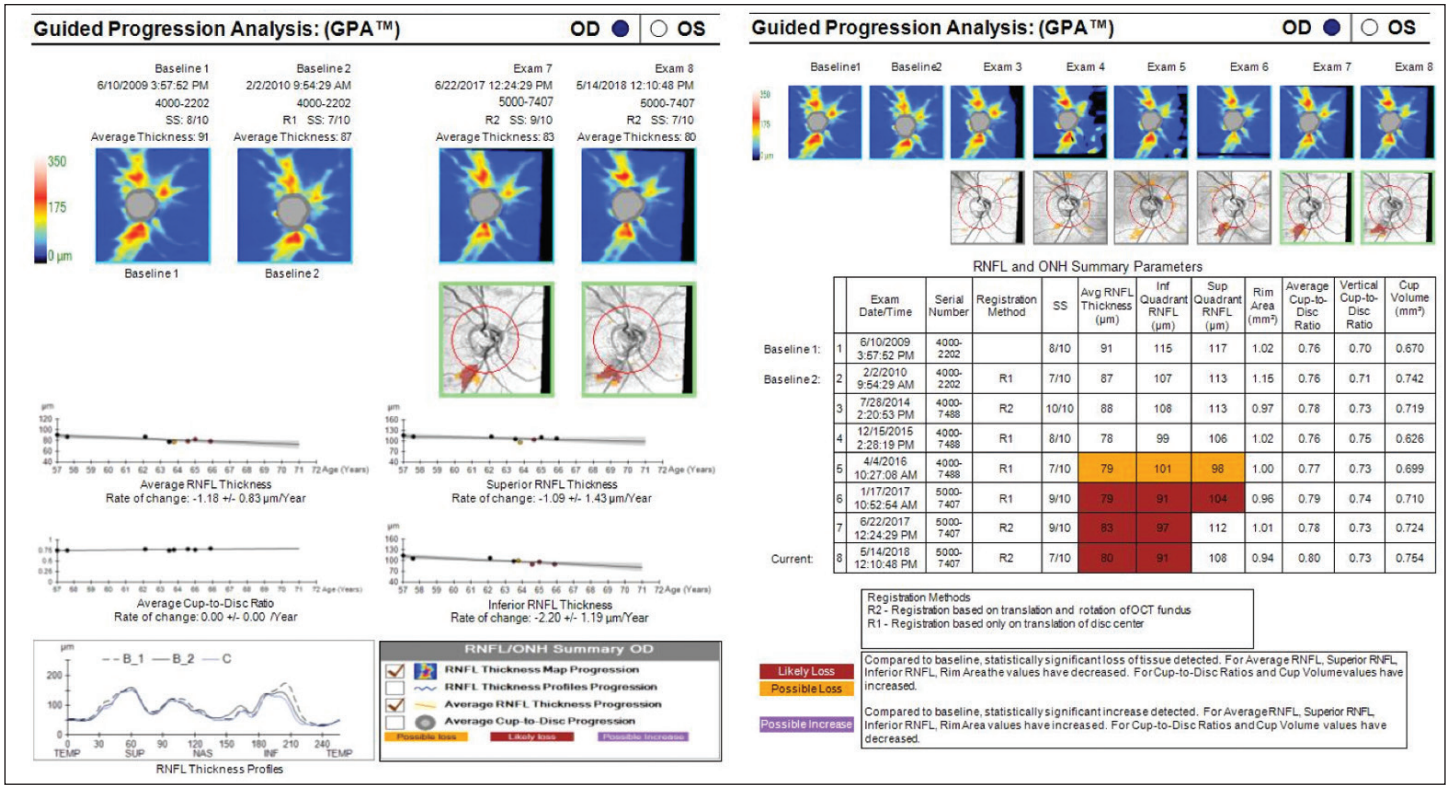
All sustained-delivery options have limitations. Contact lenses are not necessarily easy to put in. The rings come with cosmetic implications. Punctal plugs have a retention rate. Injections come with a risk of invading the wall of the eye. That said, they all have promise as tools to individualize treatment. All the different surgical tools, laser technologies, new molecules, and sustained-release devices are going to allow us to tailor the therapy to the patient sitting in front of you. We can now focus on personalized medicine and individualized therapy.

DR. SAMUELSON: How long does a sustained-delivery system have to remain effective to be considered a viable option?

DR. TSAI: It depends on the patient and the provider. There are sustained-release devices under development that last for 6 to 9 months, such as injectable implants that are placed externally in the sub-Tenon space or intraocularly in the anterior chamber. There are two in phase 3 development.[17,18] Both provide up to 6 months of IOP control from one injection. I'd say 3 to 4 months is enough, as long as it provides even distribution and has great tolerability. Sustained release will be very helpful in the future to eliminate the challenges and barriers to medication adherence.

DR. SAMUELSON: Not only is it difficult to remember to take medicines or adhere to the dosing, but some patients are in denial. Sometimes patients believe disease progression and blindness won't happen to them, so they tend not to comply early on. One of my favorite things to do is to show them their nerve fiber layer or their visual field progression to illustrate, graphically, how their disease has worsened. That seems to improve compliance.

