Ocular Hypertension and Primary Open-Angle Glaucoma

AN UPDATE ON TREATMENT REGIMENS

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Ocular Hypertension and Primary Open-Angle Glaucoma: An Update on Treatment Regimens

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TARGET AUDIENCE
This certified CME activity is designed for glaucoma specialists and general ophthalmologists involved in the management of glaucoma and associated disorders.

LEARNING OBJECTIVES
Upon completion of this activity, the participant should be able to:
• Discuss the limitations of current treatment regimens from both mechanism of action and patient compliance.
• Explain how novel therapeutics differ in their methods of action from commercially available topical medications
• Evaluate the safety and efficacy of different treatment modalities for ocular hypertension and primary open-angle glaucoma
• Assess the latest clinical trial data pertaining to new therapies
• Discuss future developments and direction of therapeutics for managing glaucoma

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OCULAR HYPERTENSION AND PRIMARY OPEN-ANGLE GLAUCOMA

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Glaucoma remains a prevalent disease, affecting more than 3 million Americans, and it is a significant cause of blindness around the world. Moreover, the aging population suggests that incidence will continue to rise, especially among high-risk populations. Fortunately, the instruments available for diagnosing and observing patients with either confirmed or presumed glaucoma, as well as those at risk for developing glaucoma, have advanced tremendously. These new tools are enhancing the ability to detect glaucoma early in the disease course when treatment is most likely to be effective. These advances coincide with tremendous growth in treatment options, including new surgeries, laser options, and medical therapies.

For the majority of patients with some form of glaucoma, pharmacotherapy remains the preferred treatment option to lower IOP. Prostaglandin analogues are the preferred first-line treatment option, and this class of medication has proven highly successful at helping patients maintain target pressure such that risk of progression is minimized. However, patients’ adherence to this and other classes of medical therapy remains less than optimal. Prostaglandins, which affect IOP lowering by increasing the aqueous drainage through the uveoscleral outflow pathway, may be complemented by other medications that have synergistic or different mechanisms of action. Again, patients with glaucoma are fortunate to benefit from advances in medical therapy, including the introduction of combination medications and alternative options for adjunctive therapies, as well as new understanding about the natural history of glaucoma that reveals novel strategies for addressing multiple aqueous outflow pathways to yield robust IOP-lowering efficacy.

There is every indication that innovations in pharmacotherapy will continue to play a crucial role in the clinical management of patients with glaucoma. During this roundtable event, noted experts in the field who are intimately involved with research efforts to develop new glaucoma drugs will discuss the current state of medical management of glaucoma and the various pipeline entities that proffer to increase the odds of helping patients with glaucoma preserve their vision. We will discuss new classes of medications, intriguing research on drug delivery devices, and exciting theories about how we approach treatment that may unveil potential curative strategies.

-L. Jay Katz, MD
L. Jay Katz, MD: What is the current standard of care for treatment of glaucoma, and what has changed in the past 2 decades with respect to how we approach treatment and management?

Yvonne M. Buys, MD: During the past 2 decades, the medicines we use to treat glaucoma have evolved significantly, from the emergence of the prostaglandin class to the introduction of combination medications, and to the appearance of generic formulations of many of the medications patients use. Each of these topics could be a long conversation in its own right.

When I started practice, the medical options consisted of beta-blockers, pilocarpine, and propine. Since that time, new classes have emerged, including topical carbonic anhydrase inhibitors, alpha-2 agonists, and, of course, the prostaglandin class, which is now the gold standard for first-line therapy. Combination therapy has been another important evolution, mostly in the adjunctive setting. However, there are shortcomings inherent to medical therapy such as patients’ compliance and the potential for side effects. These issues partly explain why there has been so much interest in laser and surgical options, including the microinvasive glaucoma therapy (MIGS) category. However, while there is interest, potential, and rationale for minimally invasive procedures performed at the time of cataract surgery, I am yet to be convinced that the strategy underlying the MIGS category is beneficial, where instead of thinking about significantly lowering IOP, the thinking has shifted to a notion that IOP in the midteens is sufficient for long-term control.

This last point—whether the goal should be to get the pressure as low as possible versus midteens being good enough—hints at some of the subtle changes in the approach to treating glaucoma that have occurred during the past 2 decades as we have learned more about the natural history of the disease. (See sidebar on The Natural History of Glaucoma for additional discussion of this topic.) On the one hand, the treatment endpoint, lowering IOP, has not changed, even as we have learned that this strategy is not effective in every patient. Moreover, the way we attempt to lower IOP has not evolved much beyond first-line medical therapy, followed by laser, and finally incisional surgery as glaucoma progresses or gets more severe. However, while the paradigm of drug, laser, surgery is the norm for most glaucoma cases, there are situations where laser may be a more appropriate first-line approach or where surgery is needed to effect large magnitudes of IOP lowering. And so, as a more robust complement of options has become available, the ideal of individualizing the approach to treatment is now plausible.

