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Current and Emerging Glaucoma Therapy: An Update on Disease-Modifying Glaucoma Treatments

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CONTENT SOURCE

This continuing medical education (CME) and continuing education (CE) activity captures content from a roundtable discussion held in March of 2017.

TARGET AUDIENCE

This certified CME/CE activity is designed for optometrists managing glaucoma patients and 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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Current and Emerging Glaucoma Therapy: An Update on Disease-Modifying Glaucoma Treatments

Glaucoma is a leading cause of preventable blindness in the United States, with approximately 2.7 million Americans suffering from this chronic, incurable disease.[1] The prevalence of glaucoma increases with age, and, given the rapid increase in the aging American population, the number of people in the United States with glaucoma is expected to more than double by 2050 to 6.3 million.[1-3] One of the greatest challenges of diagnosing and treating glaucoma, or the "silent thief of sight," is the fact that it is largely asymptomatic. Patients may lose more than 40% of their ganglion cells before a visual field defect is seen, which makes early diagnosis more difficult.[4]

The goal of glaucoma treatment is controlling IOP in order to stave off visual field loss, which may be caused by this complex multifactorial disease. Topical prostaglandin medications are currently the first-line treatment.[5,6] Fixed-combinations are often the next agent added as they increase patient compliance and are often as potent as their individual components.[7]

Other first-line treatments are emerging that may supplement prostaglandins as the first-line standard of care. Rho-kinase inhibitors are a novel class of drugs that relax the trabecular meshwork and lead to improved aqueous outflow.[8-10] At a minimum, such agents will be formidable options for initial adjunct therapy to prostaglandin agents. Sustained-delivery systems are also emerging, and they may also help with patient compliance.

This roundtable discusses the current options and emerging therapies for the treatment of glaucoma as well as their pros and cons, appropriate patient selection, and how to improve patient compliance.

—Thomas Samuelson, MD, moderator

GLAUCOMA TREATMENT IN THE FIRST-LINE SETTING

Thomas Samuelson, MD: In newly diagnosed patients, once you have completed the examination, visual field, and ancillary testing (optical coherence tomography [OCT] and pachymetry), and determined a patients' IOP needs to be lowered, what is your usual first-line class of medication?

L. Jay Katz, MD: First-line treatment options for glaucoma are medications, laser trabeculoplasty, or surgery such as trabeculectomy or drainage devices. The risk profile for surgery is significant, however, and can lead to vision-threatening complications such as endophthalmitis, suprachoroidal hemorrhage, and hypotony maculopathy associated with blebs.[11,12] Because of these potential complications, medications and, to a lesser extent, laser therapy such as selective laser trabeculoplasty (SLT) and argon laser trabeculoplasty (ALT) are the most frequently used treatments in the first-line setting.[5,6,11]

That being said, I do discuss both options with patients. The majority of the patients opt for medications, predominately prostaglandins. It is a once-a-day drop, relatively inexpensive (although any cost can be prohibitive for some patients), and effective at lowering IOP.[13]

However, laser therapy may be the less expensive option in certain situations. A number of studies have been conducted comparing the cost of laser therapy and medications in the United States and Canada.[14,15] The Canadian study found that the 6-year cumulative cost savings from SLT over one-, two-, and three-drug therapy to treat patients 65 years or older with open-angle glaucoma was $581, $2,043, and $3,367, respectively, in Canadian dollars.[15] The US study showed similar results, with the cost of laser therapy about $2,000 less than medications or filtering surgery.[14]

Systemically, prostaglandin therapy is very safe, but there are potential ocular side effects, such as hyperemia and heterochromia, which are the biggest drawbacks.[16] Nonadherence to medical therapy is another significant drawback to prostaglandin use, which is caused by a number of factors such as patient forgetfulness, difficulty physically using the eye drops, and the cost of medications.

Jason Bacharach, MD: Like Dr. Katz, I, too, discuss laser trabeculoplasty as an initial treatment option with my patients. I agree that most patients choose medical therapy, but there are a small segment of patients who are very interested in the laser as their first-line treatment option.