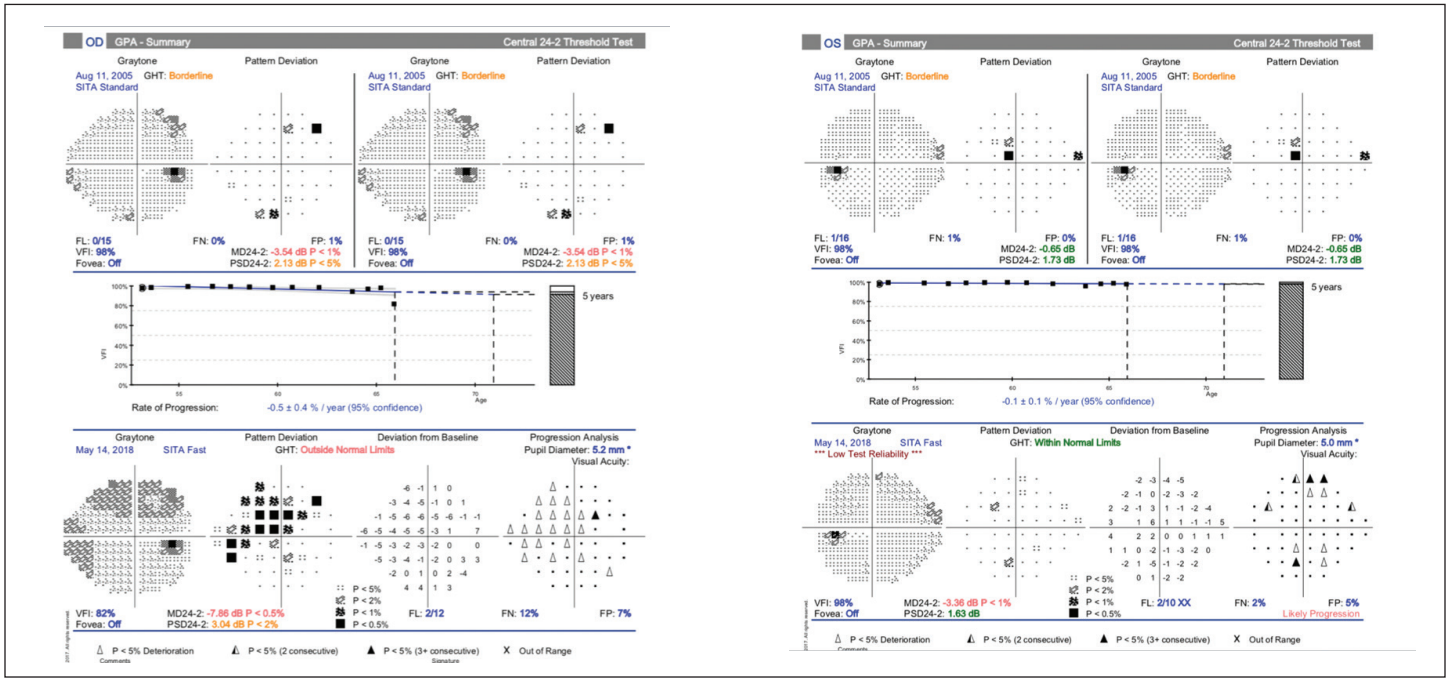
DR. FINGERET: I do a similar type of education where I'll show them their own optic nerve optical coherence tomography (OCT) or visual field to give the patient some perspective of what's happening (Figures 1 and 2). I'll then create a dosing regimen, talking in terms of their day-to-day lifestyle. I try to have them think about taking their eye drops as part of something else that they're doing that day and integrate it into their life.



		Exam Date/Time	Serial Number	Registration Method	SS	Avg RNFL Thickness (µm)	Inf Quadrant RNFL (µm)	Sup Quadrant RNFL (µm)	Rim Area (mm²)	Average Cup-to-Disc Ratio	Vertical Cup-to-Disc Ratio	Cup Volume (mm³)
Baseline 1:	1	6/10/2009 3:57:52 PM	4000-2202		8/10	91	115	117	1.02	0.76	0.70	0.670
Baseline 2:	2	2/2/2010 9:54:29 AM	4000-2202	R1	7/10	87	107	113	1.15	0.76	0.71	0.742
	3	7/28/2014 2:20:53 PM	4000-7488	R2	10/10	88	108	113	0.97	0.78	0.73	0.719
	4	12/15/2015 2:28:19 PM	4000-7488	R1	8/10	78	99	106	1.02	0.76	0.75	0.626
	5	4/4/2016 10:27:08 AM	4000-7488	R1	7/10	79	101	98	1.00	0.77	0.73	0.699
	6	1/17/2017 10:52:54 AM	5000-7407	R1	9/10	79	91	104	0.96	0.79	0.74	0.710
	7	6/22/2017 12:24:29 PM	5000-7407	R2	9/10	83	97	112	1.01	0.78	0.73	0.724
Current:	8	5/14/2018 12:10:48 PM	5000-7407	R2	7/10	80	91	108	0.94	0.80	0.73	0.754

Courtesy Murray Fingeret, OD, FAAO

Figure 1. This image is the right eye Cirrus OCT Guided Progression Analysis (GPA) of a patient with primary open-angle glaucoma. The average retinal nerve fiber layer (RNFL) thickness has decreased over time, from 2009 when it was 91 µm to the recent exam in which it is 80 µm, indicating progression. The slope of the average RNFL thickness line is going downwards with a rate of change of -1.18 µm/year. The inferior RNFL thickness rate of change is greater (-2.20 µm/year). This printout is helpful in explaining to patients the importance of using their medications and why therapy at times may need to be modified.