There have also been important advances in diagnostic and testing modalities. We have gained an ability to identify cases earlier and, therefore, to initiate treatment at a more favorable time in the disease continuum. A byproduct of this concept of early treatment, coupled with greater appreciation of the consequences of untreated or undertreated glaucoma on functional outcomes, is that treatment tends to be much more aggressive in the mild to moderate phase to hopefully stave off development of severe manifestations and consequential vision loss.

Louis B. Cantor, MD: I agree with that assessment, and I would add that, in addition to target pressure, another treatment endpoint has emerged over the course of the past 2 decades, and that is quality of life—justifiably so, I might add. Use of topical medications by themselves can be associated with compliance issues, but when the potential for topical and systemic side effects are factored in, it makes sense that some patients struggle to adhere to treatment recommendations. Using medical therapy has become complicated by the need to balance efficacy, achieving the target pressure, safety, slowing the progression of the disease, and achieving a quality of life. Of course, the complex discussion about factors potentially influencing the effectiveness of medical therapy would be incomplete without mentioning cost and the emergence of generics, both of which may affect patients’ compliance and are issues in their own right.

NOVEL MECHANISMS OF ACTION

Dr. Katz: Prostaglandins have undoubtedly been an important addition to the treatment of glaucoma. As a class, their primary mechanism of action is to regulate matrix metalloproteinases and remodel the extracellular matrix. Although prostaglandin receptors have been found at several relevant sites for aqueous outflow, including the trabecular meshwork, ciliary muscle, and sclera, prostaglandins are believed to deliver most of their benefit by enhancing the uveoscleral outflow, with a secondary and lesser benefit to the trabecular meshwork. Intuitively, it would seem advantageous to have agents that function a bit more actively on the trabecular meshwork (Table). Such agents could theoretically be added to prostaglandins to bolster efficacy or perhaps substituted to target a different pathway when first-line therapy ceases to be effective.

Are there any candidates in the pipeline that have the potential to reshape how we manage glaucoma? Do you think mechanism of action is something that is important to consider as some of the newer drugs are evaluated?

Dr. Buys: It makes intuitive sense that if a first-line agent is not effective, that you would want an adjunctive therapy that functions on a different mechanism. There are good medications that reduce aqueous production, so having a novel therapy that improves outflow, either through the trabecular meshwork or by decreasing episcleral venous pressure, is encouraging.

Dr. Cantor: The proposed mechanism of action of pipeline drugs is important in two regards: how they work as individual agents, but also how they may work in conjunction with existing medications. The potential to use multiple mechanisms of action may be beneficial for efficacy reasons and adds to the ability to use combination and adjunctive therapy. Speaking specifically, the parasympathomimetic agents largely target activity in the trabecular meshwork, and there is some intriguing work being done to target other sites, such as episcleral venous pressure.

Dr. Katz: Are any of the pipeline entities close to regulatory review?

Dr. Buys: The one furthest along in development at the current time is a nitrous oxide (NO)-donating prostaglandin F2-alpha analogue (latanoprostene bunod ophthalmic solution 0.024%), which purports to have a dual mechanism of action that increases uveoscleral and trabecular meshwork outflow.8,9 Latanoprostene bunod is a latanoprost and NO moiety; once cleaved into its two substrates, the latanoprost...
<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin analogues</td>
<td>Increase uveoscleral outflow; increase trabecular outflow; may involve relaxation of the ciliary muscle and remodelling of the extracellular matrix elements of the ciliary muscle.</td>
<td>Increase in iris pigment (particularly in hazel iris), cystoid macular edema, hypertrichosis, conjunctival injection, keratitis, and uveitis</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Inhibition of cyclic adenosine monophosphate (c-AMP) synthesis in the ciliary epithelium yields decreased</td>
<td>Bronchospasm, bradycardia, decrease blood pressure, adversely alter blood lipid profiles, CNS effect (lethargy, confusion, depression), impotence, exacerbate myasthenia gravis, mask symptoms of hypoglycemia in diabetics</td>
</tr>
<tr>
<td>Adrenergic agonists</td>
<td>Vasoconstrictive effect decreases aqueous production and c-AMP synthesis increases the outflow facility</td>
<td>Systemic: hypertension, tachycardia, arrhythmia Ocular: adrenochrome deposits, drug allergy, follicular conjunctivitis, rebound hyperemia, cystoid macular edema in aphakia, madarosis</td>
</tr>
<tr>
<td>Alpha2-adrenergic agonists</td>
<td>Decrease aqueous production; decrease episcleral venous pressure; increase uveoscleral outflow (brimonidine)</td>
<td>Systemic: dry mouth, decrease blood pressure, bradycardia Ocular: follicular conjunctivitis, ocular irritation, pruritus, dermatitis, conjunctival blanching, eyelid retraction, mydriasis, drug allergy</td>
</tr>
<tr>
<td>Parasympathomimetic agents</td>
<td>Increase trabecular outflow via contraction of the ciliary muscle</td>
<td>Direct: miosis (decrease vision), brow ache, induced myopia and variable refractive error, exacerbate inflammation, shallow anterior chamber, retinal detachment Indirect: above plus cataractogenic, iris cysts in children, increase pupillary block, prolonged effect of paralyzing agent such as succinylcholine when used concomitantly</td>
</tr>
<tr>
<td>Carbonic anhydrase inhibitors</td>
<td>Decrease aqueous production by direct antagonist activity on the ciliary epithelial carbonic anhydrase</td>
<td>Parasthesia of fingers and toes, metallic taste, nausea, malaise, depression, loss of libido, hypokalemia, aplastic anemia, metabolic acidosis, kidney stones</td>
</tr>
<tr>
<td>Hyperosmotic agents</td>
<td>Decrease vitreous volume by exerting oncotic pressure that dehydrates the vitreous</td>
<td>Headache, back pain, diuresis, angina, pulmonary edema, heart failure, obtundation, seizure, and subarachnoid hemorrhage; nausea/vomiting (oral agents)</td>
</tr>
<tr>
<td>Combination medications</td>
<td>Mechanisms of action are identical to individual components</td>
<td>Safety and efficacy of combination medications are similar to individual components</td>
</tr>
</tbody>
</table>