A number of studies have been conducted comparing the efficacy of prostaglandin monotherapy to laser trabeculoplasty. You had the development of ALT in the late 1970s and early 1980s,[17,18] Glaucoma Laser Trial Research Group studies in the early 1990s,[19,20] and a study out of the United Kingdom by Nagar et al comparing SLT with latanoprost.[21] They have all come to the same conclusion: The efficacy of laser therapy is equivalent to monotherapy with prostaglandins for 1 year out or longer.[22,23] The most recent trial, the SLT/Med Study, gave additional gravity to using laser as a first-line option by demonstrating at least equivalent IOP reduction as prostaglandins.[23]

In this study, 69 patients (127 eyes) with open-angle glaucoma or ocular hypertension were randomized to SLT or medical therapy, with 9 to 12 months of follow-up. Mean IOP in both eyes at last follow-up was 18.2 mm Hg (6.3 mm Hg reduction) in the SLT arm and 17.7 mm Hg (7.0 mm Hg reduction) in the medical arm. There was virtually no difference in efficacy between the two groups, and, although not statically significant, more treatment steps were necessary to maintain target IOP in the medication group.

But, even with this evidence, clinical practice has not changed. The vast majority of patients still prefer to be treated with medical therapy initially. There are a lot of reasons for that: there is the lack of a long-term benefit that is perceived with laser[24-26] and a lack of repeatability in many cases.[24,26,27] But some patients do better if laser therapy is the first-line treatment.

Murray Fingeret, OD: I predominantly use prostaglandins as the first-line therapy, and I rarely refer for initial laser trabeculoplasty.

That said, one of the obvious benefits of laser treatment is it takes compliance out of the equation. No procedure is completely benign, but laser treatment is safe. I have often felt that the percentage of patients getting laser treatment first should be higher than what it is.[28,29] I think part of that is based on the way we present it to patients. Maybe we do not advocate for laser treatment enough. We have to make sure patients understand that the laser procedure will work for at least 1 year. Yes, it does not have long-term, lasting effects, but that is a year they do not have to remember to put drops in their eyes every day.

Dr. Katz: I think that one of the problems with laser treatment is that it is not the traditional method. Unfortunately in today's climate, there is an element of distrust in the medical system on the part of patients. Some patients may believe that doctors are pushing laser therapy because it benefits the physician financially. Doctors do not want to look like they are pushing something just purely for financial benefit, so they back off.

There is also the challenge of clinic time. There is a lot more discussion with the patient required with laser treatment than with medication, because it is not a traditional first-line therapy. Discussion takes time and resources, which are limited in today's clinical practice.

Then there are the anecdotal stories from patients. For example, a patient may believe that their cousin Harriet lost her vision from a laser treatment gone wrong. Well, Harriet had laser treatment for proliferative diabetic retinopathy years ago, and the patient equates that situation to his or her case. Then you have to spend time explaining how laser therapy for diabetic retinopathy and laser therapy for glaucoma are different.

I think there are a lot of roadblocks and barriers to implementing laser therapy in the first-line setting. But if you get beyond that, there are many positives: there is no compliance problem like with daily drops; it is cost-effective; and the side-effect profile is good.

The drugs we have in our armamentarium are great, but they are not for everyone. We have patients who are forgetful, cannot physically put drops in their eyes, have horrible dry eye, or certain health beliefs. They do not want to take eye drops. Those patients are perfect candidates for first-line laser therapy. Despite that, in my experience, only 10% of patients opt for laser therapy first.

PROSTAGLANDINS: PATIENT SELECTION

Dr. Samuelson: The majority of patients are choosing medications, and the consensus among the three of you is that prostaglandins are preferred. Are there situations where you would not use a prostaglandin?

Dr. Fingeret: Yes, there are. I would not use prostaglandins in patients who have had previously unsuccessful intraocular surgery or a history of inflammatory eye disease. The good news is there are not too many people who fall into those categories.

Dr. Bacharach: I would classify patients unfit for prostaglandins in two groups: patients with cosmetic concerns and patients with medical issues. Cosmetic concerns include patients who need monocular therapy and are concerned about heterochromia, patients who do not want excessive lash growth, or patients who are concerned about periorbital pigmentation. Medical issues include patients who had a ruptured capsule from cataract surgery, a chronic inflammatory situation that may predispose them to cystoid macular edema (CME), or recurring herpetic keratitis.

Dr. Samuelson: Does anyone hesitate to treat unilaterally with prostaglandins if the patient only needs treatment in one eye?

Dr. Katz: There are some pretty serious cosmetic issues to consider with unilateral treatment. For example, if a patient has a mixed-colored iridis, there can be a pretty dramatic difference in iris coloration. If a patient has green or light brown eyes, and you tell them their iris color change is irreversible, a lot of patients really do not want to use prostaglandin drops. I think that is the number one reason a patient does not choose to go on prostaglandins.