Courtesy Murray Fingeret, OD, FAAO

Figure 2. Seen here are the Humphrey GPA summary visual fields for the patient seen in Figure 1. The right eye has shown significant change with a superior arcuate visual field defect developing, requiring that the treatment regimen be modified. The change is also seen as the point on the Visual Field Index (VFI) trend line indicating the last exam has fallen below previous exam points. This case is illustrative of field defects showing up later in the course of glaucoma, with significant RNFL loss required.

NOVEL PHARMACEUTICAL AGENTS

Q | DR. SAMUELSON: Two new agents have recently become available: latanoprostene bunod and netarsudil. What does the literature tell us about these two new agents and their utility? Will these new agents be better than prostaglandins as a first-line treatment in the future?

DR. RHEE: I think the next generation of molecules will be disease modifying. Right now, there is no known pathophysiology in the ciliary body. There's senescence and there's aging that occurs in the cellular body. Prostaglandins work by increasing the outflow of fluid from the eye. You can think of the prostaglandins as reversing aging or reversing senescence, but there is no pathophysiology. Therefore, we're still forced to check pressures every 3 to 4 months and wait for the patient to need an additional therapy or progression of therapy.

I think we'll start to see disease-modifying agents as our understanding of the pathophysiology of disease increases. Even if these disease-modifying agents don't have the biggest impact on IOP, interrupting the disease will be the medical treatment of the future.

Netarsudil, the first rho-kinase (ROCK) inhibitor to be available in the United States, is affecting the tissue by relaxing the trabecular meshwork, which may lead to improved aqueous outflow.[19,20] There is some evidence that indicates that trabecular meshwork cell and Schlemm canal cell stiffness are part of the pathophysiology. That's what netarsudil aims to treat. IOP reductions have ranged from 2.9 mm Hg to 6.1 mm Hg with netarsudil. Another study found that netarsudil could be combined with prostaglandins to achieve an even greater IOP-lowering effect.[21-25] Whether it's solidly a disease-modifying agent or not, I think is controversial. I'm not sure that it necessarily is able to be disease modifying.

DR. TSAI: Agents like netarsudil that enhance the trabecular meshwork outflow make sense from a pathophysiology standpoint. Gong et al suggested netarsudil creates a larger increase in effective filtration area in the episcleral veins than in the inner wall, suggesting a reduced resistance distal to the inner wall.[26] Lin et al[27] found netarsudil prevented steroid-induced elevation of proteins typically associated with fibrosis at the human trabecular meshwork.

Data for netarsudil are interesting, overall. In a double-masked, active-controlled, randomized clinical study (n=224), netarsudil 0.02% reduced mean diurnal IOP by 5.7 mm Hg and 6.2 mm Hg across all on-treatment time points. Comparatively, latanoprost reduced diurnal mean IOP between 6.1 mm Hg and 7.5 mm Hg. Netarsudil 0.02% maintained similar efficacy regardless of baseline IOP, whereas latanoprost was less effective in people who had baseline IOPs between 22 and 26 mm Hg.[28] ROCKET 2, the phase 3 registration trial for netarsudil, achieved its primary 90-day efficacy endpoint of demonstrating noninferiority of IOP lowering for daily netarsudil compared to twice-a-day timolol.[29]

We don't know what to make of all this yet because the approach is so novel. It takes time for these new agents to change minds and practice patterns.

DR. SAMUELSON: What does the nitric oxide donating moiety mean to you? And is there a patient profile that would benefit more from this type of medication than other patients? In other words, who fits the patient profile for this compound?

DR. RHEE: Nitric oxide donating has been shown to work at the endothelial cell level, which applies both to the trabecular meshwork and Schlemm canal cells. It induces a relaxation of the cell cytoskeleton, so both these new medications have that in common.

Phase 2 and phase 3 trials did show some advantage to the latanoprostene bunod over both timolol and latanoprost at certain time points, but I don't know that you can say it's superior. The phase 3 APOLLO study (n=420), for example, compared the efficacy and safety of 3 months of latanoprostene bunod with 3 months of timolol.[30] To be eligible, patients had to have an IOP of ≥ 26 mm Hg, ≥ 24 mm Hg, and ≥ 22 mm Hg for at least one time point. They also required an IOP of ≤ 36 mm Hg at all three time points in both eyes at baseline. Mean IOP in the study eye was significantly lower in the latanoprostene bunod group (range, 17.8–18.7 mm Hg) than the timolol group (range,19.1–19.8 mm Hg). The phase 3 LUNAR study (n=420) had a similar design as APOLLO where safety and efficacy of latanoprostene bunod versus timolol was compared over 3 months.[31] Mean IOP was found to be significantly lower in the latanoprostene bunod group versus the timolol group in all measured time points but one. Results from both these studies show that latanoprostene bunod reduces IOP by 7.5 to 9.1 mm Hg over 3 months of treatment.

