New Trends in Medical Treatment of Glaucoma

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New drugs and delivery systems can broaden treatment options for glaucoma. More importantly, they will offer opportunities to overcome longstanding hurdles in medical glaucoma therapy.

Open-angle glaucoma (OAG) is a progressive optic neuropathy that affects more than 3 million Americans. 1,2 The prevalence of the disease significantly increases in older individuals. 3,4 As the population continues to grow and age in the coming years, it can be anticipated that the number of patients who need treatment for OAG will increase substantially.

At present, all available treatment modalities for glaucoma are aimed at lowering intraocular pressure (IOP). Traditionally, the first choice of therapy for patients with OAG is medical. The pharmacotherapy options for glaucoma were once limited but have continually increased over the past few decades. Notably, beta-blockers were introduced in the late 1970s; and topical carbonic anhydrase inhibitors (CAIs), alpha-adrenergic agonists, and prostaglandin analogs (PGAs) in the mid-late 1990s, significantly expanding the range of IOP-lowering agents to choose from. The PGAs have been the drug of the class.

For the initial medical treatment of glaucoma, we now have a great range of IOP-lowering agents to choose from. The PGAs have been the drug of choice for first-line therapy since their introduction in the 1990s. The family of PGAs now includes latanoprost, bimatoprost, tafluprost, travoprost, and unoprostone. In addition to the PGAs, a number of drugs—including several combination products—are available as second-line agents. To achieve lower target IOPs, we can either add more medications to the existing regi-
therapy before the advent of PGAs, but their use is contraindicated by many systemic conditions, including asthma, bradycardia, and chronic obstructive pulmonary disease.

Furthermore, adding medications may reduce a patient’s adherence to the prescribed regimen, negating the added effect of combination treatments.6,5 While once-daily PGAs have substantially better adherence than other drug classes,7 the risk of non-adherence grows as the complexity of regimen increases.5,6

NEW MECHANISMS OF ACTION

The PGAs work by enhancing uveoscleral aqueous outflow. As very effective IOP-lowering agents (an IOP reduction of about 30% with once-daily dosing), the PGAs have set a high standard for new glaucoma drugs. That said, a drug with a similarly simple dosing schedule but additional IOP-lowering mechanisms should theoretically generate comparable or better efficacy. Such a single-agent therapy, especially if more efficacious, would be a useful tool in managing patients who require more than one medication to control IOP or who are intolerant of current medications. It may also be helpful with medication adherence, which would in turn improve the outcome of treatment.

The IOP-lowering agents currently in completed or ongoing clinical trials all have novel targets and often multiple mechanisms of action. One of particular interest is latanoprostene bunod (Vyzulta; Valeant Pharmaceuticals), a nitric oxide-donating prostaglandin analog awaiting FDA approval for launch later this year, has two distinct IOP-lowering mechanisms: latanoprost enhances uveoscleral outflow, while nitric oxide relaxes the trabecular meshwork and increases aqueous outflow through the conventional pathway (Figure 1). In two phase 3 trials (APOLLO and LUNAR), latanoprostene bunod 0.024% administered once daily produced a greater IOP-lowering effect than twice-daily timolol, with a reduction in mean IOP of 7.5 to 9.1 mmHg from baseline between 2 and 12 weeks of treatment.8

Netarsudil mesylate 0.02% (Rhopressa; Aerie Pharmaceuticals), also known as AR-13324, is a Rh kinase (ROCK) and norepinephrine transporter (NET) inhibitor and another medication in a phase 3 trial (Rocket 4) that I am excited about. It is thought that netarsudil reduces IOP by three separate mechanisms: increasing trabecular outflow through ROCK inhibition, decreasing aqueous production through NET inhibition, and reducing episcleral venous pres-
pressure, presumably through NET inhibition. In two phase 3 studies (Rocket 1 and 2), AR-13324 was shown to be non-inferior to timolol in patients with baseline pressures between 20 and 25 mmHG, which, according to the Baltimore eye study, represents approximately 80% of diagnosed glaucoma patients. Rhopressa is very promising in that it may provide patients with a new once-daily alternative without the systemic side effects of beta blockers, alpha agonists, or CAIs. A fixed combination of netarsudil 0.02% and latanoprost 0.005% (Roclatan; Aerie Pharmaceuticals) is also in phase 3 trials (Mercury 1 and 2). With an additional mechanism of action to latanoprost, the combination drug has the potential to reduce IOP to an even greater degree.