*Information for Table was adapted from: Medical Management for Primary Open Angle Glaucoma. Available at: http://eyewiki.aao.org/Medical_Management_for_Primary_Open_Angle_Glaucoma. Accessed July 8, 2016.*
Current Thoughts on: Rho-kinase

One of the major benefits of the rho-kinase class is the ability to lower IOP effectively independent of the presenting IOP. Rho-kinase inhibitors also have been demonstrated to be synergistic with the use of prostaglandin analogues. I can envision adding this agent to my armamentarium in many clinical situations. For example, a patient the other day in the office presented with the following clinical situation.

HYPOTHETICAL CASE

A 65-year-old woman presented with glaucoma and is currently on propranolol therapy. Her IOP ranged from 19 to 22 mm Hg. Pachymetry measured 540 µm in both eyes. Optical coherence tomography revealed early changes, however, visual fields were normal. A recurrent optic nerve hemorrhage in an area of a notch was evident in both eyes. Relevant medical history included chronic obstructive pulmonary disorder. The target pressure established for this patient was low to mid teens.

In this patient, additional treatment would be warranted due to progressive changes on optical coherence tomography and recurrent optic nerve hemorrhage. I would like to have a treatment that might not reduce ocular perfusion pressure (ie, beta-blocker) but that would add to the prostaglandin. Due to the concomitant chronic obstructive pulmonary disorder, it would be important to have a drug class that would not potentially affect the respiratory system as well. The ideal treatment would not be onerous in number of applications (preferably once daily). Thus, the rho-kinase class would seem to be an excellent consideration.

—Jason Bacharach, MD

acid functions to increase aqueous outflow, and the NO relaxes the trabecular meshwork, thereby increasing outflow capacity. The NO component may modify the mechanical and vascular stresses in the open-angle glaucoma pathogenesis while reducing myosin light chain-2 phosphorylation.

In the phase 2b VOYAGER trial, which compared once-daily latanoprostene bunod with its individual components, the latanoprostene bunod group exhibited slightly better pressure-lowering efficacy compared with latanoprost at 28 days, with a similar safety profile compared with latanoprost 0.005% ophthalmic solution. There was a numerically higher incidence of treatment-emergent adverse events in each of the latanoprostene bunod treatment groups compared with latanoprost, with the most frequently reported event being instillation site pain. Hyperemia was similar across all treatment groups. This study noted a 1.23 mm Hg greater reduction in diurnal IOP in the latanoprostene bunod compared with the latanoprost group. It should be noted that there was a favorable responder rate compared with latanoprost alone.

The pivotal phase 3 APOLLO and LUNAR studies achieved their primary endpoint of noninferiority to timolol, with latanoprostene bunod demonstrating a reduction in mean IOP of 7.5 to 9.1 mm Hg from baseline between 2 and 12 weeks of treatment. The investigators reported no significant safety findings in either study. The drug sponsor has also initiated the phase 3 JUPITER study and phase 1 KRONUS study, both in Japan. An application has been submitted to the FDA, and a decision is expected soon.

Dr. Katz: How might these agents fit into the treatment of glaucoma?

Dr. Bacharach: It is likely that the prostaglandin class will continue to be the preferred first-line option in glaucoma management. However, netarsudil in an adjunctive setting added to latanoprost may provide extra efficacy. In a study, a fixed-dose combination of the compound and latanoprost provided an additional 1.9 and 2.6 mm Hg IOP lowering over latanoprost or netarsudil monotherapy, respectively, components (NCT02207491).

Dr. Cantor: In the first ROCKET study of once-daily netarsudil, the primary endpoint of noninferiority to twice daily timolol was not met,
although the data may have been skewed by lack of response among patients with high initial IOP. In the study, netarsudil was superior to timolol among the subset of patients with initial IOP below 26 mm Hg but not among patients with higher presenting pressures. In a follow-up study, however, clear noninferiority was demonstrated. The conflicting results may be due to the particular study populations enrolled in each of these studies.