The VOYAGER trial (n=413) was a phase 2 dose-ranging study that compared the safety and efficacy of latanoprost with four different doses of latanoprostene bunod (0.006%, n=82; 0.012%, n=85; 0.024% n=83; and 0.040%, n=81).[32] Patients were dosed once a day for 28 days. All doses resulted in significant IOP reductions from baseline at all follow-up visits, but latanoprostene bunod 0.024% was the most effective dose, achieving a greater IOP reduction than latanoprost.

I've used latanoprostene bunod on patients whose pressures were not controlled on maximally tolerated medications. I've only had a very small minority of patients who achieved a lower pressure. That said, this is the most challenging situation to put an agent in because the patient is on their fourth medication at this point; a new agent is probably not going to work. I will say that the tolerability of latanoprostene bunod was quite good. I think it has promise and will be more successful as a first-line agent.

DR. TSAI: I have had more experience with latanoprostene bunod than netarsudil. I've used latanoprostene bunod on patients who have had some success with latanoprost, but ultimately the IOP was not at the level I desired for the patient. As a clinician, if you are considering recommending surgery, you will likely try a substitution from latanoprost to latanoprostene bunod to see if there's any benefit. I have seen a couple millimeters of additional pressure reduction in some patients, but not enough to gain an overall sense

of the benefits of this substitution. I believe that it's still too early to determine the overall real-world efficacy of the medication.

DR. SAMUELSON: We speak of both drugs as being new, but they are new to different degrees. Latanoprostene bunod is a modification of an existing class of agent, whereas netarsudil is a brand-new category. Who do you recommend using these drugs on and what have the early results been so far?

DR. FINGERET: I look at latanoprostene bunod as an example of a prostaglandin somewhat more effective than latanoprost. I would use it in patients who need a little extra IOP reduction. In addition, there are some properties related to nitric oxide and enhanced blood flow that need further elucidation because they may have also positive properties for the therapy of glaucoma.

Netarsudil is a fascinating drug. I look at it as more of a second-line or adjunctive agent to a prostaglandin. Compared to other adjunctive agents, netarsudil has some theoretic advantages in that its systemic side effect profile is excellent. There are some side effects that we are learning about, however, such as small conjunctival hemorrhages found at the limbus, corneal verticillata, and hyperemia. It is also a once-a-day drug as compared to other second-line agents, which are taken up to three times a day. Having a once-a-day agent that can be taken a couple of minutes apart from a prostaglandin may help improve compliance.

DR. SAMUELSON: Some people say netarsudil has a trimodal mechanism of action. How novel is this?

DR. TSAI: I think it is quite novel. Netarsudil lowers IOP by inhibiting both ROCK and the norepinephrine transporter (NET). The ROCK inhibitor enhances trabecular outflow and reduces episcleral venous pressure, while NET inhibitors decreases aqueous production.[20,23-25] The primary effect on the trabecular meshwork, enhancing outflow, is quite exciting. The other medication that has a trabecular meshwork effect is pilocarpine, and we all know it comes with significant challenges and side effects such as nausea, sweating, and diarrhea.[33]

I think there are instances where we may select netarsudil if we believe that it will be more effective than opening up the uveoscleral pathway, as prostaglandins do. It is great that netarsudil has proposed triple action, but I am looking for more studies that demonstrate that.

DR. SAMUELSON: If outflow enhancement is a well-accepted mechanism of ROCK inhibition, how real is the potential aqueous suppression and the lowering of episcleral venous pressure as possible adjunct mechanisms?

DR. RHEE: One of the great things about this class of medication is that the mechanism of action has been researched for at least 2 decades. In my mind there is no question about the relaxation and the effect it is having on the cell cytoskeleton of the endothelial cells. Its impact on blood flow and aqueous suppression has been less studied, and I think some secondary validation studies should be done. We need validation studies in human beings. Blood flow is a soft mechanism of action. Every commercially available medication has a paper showing a beneficial effect on either capillary dilation or velocity of flow. But how much benefit that actually provides our patients beyond IOP reduction hasn't been shown. It's great that netarsudil may have some blood flow capabilities, but I don't think we know what the positive benefit of that is for this class, or any class, of medication.

DR. SAMUELSON: Do you think netarsudil will be used as an initial therapy more than prostaglandins in the future? If not, when would you add netarsudil to an existing prostaglandin?

DR. FINGERET: I cannot see netarsudil cracking prostaglandins as a first-line agent. Prostaglandins are a once-a-day drug also with few side effects and an IOP-lowering efficacy around 30%. Although netarsudil is a once-a-day agent, the IOP-lowering efficacy is closer to 25%, which is similar to timolol. I see netarsudil as a second-line agent. The beauty is that it's a once-a-day drug, which enhances its value as a second-line therapy. One study found that netarsudil has a 24-hour efficacy, meaning it's effective during the nocturnal hours as compared to the brimonidines and timolol, which are not.[34] We are waiting for Roclatan, the fixed-combination agent containing latanoprost and netarsudil to be approved (it was recently filed with the FDA), which will be a first-line agent. This medication will contain the features of latanoprost and netarsudil and provide significant IOP reduction on a once-per-day use.

DR. TSAI: Our experience with netarsudil is still early. It took years for the prostaglandins to dethrone timolol. There's no doubt that there's great interest in it, but it's going to take some time to learn how to use it effectively. The fact that it enhances trabecular meshwork outflow rather than opening up a new outflow pathway is pretty exciting. It may be a competing first-line agent in the future, but it will come down to the cost and the overall benefit. Prostaglandins are easily embraced these days because there are so many generic options.