Another glaucoma drug being studied in phase 3 clinical trials is trabodenoson (previously INO-8875; Inotek Pharmaceuticals), a highly selective adenosine type 1 receptor agonist. Trabodenoson also targets the trabecular meshwork and lowers IOP by enhancing trabecular outflow. In phase 2 trials, trabodenoson demonstrated IOP-lowering efficacy similar to that of the PGAs.

IMPROVING DRUG DELIVERY

No matter how efficacious an agent is at lowering IOP, the success of medical glaucoma therapy is ultimately limited by patients’ adherence—some patients forget to instill even one-a-night drops. It is believed that sustained-release drugs, which are designed to be applied by clinicians once every few months, will offer a solution to much of the adherence problem that so prevails among glaucoma patients.

Sustained-release drug delivery for glaucoma has been the subject of intensive research and development. The approaches that are being studied cover a wide range of products: punctal plugs, ocular surface inserts, drug-eluting contact lenses, microparticles, and intraocular depot implants. The punctal plug delivery system is the most studied because of its prior use in dry eye treatment. One particular sustained-release drug I am excited about is sustained-release travoprost (OTX-T; Ocular Therapeutix), an intracanalicular depot composed of polyethylene glycol hydrogel and drug-containing microparticles. The device is visible under blue light with fluorescence, easy for the clinician to find out whether it has dislodged or not. In phase 2 clinical studies, sustained-release travoprost produced clinically meaningful IOP reduction for up to three months. Two phase 3 trials have been planned, the first of which is to begin in the second half of this year.

THE NEW TRENDS

Over the past 20 years, no new class of glaucoma drugs has been brought to market. This could change drastically in the next few years. One thing the drugs in development have in common is that they all target the trabecular meshwork, the primary outflow pathway that accounts for 70% to 90% of aqueous drainage and the main location of pathology responsible for elevated IOP in open-angle glaucoma (Figure 2). Up to now, we have been largely unable to medically treat trabecular outflow, but we may soon reach that goal with medications such as latanoprostene bunod, netarsudil, and trabodenoson.

Although the exact mechanisms by which each of the new drugs alters the trabecular meshwork await further elucidation, it is clear that multiple mechanisms of action are involved. Whether or not these multiple action agents might be more effective than current therapies remains to be seen, but presumably targeting the site of disease directly should have some advantage over working around it.

The new therapies in the pipeline can potentially transform various aspects of glaucoma therapy. If the multiple-action drugs prove more efficacious, either as standalones or combined with currently available agents, we might be able to offer treatments that can better address patients’ specific needs, such as additional IOP.

CORE CONCEPTS

- Few of the currently available glaucoma medications target the primary trabecular outflow pathway. The PGAs, the most effective IOP-lowering agents in clinical use, lower IOP by increasing uveoscleral aqueous outflow.
- A significant portion of glaucoma patients require more than one medication for adequate IOP control. There is a clear need for additional and more efficacious therapies to treat glaucoma.
- Several new classes of glaucoma medications with strong and potentially greater efficacy are moving closer to market. These agents act on the trabecular meshwork to lower IOP, most likely through multiple mechanisms of action.
- Sustained-release devices currently in studies for treating glaucoma may overcome medication nonadherence, a common problem among glaucoma patients that has limited their therapeutic success.

FIGURE 2 The trabecular meshwork is the primary outflow pathway that accounts for 70% to 90% of aqueous drainage and the main location of pathology responsible for elevated IOP in open-angle glaucoma.
reduction in patients with normal tension glaucoma. At the same time, sustained-release technologies can help reduce patients’ drug administration burden and improve adherence. A drug-eluting system like a punctal plug could provide a baseline treatment effect, and if we needed to add a drop, at least we would not be adding on top of another drop. With patients not having to apply multiple drops every day, our chance for improving medication adherence would greatly improve.