Some of the angriest patients I have seen are people who were prescribed prostaglandins without being told about the iris coloration changes. You would think it is just a cosmetic thing, but some people are irate that they were not told about it.

Another hot topic right now is periorbital fat atrophy, which causes enophthalmos, especially if you are using prostaglandin drops unilaterally. This was first reported by Peplinski and Albiani Smith in 2004, and then again by Filippopoulos et al in 2008.[30,31] A number of other studies since have reported similar affects as well.[32-35] Enophthalmos can cause a striking asymmetry between the eyes with long-term prostaglandin use. You can get some significant cosmetic changes with long-term use, so you have to be careful and make sure you are communicating that possibility to the patient.

For me, the number one reason that patients stop using prostaglandins is hyperemia. Especially with monocular use, patients can be very unhappy if one eye is extremely red.

Dr. Bacharach: Do you stop prostaglandins around the time of cataract surgery?

Dr. Samuelson: I used to stop prostaglandins postoperatively, but I have recently continued with them as my preferred class because of their high efficacy and favorable, once-daily dosing. In general, most uveitis specialists do not believe that prostaglandins cause inflammation denovo. However, many believe prostaglandins can exacerbate existing CME.[36] I might recommend stopping prostaglandins if CME is present or if a patient is prone to it. But I have not experienced issues with continuing prostaglandin treatment after cataract surgery.

Dr. Bacharach: If you are going to perform a microinvasive glaucoma surgery (MIGS) on a patient on multiple drops, which drop do you stop or reduce after the patient has seen benefit from MIGS?

Dr. Samuelson: I like prostaglandin analogs because of their once-a-day dosing, their mechanism of action, and their efficacy. I tend to stop medications that I think are contributing to patient's ocular surface disease. Brimonidine is frequently implicated as a

highly antigenic molecule, so I discontinue the brimonidine-containing compound if a patient has low-grade follicular conjunctivitis. But I frequently turn to the patient and ask them which drug they would like to stop first following surgery.

Dr. Katz: I used to be concerned about CME with prostaglandins postoperatively but, nowadays, this is not a big risk. Patients have good outcomes from routine cataract surgery, very little iris manipulation, and intact capsules. That said, even if MIGS is relatively atraumatic, beta-blockers, brimonidine, and topical carbonic anhydrase inhibitors are, for me, preferred in the immediate postoperative period over prostaglandins.

If I am going to discontinue a drug, it will be the prostaglandin, because I believe those other drugs are more effective in blunting the potential pressure spikes that you might have after cataract surgery. I would not say it is wrong to use a prostaglandin. I think it is a matter of preference.

BRANDED VERSUS GENERIC MEDICATIONS

Dr. Samuelson: Quite often, due to formulary limitations, it is not in our hands which medicine we prescribe. Do you differentiate between the four prostaglandins readily available for routine prescribing?

Dr. Fingeret: At my institution, we have a formulary that dictates the first-line agents we prescribe. We use a generic first, and if we find that is not effective, then we move on from there. The generic selected varies and depends on the company with the contract.

Dr. Katz: For me, in terms of potency, bimatoprost is the most powerful prostaglandin that we have for lowering pressure. Latanoprost is probably the best tolerated overall. For patients with surface disease, travoprost offers some benefit there. Tafluprost is preservative-free and therefore well-tolerated, but it is probably the least potent of the prostaglandins and the most costly for our patients. However, sometimes a patient with surface disease cannot tolerate any other prostaglandin, and they do very well with tafluprost.

Dr. Bacharach: I prefer branded products over generics whenever possible. There are a multitude of studies that have questioned the efficacy and the drug concentration of generics. Kahook et al published a study in *Current Eye Research* that examined the effect of temperature on the concentration of active ingredients and preservatives in brand name versus generic glaucoma medications such as dorzolamide and timolol, or latanoprost.[37]

The study found that exposure to temperatures of 25°C and 50°C for 30 days significantly reduced the concentration of active ingredients in the generic formulations. Two generic formulations of latanoprost lost more than 10% of their mean active ingredient concentration at 50°C. Latanoprost was actually demonstrated to be outside the FDA-mandated range for a generic.[37]

A 2007 study published in the *Indian Journal of Ophthalmology* found significant differences in efficacy between branded Xalatan (latanoprost; Pfizer) and latanoprost. Xalatan reduced IOP by about 37%, while generic latanoprost reduced IOP by only about 25%.[38]

For these reasons, as well as some clinical differences that I have noted in my practice, I prefer to use a branded product whenever possible.