DR. RHEE: If we are only reliant on lowering IOP, then yes, the prostaglandins are very effective based on cost and tolerability. When I start a patient on a prostaglandin, the odds are high that they will march through medications and require advanced therapy because the disease is continuing to progress. However, if we get a true disease-modifying therapy, as netarsudil may be, the patient could be on that therapy long term because the agent will interrupt disease progression. That's when we will see cost savings and a better patient experience; the patient won't need so many medications. It will take years to fully assess this, however.

DR. SAMUELSON: We all know that when patients are recruited to a drug study, the minimum entry pressures are usually mid-20s

and higher. Those high pretreatment pressures are selected because it is easier to lower pressure on an individual with a higher pressure than it is to lower pressure on an individual with physiological pressure. How important is the clinical finding that netarsudil did better relative to latanoprost in patients with physiological pressures than it did relative to latanoprost in patients with elevated pressures? Might you select netarsudil specifically to try to lower pressures more when you're at a physiologic starting point?

DR. RHEE: Yes, I would. I would be happy to have that tool. We all have patients who are progressing with pressures in the low to mid-teens. I will use whatever tools I have to potentially avoid doing a relatively invasive surgical procedure like a trabeculectomy to lower their pressure.

DR. SAMUELSON: One fascinating concept is pressure-sensitive outflow. That is, the trabecular meshwork outflow is pressure sensitive, whereas the uveoscleral outflow is not. It seems to me that another potential advantage of netarsudil and latanoprostene bunod, is because we're augmenting pressure-sensitive outflow, it may be disease modifying because it may flatten out that diurnal. That's conjecture right now, but is there a potential benefit to that or is this purely theoretical?

DR. TSAI: I am in that camp of glaucoma specialists who believe that IOP fluctuation is important. Therefore, drugs that could potentially flatten the diurnal curve or minimize diurnal fluctuation are very helpful. Konstas et al showed that IOP range had an average fluctuation of 4.8 mm of mercury in a 24-hour period in patients who were medically controlled.[35] Then he showed that range was 2.2 mm of mercury in patients who were surgically controlled with trabeculectomy. We are clearly not doing a good job minimizing IOP fluctuation in patients who we think are adequately controlled. I'd love for investigators to explore if netarsudil blunts the fluctuation that we see in the real world.

DR. RHEE: I am in the same camp. There is evidence showing that diurnal fluctuation is important to disease control.[36-40] Nouri-Mahdavi et al found that IOP fluctuation increased the odds of visual field progression by 30% for each 5-year increment in age and 1 mm Hg increase in IOP.[38] Caprioli and Coleman found that long-term IOP fluctuation was associated with visual field progression in patients with low mean IOP but not in patients with high mean IOP.[39] Rao et al found that long-term IOP fluctuation was the most important parameter associated with increased visual field loss.[40]

The literature is mixed with some studies showing that high circadian variations of IOP as well as intervisit IOP variability correlates to greater disease progression as measured by visual field. However, some studies show no correlation. In my opinion, the preponderance of the literature supports the assertion that high circadian variations of IOP and large fluctuations of IOP in between visits correlates to progression of disease.

I will take any tool we have to flatten the curve, especially if it's additive. Aqueous suppressants on their own don't flatten the curve well. We all know timolol doesn't flatten the curve well, especially at night. Topical carbonic anhydrase inhibitors (CAIs) are better, and there's some controversy about selective alpha-2 agonists or brimonidine. It's the outflow agents that have the most potential to flatten the curve. The studies do not uniformly support brimonidine having a strong effect over diurnal IOP fluctuation.

It is great we have another mechanism to accomplish this in addition to prostaglandin analogs. There is ample opportunity to look at not just netarsudil's effect alone, but what is the best additive to flatten diurnal variation?

DR. SAMUELSON: We currently have four dominant classes of pharmacotherapeutics: prostaglandins, topical CAIs, alpha-2 agonists, and beta-blockers. With the arrival of latanoprostene bunod and netarsudil, what does maximum medical therapy look like?

DR. FINGERET: I define maximum medical therapy as the amount a person can afford and remember to take without causing undue side effects. That tends to be two bottles, three medicines. On rare occasions, I may extend that to three bottles if the patient has undergone laser or another procedure, but I don't see that as viable for compliance, affordability, or efficacy.

DR. RHEE: I completely agree that the definition of maximum therapy is whatever the patient can tolerate. Most of my patients will want me to prescribe all the different medications before we do anything they perceive to be invasive. In their minds, the advantage of medications is that it's reversible, and it is a little more difficult for patients to accept other procedures. I actually do see the potential use for five medications. I don't know how many patients will be open to taking five medications, but it doesn't mean that some patients won't want me to try.