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REFERENCES
Caring for Patients Who Undergo Glaucoma Surgery

SCOTT G. HAUSWIRTH, OD, FAAO

Co-managing the surgical glaucoma patient—a rewarding added dimension to optometry practice—requires an understanding of available options and working closely with ophthalmology colleagues.

Optometrists are becoming increasingly involved—sometimes as the principal touchpoint—in pre- and post-surgical glaucoma care. Various dynamics have contributed to the trend. One is that, in many places, there is increasing acceptance for a widening scope of optometric practice, including care for glaucoma at nearly all levels of disease. Also, an increasing proportion of practices are using an integrated care model in which optometrists and ophthalmologists work closely together. Increased collaboration between ophthalmology and optometry means more optometrists can gain exposure to patients preparing for, undergoing, and recovering from surgery. With reduced reimbursements in many categories of care, more ophthalmic surgeons—of which there are fewer than in years past—are choosing to focus on surgery and are including their optometric colleagues in perisurgical monitoring.

APPROACHING REFERRAL
Whatever their background, clinicians who provide glaucoma care are unified in their goal to decelerate and hopefully halt vision loss. Practicing in a tertiary care center, I see patients at every stage of glaucoma, including those with advanced, longstanding disease. Depending on the patient, my role may be to initiate ocular hypotensive therapy, modify an existing regimen, recommend surgery, or monitor the patients from day one following glaucoma surgery. An important role includes discussing surgical options when appropriate, especially in instances when IOP-lowering medica-

cions are not effective, not tolerated, or a patient’s disease is particularly aggressive.

When approaching a potential surgical candidate, it is important to remember that the idea of surgery is often very frightening, especially to patients who are already dealing with a chronic disease they associate with blindness. Including surgical options early in your management strategy and ensuring that you and your patients will make treatment decisions together—as a team—can make the prospect of surgery less scary. Managing glaucoma is a long-term prospect usually lasting several years, and by introducing surgery into the discussion early, patients will be better mentally prepared to move forward when the time is right. The advent of selective laser trabeculoplasty (SLT) and minimally invasive glaucoma surgeries (MIGS), procedures which are better suited for more early to moderate stage disease, has made it even easier to broach the subject of surgery early.

The logistics around referring patients for surgical consultation—and effective monitoring afterwards—depend upon the needs of the patient but is contingent on good communication skills and the comfort level of both the optometrist and the surgeon. In an integrated model such as the one I practice in, I am fortunate to work with several glaucoma surgeons; I am often able to walk down the hall and discuss potential surgical cases with my partners face to face. More typically, however, a referral from outside the practice is made via letter, email, or even a phone call for more urgent cases. When introducing a patient for surgical consultation, it is helpful to get right to the point, highlighting what medications have been tried, the patient response, an assessment of what might be a logical next step, and whether or not the referring doctor would like to be involved in the postoperative management. In my experience, surgeons appreciate a concise referral letter and will delve into a patient’s clinic notes in more depth as needed. It is especially helpful to include serial visual fields and/or imaging to help document progression and justify the need for surgical intervention.

It is important to become familiar with the range of surgical options
that are available, their benefits and risks, and what type of follow-up care is needed. For example, a patient who is struggling with compliance and has mild to moderate glaucoma may be referred for consideration for laser surgery, such as SLT, argon laser trabeculoplasty (ALT), or micropulse laser trabeculoplasty (MLT). ALT uses a single spot to directly target the trabecular meshwork, creating perforations and scar tissue, which makes it more permeable to aqueous outflow. MLT and SLT lower IOP by using a lower energy than that used in ALT, essentially “cleaning out” the trabecular meshwork with less damage to the cells of the TM and increasing outflow. These procedures are all generally well tolerated by patients and carry a much lower risk for complication compared to conventional glaucoma filtering surgeries. A patient undergoing ALT or SLT might require only a brief evaluation by the surgeon, have the procedure performed at the same visit or soon afterwards, and be sent back to the referring optometrist for monitoring.

Likewise, patients with mild to moderate glaucoma who have cataracts warrant special consideration, since removing the cataract will often enhance IOP reduction and may reduce or even eliminate the need for hypotensive medications. Patients with mild glaucoma or a narrow angle might simply have their cataract removed and then be followed for the effect on IOP. A combined cataract surgery and MIGS procedure may be a good option for these individuals as well.