FIXED-COMBINATIONS IN THE SECOND-LINE SETTING

Dr. Samuelson: What are your strategies for second-line therapy if a patient's IOP increases on prostaglandins a few years after initially establishing efficacy? Do you think the IOP increase is caused by tachyphylaxis or is it disease progression?

Dr. Katz: I would be concerned about compliance and disease progression more than tachyphylaxis. First, I would make sure the patient was taking his or her medication. If the patient is not, then I would see how I could help with that issue.

For example, maybe it is a financial problem. Is the patient on a branded medication, and, if so, is there a generic that is less expensive that would work better for him or her financially? Is the patient forgetful and maybe does not fully understand the severity of his or her disease? Does the patient have a physical issue that hinders him or her from using the drops? In those cases, I will loop in a family member to see how he or she can help with compliance.

If it is not a compliance issue, but the patient is on a generic, I may try a branded product and intraclass switch just to keep things simple if the pressure goal is not too far off. If the pressure target is significantly off, say 6 mm or more, I may add a drop to their regimen or go to a fixed-combination.

Dr. Samuelson: Does anyone prefer to go to a fixed-combination as their second choice?

Dr. Fingeret: I started using fixed-combinations such as dorzolamide and timolol (Cosopt; Merck) or brimonidine and timolol (Combigan; Allergan) some years ago. Another fixed combination agent is brinzolamide and brimondine (Simbrinza; Alcon). I think they work well. It is a simpler regimen, which may help with patient compliance. It may ultimately be cheaper for patients, too, since they only purchase one bottle and may have one copay. However, there is always the issue of side effects, which may include allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging.[39,40]

Dr. Samuelson: Are there specific fixed-combinations you like to use?

Dr. Bacharach: There are situations where I will use different add-on therapies. I will use preservative-free dorzolamide/timolol in eyes that have tolerability or ocular surface issues. Brimonidine/timolol has excellent efficacy and good formulary penetrance. It is a cost-effective alternative, and I tend to use that as my go-to drug.

Dr. Samuelson: The dorzolamide/brimonidine combination has one advantage in that each constituent is dosed appropriately. Some physicians believe that giving the combination dorzolamide/timolol or brimonidine/timolol gives a little more beta-blocker than patients actually need. What are your preferences for those combinations?

Dr. Katz: Brimonidine/timolol is probably the most potent out there in terms of fixed-combinations, but dorzolamide/timolol may be more cost effective.[41] If there is an issue with cost, then dorzolamide/timolol is perfectly reasonable to prescribe.

Brinzolamide/brimonidine is great for patients who are not candidates for timolol. The big drawback to timolol/brimonidine and dorzolamide/timolol fixed-combinations is you are dosing the patient twice with timolol. There are certain populations where you may worry about that, like in patients with normal tension glaucoma, in particular.

Dr. Bacharach: I would choose brimonidine/brinzolamide for patients with low perfusion pressure, low tension glaucoma, bradycardia, or pulse rate issues. Feldman et al published a paper in the *American Journal of Ophthalmology* in 2016 that showed that brimonidine/brinzolamide had an excellent additive effect to a prostaglandin.[42] The brimonidine/brinzolamide additive resulted in lower mean diurnal IOP after 6 weeks of treatment compared to travoprost monotherapy.

Dr. Samuelson: Does the concept of nocturnal pressure reduction change your strategy?

Dr. Fingeret: That is an excellent point. Brimonidine and timolol do not appear to work during the nocturnal hours, but brinzolamide, in particular, does.

Dr. Samuelson: What is your maximum medical therapy? Does anyone use oral agents or pilocarpine other than to stabilize an emergency?

Dr. Katz: By and large, oral agents are regulated to a small percentage of patients. But there are always exceptions. Pilocarpine may work well in patients with pseudophakia, for example.

STRATEGIES FOR MAXIMIZING PATIENT COMPLIANCE

Dr. Samuelson: What are the top factors that affect patient compliance, and what strategies do you have to improve compliance within your practice?

Dr. Fingeret: The most obvious factor is drug cost. Being in Veteran Affairs, cost is minimized compared to most places. Many compliance issues have to do with patient forgetfulness and remembering to include medications into their daily schedule. Patients do not quite understand their condition or the importance of using the medication. And then they forget to renew their prescription. Continuous education on what the disease is, what it does, and why they need the medication is critical.