DR. TSAI: I agree that patients want the maximum effect of medications prior to considering what they perceive as invasive surgery. However, I don't agree that we will use five agents as maximum therapy in the future because I think we'll have more combination agents available. A common complaint about the topical treatments is the toxic effects of their preservative formulation because they can lead to dry eye and other ocular surface issues. Pharmaceutical companies are attempting to address those issues by either removing/modifying preservatives or by combining agents in an attempt to improve patient compliance while also reducing the overall ocular surface exposure to preservatives. Outside the United States, there are combinations of timolol and prostaglandins dosed once daily, but these have not received US regulatory approval.[41-43]

Most recently, a fixed combination containing brimonidine 0.2% and brinzolamide 1% was approved in 2013; side effects are similar to those of the individual components while efficacy was similar to prostaglandins.[44] To date, the only preservative-free prostaglandin available in the United States is tafluprost 0.0015%, approved in 2012. The

combination dorzolamide hydrochloride 2%/timolol maleate 0.5% and timolol maleate 0.5% are also preservative free, but cost and convenience can be a limiting factor for many patients.[45]

In addition to the availability of combination agents, I think we will have sustained-release devices that will be personalized to the patient. We'll have better diagnostic tools that will allow us to know when a topical beta-blocker is contraindicated because there's a potential blood flow effect that is exacerbated by the topical beta-blocker agent. We're not currently doing that in patients. I do see a day where we will be more selective in our drug selection.

I think the intriguing part about netarsudil is it may very well be a game-changer when you have a drug that could be disease reversing or disease delaying. The really effective agents—prostaglandins, netarsudil, beta-blockers—have three very different mechanisms of action, but they all lower IOP. In the future, hopefully IOP will not be the only thing we focus on as we treat patients.

DR. RHEE: For many patients, two bottles is the maximum amount of medication they can take. Once you start combining agents or implementing sustained release, suddenly you can give classes of medications with a minimum number of bottles. That's the real wild card that has the potential to be a game-changer.

DR. SAMUELSON: When prostaglandins first came out, there was a lot of trepidation about some of the unfamiliar effects, like lash growth and iris pigmentation. Are there any similar concerns with either latanoprostene bunod or with netarsudil? Anything that the readers and clinicians should be aware of that they might have to monitor for?

DR. FINGERET: There are two things that stand out with netarsudil. One is the corneal verticillata. Although this appears to be mild, ophthalmologists are not used to seeing corneal deposits due to a topical drug. The corneal verticillata doesn't appear to impact vision and, once the medicine is stopped, it appears it goes away. The other concern is the tiny conjunctival hemorrhages at the limbus that are variable and come and go. Both of these side effects will take some getting used to. Ophthalmologists will have to learn to become comfortable with them.

DR. SAMUELSON: Will these side effects cause someone to stop the medication?

DR. FINGERET: They are not cause to discontinue therapy. The hemorrhages are variable; they will last a couple of weeks and then go away. The verticillata will be present as long as the person is on the medicine, but it doesn't continue to get worse. It reaches a certain level and then plateaus. I think it is more about the realization that these are side effects that can occur, but they should not be considered grounds to discontinue the medicine.

DR. RHEE: I agree. I would make note of the findings but not feel compelled to stop the medication unless the side effects were bothersome to the patient.

DR. TSAI: I also agree. I think that's one of the reasons why it's been easy to enroll patients on latanoprostene bunod clinical trials. That compound is very similar to latanoprost, which most of our patients are comfortable using. Latanoprostene bunod is essentially a nitric oxide moiety added to latanoprost. That said, whenever you start a patient on a new medication, you need to review the potential side effect profile so they aren't alarmed if they hear about it or experience it.

DR. SAMUELSON: All things being equal, including cost and insurance coverage, would you prescribe latanoprostene bunod over a prostaglandin? Or would you require a specific reason to step up from standard prostaglandin therapy to nitric oxide donating?

DR. TSAI: After cost considerations, you're left with two other variables: efficacy and tolerability. Efficacy, to me, is the most important factor that I look for, but I also consider tolerability. Latanoprost is very tolerable, but a preservative-free medication is even more well tolerated. That's very attractive.

DR. SAMUELSON: Tafluprost is preservative free, yet is having a hard time getting significant market share. Is that because of cost? Is that because latanoprost is relatively well tolerated even though it's got a fair amount of benzalkonium?

DR. RHEE: It's both. Many patients aren't able to afford it, and the generic is cheaper.

NOCTURNAL PRESSURE REDUCTION

Q | DR. SAMUELSON: What drugs do we currently have available that work at night?

DR. RHEE: The literature is uniform in agreement that prostaglandins and topical CAIs work at night. There's some controversy with selective alpha-2, but the preponderance of literature indicates that brimonidine works very poorly at night if at all.[46-48]

DR. SAMUELSON: When you dose some of the fixed-combination agents, do you have a strategy to try to get that second dose in but still avoid an "at bedtime" beta-blocker, for example? If a patient is on dorzolamide/timolol or brimonidine/timolol, how do you dose those?

DR. FINGERET: My concern with the brimonidine/timolol is that I'm not certain it's effective during the nocturnal hours. I am not certain you'll achieve adequate pressure reduction even if you dose twice a day, with one being at nighttime. That is why I like a topical CAIs; they have a little better nocturnal reduction. When combined with a prostaglandin, I tend to use it twice a day at nighttime. When I really need some extra pressure reduction, I'll use it three times a day.

Work has been done using a sleep lab to measure IOP over a 24-hour period. The studies, done on different eye ranges and in

healthy individuals as well as those with glaucoma, have shown that both brimonidine and timolol, while effective in reducing IOP during the waking hours, provide little if any IOP reduction during the hours when one is sleeping (nocturnal).[47,49,50]

When I use beta-blockers, I am always concerned that the IOP may not be adequately reduced during nighttime hours. Compliance is another issue with nighttime dosing; sometimes patients fall asleep and forget to take their medication. Therefore, I prefer my patients to use prostaglandins in the morning because I know they are more likely to remember the dosing.