Patients who have more aggressive or advanced disease might require a more invasive technique such as tube shunt placement or trabeculectomy, or a newer option such as micropulse transscleral diode cytophotocoagulation (MDCPC). For those who also have cataracts, performing a combined procedure (eg, cataract removal with a trabeculectomy or tube shunt) helps to maximize effect and reduces the likelihood of further procedures down the road. Since tube shunt and trabeculectomy patients have a higher risk for vision loss and postoperative complications, follow-up would be more intensive and would likely involve the surgeon to a greater degree.

**SURGICAL OPTIONS: A CLOSER LOOK**

Glaucoma patients may benefit from an increasing array of surgical options. MIGS stent procedures are becoming popular for the treatment of patients with mild to moderate glaucoma wishing to reduce dependence on or avoid long-term toxicity from topical medications. As the name implies, MIGS techniques are associated with lower complication rates along with better preservation of the conjunctiva compared with conventional filtering surgeries. MIGS procedures use one of four IOP-reducing mechanisms: (1) Trabectome (Neomedix, Tustin, CA, USA), iStent (Gliakos Corporation, Laguna Hills, CA, USA), Hydrus Microstent (Ivantis, Inc, Irvine, CA, USA), gonioscopy-assisted transluminal trabeculotomy, and excimer laser trabeculotomy all increase outflow by bypassing the juxtaocular trabecular meshwork; (2) suprachoroidal shunts (eg, Cypass micro-stent; Transcend Medical, Menlo Park, CA, USA) increase uveoscleral outflow; (3) endocyclophotocoagulation reduces aqueous production from the ciliary body; and (4) subconjunctival filtration (eg, XEN gel stent; Aquesys, Inc., Aliso Viejo, CA, USA) creates a subconjunctival drainage route.

Patients with very aggressive or refractory glaucoma, (eg, pressure in the 30s or 40s despite multiple medications and/or prior surgeries) may be good candidates for MDCPC. This procedure effectively destroys the ciliary processes where aqueous is produced and possibly increases uveoscleral outflow. It differs from traditional transscleral CPC in that the energy pattern delivered is delivered as a micropulse instead of a continuous wave, resulting in less inflammation and effective IOP-lowering with less risk of hypotony. An effect is typically seen within a few weeks of the procedure, with maximal effect at about 6 to 8 weeks. If the resulting IOP drop is suboptimal, the procedure can be repeated, giving it an advantage over more invasive techniques.

**POST-SURGICAL MONITORING**

Patients who have undergone surgery of any kind need to be followed carefully to ensure a satisfactory outcome. For less invasive procedures such as MIGS, follow-up may be scheduled for day one following surgery, then at one week, two weeks, one month, three months, and so on, assuming everything goes well. For patients undergoing traditional filtering surgeries, follow-up needs to be a bit more frequent—usually at day one and then day five following surgery to start—to assure that healing is proceeding as expected. If the eye heals too aggressively, the scleral flap may stick down or scar, resulting in a failed surgery. Especially in the first six or so weeks following a filtering procedure, I usually keep the surgeon informed of how the patient is doing at each visit.

Understanding the mechanics of the post-surgical eye is critical to managing patients in the postoperative phase. For patients who have undergone trabeculectomy, which involves creation of a scleral flap, there is a balance between managing postoperative inflammation in the conjunctiva—which may result in healing of the scleral flap and a failed surgery—and managing IOP, which can vary in the first couple weeks following surgery. It is fairly common to see a paradoxical rise in IOP in the first week following trabeculectomy due to a blood clot near the flap or taut scleral flap sutures. The natural reflex of the doctor co-managing a patient with this scenario might be to attempt to lower IOP by using an ocular hypotensive medication; however, doing so reduces the rate of aqueous flow through the scleral flap and will increase the chances of the flap sealing off, causing surgical failure. Rather than medicating, a moderately high IOP at this stage should be managed by performing either gentle digital massage or cotton-tip massage at the slit lamp, targeting the limbus adja-
Inflammation—a natural response to surgical trauma—must also be well controlled with antiinflammatory agents, typically topical ocular corticosteroids, since inflammation can interfere with the patency of the flap. Increasing corticosteroids early in the postoperative period to an eye with a mildly increased IOP following surgery may feel counterintuitive, since corticosteroids are known to induce ocular hypertension. For postoperative patients with increased IOP, then, one might be tempted to taper corticosteroids, which would be the wrong approach if excessive inflammation is compromising outflow through the scleral flap and causing the IOP rise. A better choice would be to maintain or increase the corticosteroid frequency, perform digital or cotton-tip massage to manipulate fluid flow via the trabeculectomy site, and monitor the patient closely. Again, proper handling of these patients early in the postoperative period is critical to their surgical success. Good communication between the co-managing optometrist and surgeon is critical to patients’ success.