Dr. Bacharach: Patients struggle to remember the number of doses they need daily, especially the mid-day dose. I tell my patients to move their dosing earlier in the day. For example, traditionally patients use prostaglandins before bed. But patients will complain that they fall asleep before the drop goes in. So what I will do is have patients take their prostaglandin with their beta-blocker monotherapy in the morning, as long as they wait 5 minutes in between dosing. I might forego a little bit of efficacy by dosing the prostaglandin in the morning, but I feel like this strategy improves compliance.

Dr. Fingeret: I try to have my patients take their medications at a time that they can relate to, like when they eat breakfast, brush their teeth, or eat dinner. It is very important to attach a time to dosing because, otherwise, patients will forget.

It is also very important to ask the patient open-ended questions in the clinic. One study out of the Wilmer Eye Institute videotaped physician-patient encounters and analyzed the recordings using validated sociolinguistic approaches. The conversations were universally physician centered; physicians spoke 70% of the words and asked closed-ended questions that restricted the patient's contribution to "yes/no" or brief responses.[43] Physicians who spent most of the appointment talking rather than listening and asking the patient questions were less effective at detecting noncompliance.[43]

Dr. Katz: It is hard for us to understand why a patient would not take his or her medication, but many of our patients are elderly. It is an uphill battle to explain to them the concept of glaucoma, and that they will have to take a medication that will not seem efficacious to them. It will not make them see better or feel any better, but it is going to cost them money and may have some side effects. These are big hurdles. Success takes constant reinforcement and a fair amount of education. Ask your patients what they believe the drops will do for them. You will learn a fair amount from their answer such as their understanding of their condition and their health beliefs. It is also helpful to include family members in the education so they understand what is going on with their spouse or parent and can help them with compliance.

You also have to show patients how to put in their drops or have a family member help them. Many people, especially the elderly, really struggle with physically getting the drop in their eye. This may be manageable for once-a-day or twice-a-day dosing, but not for three times a day. It is just not going to happen. I always try to give the patient and their family extra material or a list of trusted websites to read.

Many patients will also have gaps where they are not using their medications because they have run out, and insurance will not cover a refill. For these patients, where cost is a real issue, they are not going to renew their prescription until insurance kicks in. So, I am always asking patients if they have enough medication just to make sure because sometimes they are embarrassed to talk about it. I agree that you want to ask open-ended questions to tease out some more information from the patient rather than a simple "yes" or "no."

Dr. Samuelson: What percentage of patients do you think are missing their assigned doses?

Dr. Katz: My estimate is that about half of patients are missing their drops regularly.

Dr. Fingeret: I would say 50% is about right. It is a huge number of patients not taking their drops.

Dr. Bacharach: A number of studies have been done on patient compliance. Glaucoma Adherence and Persistency Studies (GAPS) found that 90% of patients self-reported taking their mediations as prescribed, but in reality, the rate was 60% to 65% according to claims data.[44-46] I agree that the number could be as low as 50%. It is also worth noting that GAPS also showed that doctors are no better than chance at identifying which patients were not fully compliant or adherent to their dosing regimen.

ALTERNATIVE DRUG-DELIVERY METHODS

Dr. Samuelson: The landmark Ocular Hypertension Treatment Study found that 40% of glaucoma patients required at least two medications to lower their IOP by 20%.[47] Given all the issues with patient compliance that we have discussed today, do you think the alternative-delivery methods coming down the pipeline could be game changers in glaucoma treatment?

Dr. Bacharach: There are a number of alternative drug-delivery methods being explored. Knight et al reviewed novel drug delivery systems for glaucoma and found studies suggesting nanoparticle-based formulations, drug-eluting contact lenses, punctum inserts, and bioadhesive matrices were all viable options that improved drug delivery and could overcome some patient compliance issues.[48] I am very excited about these technologies. I think they are a novel way to deliver medication. The various delivery devices have the opportunity to deliver different medications, so they are not necessarily locked to delivering a single pharmacologic agent. We will learn more about that as time goes on.

Dr. Katz: I think sustained-delivery systems have the potential to be revolutionary. If you can deliver a drug consistently, take compliance out of it, reduce the amount of medication exposure, and eliminate preservatives, then that is huge.