DR. SAMUELSON: Do you dose your beta-blocker differently than the second dose of your fixed-combination beta-blocker CAI or beta-blocker alpha-2 agonist? How do you dose that second dose?

DR. RHEE: If it is a beta-blocker on its own, then I go with just morning dosing. We're just not really sure if it works at night. I actually do not dose the combination beta-blocker agents differently. I tell my patients to use all their evening drops right after dinner, because I completely agree that many patients fall asleep before they use their second dose.

DR. TSAI: I tend to use a timolol combination agent. I only dose it once a day in the morning because the biggest concern with a timolol-based agent is the morning pressure spike the patient will have if it is not working at night. But if they already have a prostaglandin on board, I am more comfortable with that. I am also concerned about some of the nocturnal perfusion effects of beta-blocker agents. We don't have to be as concerned with dosing timolol agents twice a day (when used as an adjunctive agent to prostaglandins) since I believe the prostaglandin agent dosed nightly will blunt any potential morning pressure spikes.

DR. SAMUELSON: Do we expect netarsudil to work at night?

DR. TSAI: Yes, I do. With netarsudil, the triple action of increased trabecular meshwork outflow, the decreased episcleral venous pressure, and the reduction in aqueous suggests it will work during nighttime hours.

ADVANCES IN COMBINATION THERAPIES

Q | DR. SAMUELSON: What have the data told us about combination netarsudil/latanoprost? Are they additive?

DR. TSAI: The combination would be a very valuable treatment option for patients as well as clinicians since the eye drop would have the traditional efficacy of a prostaglandin analogue combined with the trabecular meshwork outflow effects of a ROCK inhibitor.

DR. FINGERET: The combination provides at least 2 mm Hg of additional IOP reduction with side effect profiles similar as you'd expect for both medications, including conjunctival hyperemia.[19] The agents work on different aspects of the outflow system. The phase 2 trial of latanoprostene bunod illustrated about 1.25 mm Hg greater efficacy than just latanoprost.[51] Netarsudil/latanoprost provides an even greater IOP reduction, which is very exciting.

DR. SAMUELSON: And it is worth noting that it's not easy to improve on latanoprost in a fixed-combination product. The fixed-combination of latanoprost/timolol was not approved in the United States because it failed to show adequate additivity to latanoprostene alone. On the other hand, latanoprost bunod demonstrated clinically significant greater efficacy than latanoprost alone. The fixed-combination of latanoprost/netarsudil will be a nice adjunct to try to simplify some of these complex regimens that we anticipate with now five classes of medications.

How does this pharmacologic renaissance marry to the surgical renaissance we've been experiencing? I have always felt that microinvasive glaucoma surgery (MIGS) alone is not enough unless the glaucoma is very mild. For many patients, you need MIGS and medication, although patients may not need as many medications as they did pre-MIGS surgery. Considering that, what does glaucoma management look like 5 to 10 years from now?

DR. TSAI: I also believe in the MIGS/medication combination. MIGS will reduce pressure to a certain level, and you can lower it from there with medication. In order to get once-a-day dosing, the thought used to be that you'd have to add a prostaglandin to MIGS or prescribe a timolol-based agent. But netarsudil gives you a once-a-day alternative to a prostaglandin, especially in the setting of being used as an adjunctive agent to a MIGS procedure.

DR. SAMUELSON: I think we still need transscleral surgery, we still need trabeculectomy, and we're still going to see very advanced disease either from noncompliance or late diagnosis. We will still be doing some version of transscleral bleb-forming surgery, but we'll probably be doing less of it.

DR. RHEE: My experience with MIGS is that the majority of patients still require medication. As for the future of glaucoma management, it will be a tough sell to ask patients to take five bottles for maximum medication. There will be patients who do it, but many who won't be able to or won't be able to afford it. Sustained-release therapy and combination agents are very exciting. I think we will have a sustained-release delivery system within the event horizon of 5 to 7 years.

I do think there are some opportunities that we have to investigate like the efficacy of medications. Will prostaglandins be effective after a supraciliary shunt? In my anecdotal experience, they will be. Will netarsudil be additive after you've done a trabecular meshwork bypass procedure? We don't know yet, but, based on what I've seen with the other medications, I think it will be.

Those questions will need to be solved but, in the event horizon of 10 to 15 years, I'm hoping to see true disease-modifying therapy where the disease process will actually halt or slow down so dramatically that additional therapies might not be needed.

DR. SAMUELSON: You brought up some interesting points about the added advantages or the synergies of some of the newer drugs with some of the surgical procedures we have. I think you can make a theoretical case at this point that cataract surgery is favorably improving the aqueous humor dynamics. It gives me pause to do canal-based procedures that cause a lot of tissue damage now that we have drugs that can improve trabecular function.

For example, I wouldn't take a patient with very mild disease and do a gonioscopy-assisted transluminal trabeculotomy (GATT). I'm a GATT enthusiast, but I wouldn't do it for a very mild disease or maybe even mild to moderate disease. But I might place a stealth device because I'm retaining 98% of the meshwork. This is all theoretical and unproven, but the more we can improve the ultrastructure of the canal and the trabecular meshwork, the less I'm willing to damage it in a significant way with surgical interventions.