Unlike some other classes of agents, netarsudil and other rho-kinase inhibitors appear to be equally effective in patients with lower initial IOP as they are in patients with higher IOP. This may become important for the newly diagnosed patient, who typically has IOP in the low 20s, whereas initial pressures of 30 to 40 mm Hg are relatively uncommon.

**Dr. Katz:** What about the safety profile?

**Dr. Bacharach:** There were no serious adverse events noted in the interim analysis of the ROCKET 2 study at 12 months on the first 118 patients. The most common adverse event reported was conjunctival hyperemia. Hyperemia increased 30% from baseline; 76% of cases were mild, and in 81% of cases, it was sporadic. Persistent hyperemia was rarely reported. Other notable adverse events, occurring at lower frequency, included corneal verticillata. Similar to hyperemia, it was rarely persistent in nature and tended to be self-limiting in most cases. There were small petechial hemorrhages noted in the conjunctival vasculature of between 5% and 23% of the patients, depending on the trial. Those small hemorrhages might have been related to the effects of netarsudil on the ocular vasculature.

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**Current Thoughts on: Trabodenoson**

There may be many situations in which accessing the trabecular outflow pathway may be advantageous, especially if efforts to reduce pressure via the uveoscleral mechanism have been unsuccessful. Following is a hypothetical case in which trabodenoson would seem to be of great benefit.

**HYPOTHETICAL CASE**

A 66-year-old woman presented with moderately advanced primary open-angle glaucoma. Her target IOP based on previous rates of progression is to achieve an IOP of at least 15 mm Hg or less. She failed prostaglandin therapy due to hyperemia and foreign body sensation. Beta-blockers are contraindicated due to pulmonary disease, and she has a history of a sulfa allergy. The patient is using brimonidine 0.15% and has undergone SLT, with current IOP ranging between 18 and 22 mm Hg. In this patient, a trabecular outflow drug such as trabodenoson would be appropriate and likely to achieve the target IOP.

—Louis B. Cantor, MD

**Dr. Katz:** Are there other agents under investigation that target the trabecular meshwork?

**Dr. Bacharach:** Trabodenoson is a potent and highly selective adenosine mimetic acting at the A1 receptor subtype at the site of the trabecular meshwork to improve metabolic activity and upregulate proteases that remove protein depositions that may be clogging the trabecular meshwork, thereby helping to restore and maintain an open channel for aqueous outflow. Interestingly enough, A1 receptors can also be found in the retina, so there may be additional neuroprotective benefit in addition to pressure-lowering efficacy. In a phase 2 dose ranging study (NCT01917383), trabodenoson in doses ranging from 50 µm to 500 µm demonstrated statistically significant improvement over placebo at all time points during and after 4 weeks of dosing, with reported efficacy similar to what may be expected with a prostaglandin. The investigators of this study noted that trabodenoson was well tolerated with no clinically meaningful ocular or systemic side effects: 10.2% and 15.3% of patients in the placebo and trabodenoson groups, respectively, developed treatment-related adverse events, and all were considered mild or moderate.

Based on the fact that the most consistent decreases in IOP occurred in the 500-µm group, the drug’s sponsor initiated phase 3 studies (NCT02565173) with a higher concentration. The study will compare trabodenoson with placebo as well as with timolol as the standard of care. Trabodenoson is being studied in both twice-a-day and once-daily dosing regimens.

**DRUG DELIVERY: CURRENT APPROACHES AND FUTURE DIRECTIONS**

**Dr. Katz:** As much as these pipeline candidates offer to significantly improve the ability to address the physiologic mechanism of glaucoma, our treatment paradigms are still subject to one of the most prevalent issues in medical management: patients’ adherence to medical therapy. Drug delivery, including concepts such as nanoparticle-based formulations, drug-eluting contact lenses, punctal inserts, and bioadhesive matrices, have been offered as a potential solution to this problem. What is the latest on drug development in glaucoma? Have there been any promising developments?

**Dr. Cantor:** There are a number of research programs ongoing at the current time looking at drug delivery for glaucoma. It may be convenient to think about them in two categories: devices and implants either injected or placed inside the eye and those that are used on the ocular surface or as devices externally to the eye. The latter category would include nanoparticles applied to the eye, contact lenses that elute drugs, and punctal plug delivery systems. As candidates from each of these categories get closer to market, it will be interesting to see how accepting patients will be of the concept of drug delivery and also which route they may prefer. That said, there is certainly precedent within ophthalmology: sustained-release steroid implants have had a positive impact on the treatment of diabetic macular edema, uveitis, and retinal vein occlusion. In some cases, these devices are used early in the disease process instead of or in addition to monthly injections when compliance is or could be an issue.
IOP Fluctuation: Risk Factor for Glaucmatous Progression?

By Yvonne Buys, MD

There is conflicting evidence on whether fluctuations in IOP may be an independent risk factor for glaucomatous progression. It has been suggested that the variability of IOP throughout the day and over time may be as relevant as peak pressure.