There has been a lot of interest in using contact lenses as a drug-delivery device because of patient and physician familiarity with contact lenses in clinical practice.[49] A 2009 study evaluating the efficacy of using contact lenses to deliver timolol found that the drug-delivery method was effective at lowering IOP.[50]

Degradable and nondegradable polymers are also being studied for injectable systems.[51] Nondegradable polymers such as poly(ethylene-co-vinyl acetate) exhibit long-term, consistent delivery rates without severe retinal toxicity, but one drawback is a constant foreign presence in the eye, which made lead to an immune response.[52] Degradable polymer systems are an appealing alternative and are well-suited for an in-office subconjunctival injection. These systems have been studied to deliver antibiotics after cataract surgery,[53] for example, but they have yet to have a great deal of success with glaucoma medications.

Ten years from now we may not be using eye drops. We may be using a combination of sustained delivery by alternate paths and also an evolution toward different types of very safe surgery.

Dr. Samuelson: I am going to challenge you on that a little bit, because earlier you felt you needed to gain the patient's trust in order to perform a procedure like the laser as an initial treatment. If you suggested to a new patient with glaucoma that you would like to inject a medication into his or her anterior chamber through the front of the eye, why would the patient be any more willing to do that than a laser trabeculoplasty?

Dr. Katz: That is a great question. From my perspective as a physician, injectables are exciting. I think it could be an easier sell for patients doing external delivery first. I think it will be a step-wise approach. External delivery will be much more readily adopted, in general, in the beginning. Our retina colleagues have been using anti-vascular endothelial growth factor injectables for a long time now. When you talk about how long injectables last, patients are accepting. But I do think the external devices will be an easier accepted option for the reasons you mentioned.

Dr. Samuelson: If you had a sustained-release device readily available to offer patients, what would patients choose: topical therapy, daily administration, or a sustained option?

Dr. Fingeret: I think external delivery will be the first choice. If you can implant it in the clinic and the patient does not have to come in for 6 months, and it is efficacious, that is a home run in my mind. I will believe it when I see it. I think injecting into a patient's eye for an asymptomatic condition could be a tough sell.

NEW MOLECULES

Dr. Samuelson: There are at least two new molecules coming down the pipe in 2017: modified latanoprost in the form of latanoprostene bunod, and a whole new class of agents called the Rho-kinase inhibitors. To what degree do you expect that patients will be stepped up from a standard prostaglandin to nitric oxide-donating prostaglandin, as opposed to adding a second drug?

Dr. Katz: Latanoprostene bunod is a dual mechanism, dual pathway molecule, consisting of latanoprost acid, which is known to enhance uveoscleral outflow by upregulating matrix metalloproteinase expression and remodeling of the ciliary muscle's extracellular matrix, linked to an nitric oxide-donating moiety. This enhances trabecular meshwork/Schlemm canal outflow by inducing cytoskeletal relaxation via the soluble guanylyl cyclase-cyclic guanosine monophosphate (sGC-cGMP) signaling pathway.[54]

Its safety and efficacy has been evaluated in a number of trials including the phase 3 APOLLO,[55] LUNAR,[56] and JUPITER trials.[57] Both APOLLO and LUNAR trials found that latanoprostene bunod 0.024% was more effective at lowering IOP than timolol 0.5% in glaucoma patients at various points in time over 3 months. JUPITER found that latanoprostene bunod 0.024% was safe and well tolerated when used for up to a year and provided significant and sustained IOP reduction.[57]

Dr. Bacharach: Both the APOLLO and the LUNAR studies demonstrated that latanoprostene bunod was a very well-tolerated agent. In fact, the hyperemia rates were very similar to what was found with latanoprost, and latanoprostene bunod did provide additional efficacy over latanoprost.

Dr. Katz: My takeaway is that latanoprostene bunod is a good choice if you are looking to reduce IOP an additional few millimeters beyond what latanoprost provides. For example, it is appropriate for patients with a pressure of 20 mm Hg on latanoprost but aiming for a target pressure of 18 mm Hg. However, if you are looking for a large pressure drop beyond a prostaglandin, then latanoprostene bunod may not be the most successful choice.

Dr. Samuelson: What is your experience with the Rho-kinase inhibitors?

Dr. Katz: Rho-kinase inhibitors are a brand new class of drugs. We have not had a new drug class for glaucoma in 20-some years. It is always exciting to get something that is new and has a different mechanism of action.

Glanatec 0.4% (ripasudil hydrochloride hydrate; Kowa Company) was approved in Japan in 2014 as a twice-daily treatment for glaucoma and ocular hypertension.[58] In the United States, Rhopressa 0.02% (netarsudil; Aerie Pharmaceuticals) is awaiting approval.