GAINING EXPERIENCE

Of 40,000 optometrists in the US, perhaps only a few hundred specialize in glaucoma care in tertiary care centers. But a significant proportion, perhaps 10% to 15%, are actively co-managing glaucoma alongside their ophthalmology colleagues and retaining patients in their practices throughout the course of disease. That proportion will likely grow over time.

Optometrists who have referred glaucoma patients for surgery and wish to gain experience in postoperative care might call on that surgeon and request the chance to shadow them through an OR and postoperative day. This would be invaluable for understanding why certain procedures are chosen and performed, and it is very helpful in understanding how the anatomy of the eye is altered by surgery.

CONCLUSION

Caring for glaucoma patients involves managing a disease that may progress over months to years, despite medical therapy. It is useful to think well ahead and inform your patient early on about surgical options. This plants the seed early on and makes the decision to move to surgery may be a smooth and less scary experience for the patient, should it become necessary.

REFERENCES


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1. Which of the following mechanism of action has been associated with latanoprostene bunod?
   A. Increased trabecular outflow
   B. Decreased aqueous production
   C. Increased uveoscleral outflow
   D. Both A and C

2. Which of the following is true regarding selective laser trabeculoplasty (SLT)?
   A. Induces less collateral damage to trabecular cells compared with ALT
   B. Is administered in pulsed waves
   C. Is associated with better long-term outcomes compared with trabeculectomy
   D. Is NOT a type of MIGS

3. Which of the following should be included in the first mention of potential glaucoma surgery to patients?
   A. Importance of stopping glaucoma progression
   B. Limited success with past medications
   C. That they can participate in their treatment decisions
   D. All of the above

4. Which of the following is the common target of the new glaucoma drugs being developed?
   A. Trabecular aqueous outflow
   B. Uveoscleral aqueous outflow
   C. Aqueous production
   D. Episcleral venous pressure

5. Which of the following patients will be best suited for the new sustained-release therapies?
   A. Patients with target pressure controlled by topical agents
   B. Patients with normal tension glaucoma
   C. Patients who do not adhere to prescribed regimen
   D. Patients with advanced glaucoma

6. Which of the following statement about PGAs is NOT true?
   A. They lower IOP by improving uveoscleral outflow
   B. They lack systemic side effects
   C. They are adequate as monotherapy for IOP control in most patients
   D. They have better adherence than other commonly used glaucoma drugs

7. Which is true regarding IOP in the first few weeks following trabeculectomy?
   A. High IOP requires additional hypotensive medication
   B. Very low IOP is needed to prevent hypotony
   C. IOP rise may be addressed using gentle massage
   D. All of the above

8. Which of the following systemic conditions is a contraindication for beta-blockers?
   A. Asthma
   B. Bradycardia
   C. Chronic obstructive pulmonary disease
   D. All of the above

9. Which of the following is NOT within the scope of practice of an experienced and well-trained optometrist?
   A. Making a diagnosis of glaucoma
   B. Modifying antiglaucoma medical therapy
   C. Placing a subconjunctival stent
   D. Post-trabeculoplasty follow-up

10. Which of the following is NOT a class of MIGS?
    A. Increased outflow by bypassing the trabecular meshwork
    B. Destruction of a portion of trabecular meshwork cells
    C. Subconjunctival filtration
    D. Reduced aqueous from the ciliary body

To take the test online and obtain CE credit for this activity, go to http://www.neco.edu/academics/continuing-education/online-ce/key-issues-glaucoma.