Data from the Advanced Glaucoma Intervention Study (AGIS) suggested that IOP fluctuation predicts visual field loss, with a greater magnitude of effect among patients with lower baseline pressure at the start of the study. A similar pattern was noted in an analysis of patients enrolled to either the Early Manifest Glaucoma Trial (EMGT) and Ocular Hypertension Treatment Study (OHTS). Yet, a separate analysis from the EMGT, as well as data from other major clinical trials, including the European Glaucoma Prevention Study and the Diagnostic Innovations in Glaucoma Study, found no such correlation.

There could be several explanations for these variations, the most obvious being that IOP fluctuation has no true effect on risk of progression. Equally as likely is that if fluctuation is a risk factor, then the variation in separate studies may be due to different enrollment criteria and differences in patient characteristics. Finally, the current ability to measure IOP over a 24-hour period is limited. Even in sleep studies, the patient has to be awoken, which may influence IOP.

And so, insufficient ability to accurately track and monitor fluctuations may obfuscate the clinical relevance of fluctuations occurring during the short- and intermediate-terms, and those occurring between office visits.

There are several devices that offer to track and measure patients’ IOP throughout the day in preclinical or early stage development. Most fall under the category of implantable devices that are either coupled with an intraocular lens or devices implanted inside the eye, or those affixed to the sclera. One novel approach is the Sensimed Triggerfish, which is a contact lens worn on the eye that measures changes at the limbus occurring as a result of pressure changes as a surrogate marker of IOP fluctuation. However, it is unclear how these measurements correlate with data derived from Goldmann applanation tonometry.

Gaining the ability to measure diurnal fluctuations may be less important than understanding how a particular medicine controls the disease over time. For instance, it has been suggested that while prostaglandins are somewhat effective at achieving diurnal control, beta-blockers are relatively ineffective at lowering pressure during nighttime. If it is learned that control of diurnal IOP is relevant for delaying the progression of glaucoma, then interventions may need to be tailored to this treatment goal. Approaches could include surgery, the use of laser trabeculoplasty, or novel medications currently under investigation that either replace or augment the current armamentarium. In addition, sustained delivery devices could become increasingly important if they provide the ability to safely achieve robust drug concentrations at the intended therapeutic target while efficaciously maintaining target pressures. Of course, proving that will require better systems for monitoring IOP fluctuations over the course of the day, during regular life activities, and between office visits.


Dr. Katz: While drug delivery is an area of interest in our field, are there practical concerns we should be aware of? Should we temper our excitement?

Dr. Cantor: There are questions about both the internal and external devices. With the internal devices, we need compelling data that the drug being delivered is durable, but also an understanding of when an implant or other device may need to be readministered or refilled. The safety profile of each approach, especially with active drug consistently inside the eye, will be important to consider. With the external devices, the question of durability changes a little to one of retention at the intended site. For example, a punctal plug may fall out without the patient realizing it, and so ensuring that these devices are retained at the site of activity will be important. A contact lens-like approach can have all the same potential issues as any contact lens, especially if it is used for an extended period of time.

Dr. Katz: What are some of the approaches being investigated, and where are they in the pipeline?

Dr. Cantor: One of the intriguing proposals is a biodegradable, intraocular bimatoprost implant to the anterior chamber. In a phase 1/2 trial, IOP was reduced a mean 7.2 to 9.5 mm Hg, while pooled fellow eyes receiving once-daily treatment with topical bimatoprost 0.03% had
The Natural History of Glaucoma

By Jason Bacharach, MD

Glaucoma should more properly be understood in the plural, as the term does not describe a single disease entity but rather a group of diseases with common characteristics that include progressive irreversible damage to the optic nerve head and retinal ganglion cells with corresponding visual field loss. The strict definition of glaucoma has evolved from a disease of eye pressure to one characterized by optic nerve loss. Yet, IOP remains the only modifiable risk factor for glaucomatous progression and, thus, is the target of treatment, which is intended to prevent optic neuropathy.

Glaucoma has two main subtypes that are characterized with respect to the anterior chamber angle. Glaucomas that result from the opposition of the iris to the trabecular meshwork are termed angle-closure glaucoma (ACG), whereas open-angle glaucoma (OAG) is characterized by increased resistance to outflow that may yield chronic optic neuropathy and changes in the optic disc and visual field. OAG is most typically associated with elevated IOP, although it may also manifest as normal-tension glaucoma (NTG). A third category, the developmental glaucomas, is further subdivided into primary and secondary types.

Each glaucoma category is understood to follow a distinct disease course and progression, although there are fundamental similarities in optic nerve morphology.1 The earliest stage of glaucoma is a complex series of biochemical events that yields ganglion cell damage and loss that results in axonal damage2,3 occurring around site of the lamina cribrosa4 with subsequent damage to the retinal nerve fiber layer5-7. However, the inciting pathophysiologic mechanism for ganglion cell loss, and for glaucoma in general, is not entirely understood. Two theories have emerged: The mechanical theory holds that compression of the axonal fibers (perhaps due to increased IOP8) distorts the lamina cribrosa and interrupts axoplasmic function, the result of which is ganglion cell death.9,10 The vascular theory proposes that intraneural ischemia (perhaps associated with endothelial cell dysfunction11) may result from a reduction of 8.4 mm Hg23. The majority of safety events reported in the trial were related to the injection procedure—such as conjunctival hyperemia, foreign body sensation, and pain—and were all reported to be mild in nature. Based on these findings, the drug sponsor has initiated phase 3 studies. I would estimate that the prospects are good for this product, although its sponsor is assuming a somewhat risky proposition. This represents a completely new way of treating glaucoma, and as we learned in the memantine studies,24 the methodology and treatment endpoints of these kinds of trial programs can confound the results.