In a double-masked, active-controlled, randomized clinical study, netarsudil (Rhopressa; formerly known as AR-13324) 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.[59]

ROCKET 2, a phase 3 registration trial for netarsudil, achieved its primary 90-day efficacy endpoint of demonstrating noninferiority of IOP lowering for netarsudil once-daily compared to twice-daily timolol.[60] A separate phase 3 study had earlier shown netarsudil to be noninferior to timolol in lowering IOP, its primary efficacy outcome.[61] Results of the ROCKET 4 pivotal phase 3 trial found noninferiority to timolol for patients with baseline IOPs ranging from 20 mm Hg to below 25 mm Hg. Netarsudil demonstrated similar noninferiority in prespecified secondary endpoint ranges of above 20 mm Hg to below 27 mm Hg and at a range of above 20 mm Hg to below 28 mm Hg.[13,62]

We are taught that the pathophysiology of open-angle glaucoma is that the trabecular meshwork is not as functional as it should be, and there is a high resistance to aqueous outflow. We now have a drug that seems to work on that site as a predominant mechanism, as a trabecular meshwork outflow-enhancing drug. And it seems to be potent in lowering IOP.

That said, prostaglandins are a dominant drug class. It is going to be hard to displace prostaglandins as the first-line agent for the majority of patients. To have a successful new drug product in the United States, it needs to be additive. There are some exciting data about Rho-kinase inhibitors as an additive to prostaglandins, which is a major plus.[13,58]

Another big plus is that these drugs are only dosed once a day. The side-effect profile also seems to be good, with some mild hyperemia and corneal changes that do not impact vision. Netarsudil looks like it will have an immediate place in our armamentarium, and clinicians are going to use it because of its potency, dosing schedule, and side-effect profile.

Dr. Samuelson: Do we expect to use netarsudil as a standalone drug or in combination with prostaglandin?

Dr. Bacharach: We have been working with Rho-kinase molecules for many years now, including netarsudil and the fixed-combination netarsudil/latanoprost.

If clinical trials prove successful, netarsudil/latanoprost will be the first topical glaucoma medication that potentially has four different mechanisms of action to lower IOP. The phase 3 Mercury 1 safety study recently finished its 90-day efficacy readout, finding netarsudil/latanoprost dosed once daily achieved its primary efficacy endpoint of demonstrating statistical superiority over both its individual components in people with baseline IOPs from above 20 mm Hg and below 36 mm Hg in each of nine measured time points.[63] Mercury 2, a second phase 3 registration trial looking at netarsudil/latanoprost, is underway.[64]

In the United States, netarsudil will most likely be approved prior to the fixed-combination of netarsudil/latanoprost due to the timelines of the trials. Rho-kinase inhibitors appear to be a very promising, important new class of drugs. It also looks complementary to other classes of medicines.

The Japanese drug Glanatec has been demonstrated to be additive even in those eyes that reached their maximum medical therapy for IOP reduction. And that is a weaker drug than netarsudil. It is very promising.

Dr. Samuelson: Given that latanoprost is such a high bar to compete with as first-line treatment, does anyone foresee netarsudil penetrating that first-line dosing? Or will it be primarily adjunct?

Dr. Fingeret: Netarsudil is the choice for the second medication after a prostaglandin, given that it is once-a-day, has few side effects, is efficacious, and has a different mechanism of action than prostaglandins.

Dr. Bacharach: I agree, but have one caveat. Unlike all of the other classes of medicines available to us today, Rho-kinase inhibitors like netarsudil have a similar effect on IOP reduction—no matter what the starting pressure is—possibly because of their impact on the episcleral venous system. That bodes very well for low-pressure glaucoma patients. I believe that in about 20% of patients with open-angle glaucoma who have "normal" pressures, this medicine may have an important role as an early agent in modifying the disease. We will have to wait and see how it plays out clinically.

Dr. Fingeret: What I find interesting about netarsudil is the idea that it can repair the trabecular meshwork. It is a speculative idea at the moment, but there is potential for it to heal the problem, which is something we have never seen before.

Dr. Katz: I think it is very interesting that the fixed-combination of netarsudil/latanoprost has three or four different mechanisms of action for lowering IOP. It is trabecular outflow, uveoscleral outflow, decreasing aqueous production, and lowering episcleral venous pressure. It covers virtually every base.