DR. RHEE: I would agree with that.

DR. SAMUELSON: Thank you, gentlemen, for lending your thoughts and insights on glaucoma management in 2018. ■

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INDIVIDUALIZED MANAGEMENT OF PATIENTS WITH GLAUCOMA: HOW THERAPEUTIC ADVANCES WILL IMPROVE PATIENT CARE, PART 1

Release Date: July 15, 2018
CME Expiration Date: July 15, 2019
COPE Expiration Date: June 13, 2021

INSTRUCTIONS FOR CME CREDIT

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

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

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

Phone (required) _____ ❑ Email (required) _____

Address _____

City _____ State _____ Zip _____

License Number _____ OE Tracker Number _____

DEMOGRAPHIC INFORMATION

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

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

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

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

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

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

Training of Fellows ___ Yes ___ No

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Discuss the chemical structure and mechanism of action of topical glaucoma medications and evolving neuroprotective medications	_____	_____	_____
Explain the antifibrotic 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 ON YOUR ABILITY TO APPLY UPDATES IN GLAUCOMA MANAGEMENT IN THE CLINIC BASED ON THIS ACTIVITY. (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NOT AT ALL CONFIDENT AND 5 BEING EXTREMELY CONFIDENT.)**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

2. **PLEASE RATE HOW OFTEN YOU INTEND TO APPLY ADVANCES IN GLAUCOMA MANAGEMENT IN THE CLINIC. (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NEVER AND 5 BEING ALWAYS.)**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

3. **WHAT PERCENTAGE OF PATIENTS ARE NONCOMPLIANT WITH GLAUCOMA THERAPY?**
   a. 30%
   b. 40%
   c. 50%
   d. 60%

4. **WHAT IS THE CURRENT STANDARD FIRST-LINE THERAPY FOR GLAUCOMA TREATMENT?**
   a. Laser trabeculoplasty
   b. Prostaglandins
   c. Beta-blockers
   d. Carbonic anhydrase inhibitors

5. **ACCORDING TO THE PANELISTS, WHICH PROSTAGLANDIN IS THE LEAST EXPENSIVE AND THE MOST WELL-TOLERATED?**
   a. Bimatoprost
   b. Latanoprostene bunod
   c. Latanoprost
   d. Travoprost

6. **WHAT IS THE MOST COMMON REASON PATIENTS MAY BE HESITANT TO USE ALTERNATIVE TREATMENT OPTIONS SUCH AS A SUSTAINED-DELIVERY SYSTEM?**
   a. Perceived invasiveness of the procedure
   b. Cost
   c. Risk of complications
   d. Unproven effectiveness

7. **IS NETARSUDIL A DISEASE-MODIFYING AGENT?**
   a. Yes
   b. No
   c. Evidence suggests it is not, but it's inconclusive
   d. There's not enough evidence to say either way

8. **IS LATANOPROSTENE BUNOD SUPERIOR TO TIMOLOL AND LATANOPROST?**
   a. Yes; APOLLO, LUNAR, and VOYAGER all concluded latanoprostene bunod was superior.
   b. No; real-world evidence has only shown minimal benefit
   c. The data are inconclusive, and physicians need more time to evaluate
   d. It's only superior in previously untreated eyes

9. **WHAT IS THE DEFINITION OF MAXIMUM THERAPY FOR GLAUCOMA TREATMENT?**
   a. Two bottles and laser trabeculoplasty
   b. Five medications
   c. Four medications
   d. Two bottles, three medications

10. **WHAT GLAUCOMA MEDICATIONS ARE CONSIDERED EFFECTIVE FOR OVERNIGHT USE (24-HOUR EFFICACY)? (SELECT ALL THAT APPLY.)**
    a. Latanoprost
    b. Brimonidine
    c. Timolol
    d. Bimatoprost
    e. Dorzolamide

11. **THERE ARE SUSTAINED-RELEASE DEVICES IN DEVELOPMENT THAT LAST FOR HOW LONG?**
    a. 9 to 12 months
    b. 6 to 9 months
    c. 3 to 6 months
    d. More than 1 year

12. **ALL OF THE FOLLOWING ARE NOVEL GLAUCOMA THERAPIES EXCEPT:**
    a. Netarsudil
    b. Sustained-delivery systems
    c. Punctal plugs
    d. Latanoprostene

ACTIVITY EVALUATION/SATISFACTION MEASURES

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

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

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

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

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

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

_____ Cost

_____ Lack of administrative support

_____ Lack of time to assess/counsel patients

_____ Reimbursement/insurance issues

_____ Patient compliance issues

_____ Other. Please specify: _____

_____ Lack of consensus or professional guidelines

_____ Lack of experience

_____ Lack of opportunity (patients)

_____ Lack of resources (equipment)

_____ No barriers

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

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

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

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

The faculty was effective. ___ Yes ___ No

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

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

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

_____ Patient Care

_____ Practice-Based Learning and Improvement

_____ Professionalism

_____ Medical Knowledge

_____ Interpersonal and Communication Skills

_____ System-Based Practice

Additional comments:

_____

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

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

_____