There are some promising punctal plug delivery systems in later stage development. This appears to be a relatively safe and easily reversible mechanism for delivering drug. Based on that, I think that it is likely a punctal delivery system will make it to market. There are two devices for punctal delivery that are close and promising: an intracanalicular device and a more standard punctal plug. Each elutes drug into the tear film over a period of time, generally at least 2 to 3 months before the device needs to be replaced.

Another company is developing a similar concept: a ring that fits on the eye to deliver bimatoprost over a sustained period of time. It completed a phase 2 study in which it showed noninferiority to timolol at two of the nine endpoints, but the study was underpowered to determine the treatment effect. There were no unexpected adverse events, and the implant was retained in 88.5% of patients at 6 months.

Dr. Katz: While this is an area of interest, it may be a few years before these kinds of drug delivery systems are available in our clinics.

Dr. Cantor: There is definitely a lot of promise in drug delivery, but it is tough to predict which, if any, of the investigational devices will be viable for patient use. One obvious question is how sustained delivery
Several large-scale clinical trials have helped to advance the understanding of the typical disease course of OAG, including the Ocular Hypertension Treatment Study (OHTS), the Early Manifest Glaucoma Trial (EMGT), and the Collaborative Normal Tension Glaucoma Study (CNTGS). Approximately 10% of individuals with untreated ocular hypertension will convert to glaucoma within 5 years. Following conversion, 49% of untreated patients can be expected to exhibit signs of progression after 4 years and 68% after 6 years. Predictably, individuals with high IOP are more likely to progress, although 56% patients in the EMGT population with normal tension glaucoma progressed and 60% in the CNTGS population. Pseudoxfoliative glaucoma portends the worst prognosis, with up to 93% of patients exhibiting progression.

Primary angle closure is “appositional or synechial closure of the anterior chamber angle. Pupillary block is a key element in the pathogenesis of most instances of [primary angle closure].” Data on the natural history of ACG are more limited, although it is appreciated to be a serious condition sometimes warranting immediate intervention, especially if acute closure and elevated IOP are present. Further, ACG is a risk factor for development of angle closure in the fellow eye.

ACG may be subdivided into acute (sudden onset yielding rapid IOP elevation), subacute (or “intermittent”: pupillary blockage that resolves simultaneously but recurs), or chronic (closure of the angle resulting in scarring). ACG can further be understood to occur in three stages: anterior optic nerve damage and visual field defects. Unreated acute angle closure most typically leads to progressive thickening of the retinal nerve fiber layer that begins in the first few days after onset, and which is the result of morphologic degradation and eventual atrophy of the axon.

Dr. Buys: Those questions about ocular bioavailability really dovetail with questions about the safety and durability of these devices. In thinking about the external devices, there are relevant questions to ask about what effect having drug consistently available at the ocular surface will mean for the risk-benefit profile, especially as the duration of drug delivery is considered. It appears that injectable delivery systems may provide a more durable and sustained delivery of active drug without inducing untoward ocular surface effects. There is also precedent and experience to draw from our retina colleagues with regard to injectables, where implanted sustained-release steroid devices have been well received by providers and patients.

Dr. Bacharach: As we look to the future, every indication is that as more patients come into the health care system and as the population ages, the volume of patients needing glaucoma care is almost certain to rise significantly. We need additional treatment options for our patients, and there may be scenarios where injectable or external devices may be preferable. I also do not think that one is necessarily mutually exclusive of the other. It is entirely possible that some of the new drugs in development could be paired with new delivery systems.
SUPLLEMENT TO GLAUCOMA TODAY

OVERVIEW OF CURRENT MEDICATIONS FOR OPEN-ANGLE GLAUCOMA

PROSTAGLANDIN ANALOGUES
- Widely considered first-line therapy for open-angle glaucoma.
- Confer about 28% to 32% IOP lowering efficacy.
- Category C medication (all glaucoma medications are considered category C except brimonidine, which is category B) with potential risk to a developing fetus.
- Contraindicated in patients with apha, inflammation, and existing coidylus macular edema.

BETA-BLOCKERS
- Complementary mechanism of action to prostaglandin analogues often the preferred first adjective medication if no systemic contraindications are present.
- May be suboptimal efficacy for nocturnal control of IOP based on sleep laboratory study.
- Concurrent use of systemic beta-blockers may diminish IOP-lowering efficacy.
- Tachyphylaxis may occur in up to 10% of patients.