Dr. Bacharach: We have also never had a fixed-combination with a prostaglandin available to us in the United States. So, that is an exciting possibility.

Dr. Katz: Netarsudil may be particularly useful for people who have relatively normal pressures that you want to get lower possibly through the episcleral venous pressure effect.

Dr. Samuelson: Combination latanoprost/timolol did not meet FDA approval in the United States, so having a combination approved with latanoprost would be a terrific advance in the treatment of glaucoma. Nitric oxide-donating latanoprostene also has a vasodilatory effect. There is a dilation of the episcleral vasculature potential with that agent as well.

Dr. Bacharach: All the advances we have discussed today are incredibly exciting. There has never been a better time to treat glaucoma. Our surgical therapies are vastly improved. We have the opportunity to treat incrementally. Sustained-release methods are only going to enhance our ability to treat these patients. Our agents keep getting better. Now, with a brand-new class of drugs coming down the pipe, we will have five commonly used classes of medications and another fixed-combination along the way at our disposal. We also have sustained-release preparations, which will only enhance our ability to treat glaucoma. Hopefully, all these advances will translate to improved patient care. ■

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CURRENT AND EMERGING GLAUCOMA THERAPY: AN UPDATE ON DISEASE-MODIFYING GLAUCOMA TREATMENTS POST TEST QUESTIONS

1. **Laser trabeculoplasty should be considered as a first-line treatment for glaucoma for the following reasons except:**
   a. It is a more cost-effective option that medical therapy
   b. It takes patient compliance out of the equation
   c. The effects are durable, lasting 3 to 5 years on average
   d. It provides at least an equivalent IOP reduction as prostaglandins

2. **_____ is the most common first-line therapy for glaucoma.**
   a. Prostaglandin therapy
   b. Laser trabeculoplasty
   c. Cataract surgery
   d. Drainage implants

3. **The No. 1 reason patients want to stop using prostaglandins is _____.**
   a. Iris discoloration
   b. Enophthalmos
   c. Excessive lash growth
   d. Hyperemia

4. **According to the participants, _____ is the most powerful prostaglandin at lowering IOP.**
   a. Latanoprost
   b. Travoprost
   c. Tafluprost
   d. Bimatoprost

5. **According to the presenters, one study found that _____ patients take their medications as prescribed.**
   a. 40%
   b. 50%
   c. 60%
   d. 70%

6. **_____ may be considered potential drawback(s) of nondegradable polymer systems as an alternative delivery system.**
   a. Constant feeling/complaints of foreign presence in the eye
   b. Inconsistent, short-term delivery rates
   c. Severe toxicity
   d. Inability to lower IOP considerably more than prostaglandins

7. **Phase 3 studies have shown netarsudil to be noninferior to _____ in IOP lowering.**
   a. Dorzolamide
   b. Brinzolamide
   c. Brimonidine
   d. Timolol

8. **Latanoprostene bunod is best suited for patients who _____.**
   a. Need to lower their IOP 4 to 5 mm Hg
   b. Need to lower their IOP 1 to 2 mm Hg more than latanoprost
   c. Struggle with noncompliance
   d. Had an incidence of hyperemia on latanoprost

9. **_____ is the most effective strategy to reduce patient noncompliance.**
   a. Showing patients how to use their drops
   b. Involving a family member in their treatment
   c. Asking open-ended questions and listening
   d. Providing patients with additional reading materials on their condition

10. **Randomized clinical trial(s) on netarsudil found _____.**
    a. IOP was reduced by more than 10 mm Hg at some, but not all, time points
    b. IOP was reduced only in patients with mild elevated IOP (<20 mm Hg) at baseline
    c. IOP was initially reduced but duration of effect was limited
    d. Diurnal IOP was reduced across all on-treatment time points.

ACTIVITY EVALUATION

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	_____	_____	_____

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.

Name and email: _____

Do you feel the program was educationally sound and commercially balanced? ❒ Yes ❒ No

Comments regarding commercial bias:

_____

_____

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** _____

Would you recommend this program to a colleague? ❒ Yes ❒ No

Do you feel the information presented will change your patient care? ❒ Yes ❒ No

Please identify how you will improve/change: _____

Change the management and/or treatment of patients. Please specify:

_____

_____

Create/revise protocols, policies, and/or procedures. Please specify:

_____

_____

Please identify the barriers to change.

_____ 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

This information will help evaluate this CME activity. May we contact you by email in 1 to 2 months to see if you have made this change? If so, please provide your email address below.

_____

_____

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