ADRENERGIC AGONISTS (ALPHA-AGONISTS)
- Cannot be used in pediatric patients due to risk of crossing blood-brain barrier resulting in systemic hypotension, somnolence; also in patients taking oxidase inhibitors.
- Can cause local allergic reaction that may be delayed up to 18 months.
- Brimonidine may have neuroprotective effect; studies suggest it may slow visual field loss in patients with low-pressure glaucoma.

CARBONIC ANHYDRASE INHIBITORS
- May provide increased perfusion to the optic nerve.
- Use in patients with sulfa allergy may trigger allergic reaction, but evidence is not conclusive.

PARASYMPATHOMIMETICS
- Oldest class of medications used in glaucoma therapy.
- May be best suited for use as adjunctive therapy in pseudophakic eyes.

EMERGING CONCEPTS IN GLAUCOMA CARE

Dr. Katz: All of the strategies we have discussed so far center on controlling pressure as a mechanism to forestall progression of glaucoma. In recent years, the concept of neuroprotection has garnered a lot of attention. Efforts at commercialization have so far been unsuccessful, but despite this, there is still a lot of interest in the concept. Why is that? What does the potential for neuroprotection offer?

Dr. Cantor: Neuroprotection is a fascinating concept, but it may require us to rethink how we categorize glaucoma and how medications are studied. IOP is a surrogate for glaucoma, and controlling pressure is a surrogate for controlling glaucoma, whereas our real goal in glaucoma is preservation of vision and visual function. I think we really need to refocus on the outcomes of the disease, and that starts with understanding that glaucoma is not a single disease. Instead, glaucoma is a broad group of diseases that has a common final pathway of glaucomatous optic neuropathy with associated visual field loss. Glaucoma is an optic neuropathy for which there are multiple different causes. Pressure reduction is certainly a very effective therapy for the majority of patients but not for all. Not all the disease entities that fall under the category of glaucoma are equally responsive to pressure reduction, and some of them are not responsive to pressure reduction at all. Therefore, there is a need for alternative treatment approaches, such as direct neuroprotection and preventing the damage to the nerve.

However, demonstrating benefit from preventing optic nerve damage is exceedingly difficult because using structure and function as endpoints has shortcomings. Proving the concept using a functional endpoint would require repeat testing over an extended period in a very well-defined population of patients with certain degrees of visual field loss to control for natural pressure fluctuations and variations. As for structural assessment, the technology is advancing faster than our understanding of what it is that is being measured. We can take very interesting pictures of ganglion cells, for example, but we do not know what those data mean or how to use them. And so, there are very complicated but fundamental questions of trial design and treatment endpoints that need to be resolved before we even begin to collect data on how the course of the optic neuropathy may be affected by a particular treatment strategy.

Dr. Bacharach: There may be lessons from the failed phase 3 memantine trials that we can build on (NCT00168350 and...
NCT00141882). That was the most extensive program ever conducted in glaucoma, and it took a strong commitment from industry to step outside the box and look at that. You will recall the study used progression of glaucoma as an endpoint. Preclinical testing demonstrated that memantine reduced damage to neurons from ischemia. However, once the phase 3 trial failed to meet its primary endpoint, the drug’s sponsor decided to suspend development. Although there was a difference in the high-dose group compared to the low-dose group with respect to progression of glaucoma, there was no difference compared with placebo. As Dr. Cantor pointed out, using non-IOP endpoints can be challenging from a regulatory perspective, and they also raise financial and ethical questions that serve as major hurdles to research and development.

Dr. Katz: There is a product in very early stage development that blends drug delivery with the concept of neuroprotection. The company is exploring the viability of using a specific technology that allows creation of a semipermeable capsule that contains genetically modified human cells that secrete therapeutic doses of a drug. It is actively pursuing this platform technology in various disease states using different prodrugs. In the case of glaucoma, the capsule is filled with genetically modified fibroblasts that make neurotrophic factor (NT-501). A pilot study of NT-501 implanted into the eyes of glaucoma patients (NCT01408472) demonstrated some evidence that suggests that the perimeter results improved. These are very early results, but it is nonetheless a very tantalizing proposition.

Dr. Cantor: We are continually learning more about glaucoma, but one thing we definitely know is that reversal of the damage is not a feature of the natural history of glaucoma. I agree that these are early results, and I believe we need to see both structure and function outcomes to show that the disease course is being reversed. That said, the concept we are talking about is completely revolutionary in the treatment of glaucoma.

Dr. Katz: It has been somewhat established over the years that the treatment endpoint in glaucoma is to achieve stability of the disease to forestall progression. But that dogma has been challenged in recent years, and treatment has become more aggressive in terms of getting the target pressure low. The old thinking of getting patients to 21 mm Hg as a surrogate for disease control is going by the wayside. Some recent papers have shown evidence that aggressive treatment may yield improvements in perimeter and also structurally. Should we be talking about new endpoints? Is reversibility of glaucoma a plausible therapeutic goal?

Dr. Buys: At the American Glaucoma Society meeting this year, there were a number of presentations talking about improvement in visual function in glaucoma, which is something that is rarely if ever talked about in glaucoma. Certainly, with surgery, if the pressure is lowered significantly, there can be reversal of cupping, but that is usually not correlated to a functional improvement. However, studies are now starting to show examples of patients having functional improvement over time. That is a potentially very exciting shift in thinking and focus.

Dr. Bacharach: There are actually clinical examples in treatment of pediatric glaucoma where it is possible to achieve reversal of the cupping. Similar to examples in other neurologic diseases, it may be possible to reverse the glaucomatous process and, as a byproduct, achieve improvement in some of the structural deficits. That may be an extreme example, but I think it demonstrates the principle we are discussing.

Dr. Cantor: I agree completely. Glaucoma is a type of disease wherein there should be a window of opportunity where cells are perhaps sick but not dead. That may mean there is opportunity to rescue them before they die off. Glaucoma is an axogenic disease process: instead of an ischemic insult where there is immediate loss of the cell body within the nerve fiber, it is a disease process that appears to start in the axon and later yields loss of the cell body. If that is the case, there is a window of opportunity for rescue. The problem is, the current generation of functional testing is not sensitive enough to detect those very early axonal changes to identify that window of opportunity. The technology is getting better, but we may need to see a convergence of improved testing capabilities and development of new therapeutic modalities capable of reversing the disease course before we are able to determine if treating to improvement is a legitimate goal.

CONCLUSION

Dr. Katz: What we have really talked about here are new mechanisms of action for addressing the pathophysiology of glaucoma, new drug delivery devices, and new concepts in the medical management of glaucoma. The increased understanding of the basic biology of glaucoma and its natural history has contributed new targets for effecting robust and durable IOP lowering as a mechanism to control disease. Meanwhile, the conversation about treatment is evolving, and we are seeing the first glimmer of potential curative strategies.

I think we can all agree that we have seen tremendous change in this field during the course of our careers. When we first started out, our options were limited to slowing a disease process that would eventually rob our patients’ sight. Soon thereafter, new drug classes gave our patients the hope of long-term control if we were able to intervene earlier in the disease course—and advanced diagnostics added to our ability to do so. As we look to the very near future, we are looking at concepts that provide our patients even greater chance of preserving their natural vision and, in some cases, of potentially curing the glaucoma.
1. Based on the current understanding of the natural history of glaucoma, the earliest site of disease activity is ganglion cell damage that results in axonal damage.
   a. True
   b. False

2. With respect to the inciting mechanism of glaucoma, the theory stating that "elevated IOP compresses axonal fibers, leading to disruption of axoplasmic function and resulting ganglion cell death" is referred to as:
   a. The vascular theory
   b. The mechanical theory
c. The pressure theory
d. The glaucoma theory

3. What percentage of untreated patients in the Ocular Hypertension Treatment Study (OHTS) converted to glaucoma during the 5 years of follow-up?
   a. 5%
   b. 10%
c. 15%
d. 25%

4. Clinical studies demonstrate that beta-blockers are equally as effective as prostaglandins at controlling nighttime IOP.
   a. True
   b. False

5. Prostaglandin analogues deliver most of their therapeutic benefit by influencing which of the following outflow mechanisms?
   a. Uveoscleral outflow
   b. Trabecular meshwork
c. Primarily the uveoscleral outflow with a secondary benefit to the trabecular meshwork
d. Episceral venous pressure

6. Based on preclinical and clinical testing, what is the proposed benefit of the rho-kinase class?
   a. Increase in contractility of the trabecular meshwork
   b. Reduction of aqueous outflow
c. Inhibition of fluid production through norepinephrine transporter inhibition
d. Lowering of episcleral venous pressure
e. All of the above

7. What additional benefit does the addition of nitrous oxide (NO) to a prostaglandin potentially offer?
   a. NO is inert and would likely provide no additional benefit
   b. NO relaxes the trabecular meshwork
c. NO increases aqueous outflow
d. Both b and c

8. Which of the following combination formulations are currently approved for use by the US Food and Drug Administration for the treatment of glaucoma?
   a. Dorzolamide hydrochloride 2.0%/timolol 0.5%
   b. Brimonidine 0.2%/timolol 0.5%
c. Brinzolamide 1%/brimonidine 0.2%
d. All of the above
ACTIVITY EVALUATION

Did the program meet the following educational objectives?  

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Discuss the limitations of current treatment regimens from both mechanism of action and patients’ compliance.  

Explain how novel therapeutics differ in their methods of action from commercially available topical medications.  

Evaluate the safety and efficacy of different treatment modalities for ocular hypertension and primary open-angle glaucoma.  

Assess the latest clinical trial data pertaining to new therapies.  

Discuss future developments and direction of therapeutics for managing glaucoma.  

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME).

Name and email ____________________________________________________________________________________________________

Do you feel the program was educationally sound and commercially balanced?  

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Comments regarding commercial bias:  

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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?  

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Do you feel the information presented will change your patient care?  

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If yes, please specify. We will contact you by email in 1 to 2 months to see if you have made this change.  

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If no, please identify the barriers to change.  

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Please list any additional topics you would like to have covered in future Evolve Medical Education LLC CME activities or other suggestions or comments.  

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