First-line Glaucoma Therapy: Choices and Challenges

Tony Realini, MD, MPH

Since their first introduction, topical prostaglandin analogs have been the preferred first choice for the treatment of glaucoma. Today, these agents’ role as the optimal first-line IOP-lowering therapy is coming under challenge from the emergence of alternate and new therapeutic options.

Glucoma therapy, once started, is usually continued through the rest of a patient’s lifetime. Ideally, the goal is to keep the disease asymptomatic over time, but that is not always possible. In reality, the main goal of glaucoma therapy is to prevent significant loss of visual function to minimize reductions in quality of life.

At present, the only established approach to achieving this treatment goal is to lower intraocular pressure (IOP). Major clinical studies have demonstrated that IOP reduction can prevent or delay progression of glaucomatous optic nerve damage and visual field loss. These beneficial effects are achieved with all forms of IOP-lowering treatment—medications, laser therapy, or surgery. By convention, the standard initial treatment for patients with open-angle glaucoma (OAG) is medical.

THE DECISION TO TREAT

Although evidence from population-based studies supports the benefit of IOP-lowering therapy, the decision to initiate treatment is a serious one that should be made together by the physician and patient on an individual basis. While the vast majority of patients with newly diagnosed OAG receive treatment, there are rare exceptions where early glaucoma may become clinically irrelevant, such as when the patient is very old and frail or young yet seriously ill.

Some patients with OAG may progress slowly or not at all. The Early Manifest Glaucoma Trial showed that, while IOP-lowering therapy cuts the risk of progression by half, more than one third of OAG patients did not progress without treatment over a 5-year period of time. Treatment to lower IOP may be unnecessary for those at minimal progression risk, but for physicians, the clinical challenge is to identify who these patients are. At this time, our ability to reliably predict progression and therefore determine the likelihood of a patient benefiting from treatment is still limited. Glaucoma is known to have significant economic consequences thanks to treatment cost, poor adherence, medication drop-out, and a growing patient population. Even so, because today’s glaucoma therapy is benign and well-tolerated as a whole, the burden of treatment has become relatively low—even in cases that are of questionable therapeutic benefit.
SETTING GOALS FOR TREATMENT

There are several factors that can influence choice of therapy for the individual glaucoma patient. The first one to consider is the stage of disease: the more advanced the glaucoma is, the more aggressive the treatment should be in order to prevent further visual function decline. The baseline level of IOP, a predictive factor for glaucoma progression, is also important in determining the magnitude of IOP reduction needed. As with many other diseases, how we aggressively treat is inversely proportional to the glaucoma patient’s age. Younger patients are usually treated at least as aggressively, if not more, as the older patients, because they will likely live longer with the disease and thus have a longer lifetime risk of losing vision.

Patients who have had faster progression rates in the past certainly need more aggressive therapy. When deciding how aggressive to be in lowering IOP, I also factor in the status of the fellow eye and any family history of glaucoma, vision loss, or blindness. Since a comprehensive risk assessment tool is not readily available to determine a patient’s global risk for progression, physicians should subjectively collect and evaluate all relevant information on a patient-by-patient basis before making therapeutic decisions.

There is not a fixed magic number for target pressure—it differs from individual to individual and, for each individual, changes from time to time as the risk profile changes. My general approach is to aim for low, mid, or high teens depending on whether the patient’s risk of progression or stage of the disease is advanced, moderate, or early, respectively, though there are exceptions. Patients who come in with a low pressure, for example, need a lower target IOP, whereas patients with a higher IOP at baseline may do well with a higher target pressure.

CURRENT FIRST-LINE AGENTS

For medical glaucoma therapy, pros- taglandin analogs (PGAs) have been the first-line agents of choice because they are highly efficacious, well-tolerated, and conveniently dosed once daily. They have minimal systemic side effects, and their most common ocular side effects—conjunctival hyperemia, iris darkening, eyelashes elongation, and periocular skin pigmentation—are nothing more serious than cosmetic changes. Patients with hazel eyes might warrant extra caution, because they are most likely to develop an iris color change. When a patient is to be treated in only one of the eyes, it is important to keep in mind that the appearance-
related side effects, if occurring, can be markedly more noticeable in one eye instead of both.

The PGAs available in the US include latanoprost, bimatoprost, travoprost, and tafluprost. These agents are generally equivalent in efficacy, and the choices for individual patients are often based on unique features of each formulation. Latanoprost, for example, is the only PGA commercially available in a generic form, which has a cost advantage for self-pay patients or patients who have high deductibles for brand-name medications. Tafluprost, available as a preservative-free formulation, may be of benefit in cases where ocular surface health is of paramount concern. After reformulation, travoprost now contains an ionic buffered preservative system instead of benzalkonium chloride (BAK). For patients with BAK intolerance, both travoprost and tafluprost would make reasonable choices.

LASER THERAPY AS FIRST CHOICE

One effective yet underrecognized first-line treatment option for patients with OAG is selective laser trabeculoplasty (SLT). The laser procedure is simple, safe, and, as several recent clinical studies found, as effective as a prostaglandin in lowering IOP.\(^{11-14}\) While most of these studies were conducted in patients of European descent, data from an Afro-Caribbean population suggests that SLT is also highly effective in people of African descent.\(^{11}\) The nonresponder rate to SLT is similar to that of medications, about 10% to 15%.\(^{15}\)

With comparable IOP-lowering efficacy, SLT offers several benefits that medical therapy does not. There are no long-term tolerability issues, and adherence is not an issue. The procedure has few adverse effects, including mild anterior chamber inflammation and discomfort and, in some cases, a brief IOP spike. Because there is no more need to use daily eye drops, laser therapy may turn out to be less expensive in the long run.\(^{16}\) One recent study in patients with newly diagnosed OAG shows that, when medication nonadherence is accounted for, laser trabeculoplasty is indeed more cost-effective than medications.\(^{17}\) With better cost-effectiveness, SLT makes a logical option as primary therapy, especially in countries where the average patients have limited access to glaucoma medications.

A MULTI-TIERED APPROACH

Much like its predecessor (ie, argon laser trabeculoplasty or ALT), however, SLT has not been readily adopted as first-line intervention for glaucoma. In my practice, I recommend SLT as a first-line choice to all of my newly diagnosed patients in whom it would be appropriate; and I would personally opt for laser therapy as a first-line treatment if I developed glaucoma. It is true that the choice of treatment is ultimately up to the patient, but the fact is that patients will never be as informed as physicians are. When they look to us for guidance and ask how we would choose, which patients often do, it is important for us to speak our minds. I would personally choose to have SLT first, and that is what I tell my patients. Most of them then decide that they want the same.

My own algorithm for treating OAG starts with either SLT or a PGA, whichever the patient prefers, followed by the other. If SLT is performed initially and does not adequately control pressure, I add a PGA. Similarly, if a PGA as the first therapy is insufficient, then I recommend SLT. When both are employed and still more pressure lowering is needed, I would add carbonic anhydrase inhibitors (CAIs) because they have been shown to provide the best available IOP control as an adjunct to a prostaglandin.\(^{18}\) Sometimes I use a fixed combination in place of a CAI as my first adjunct for additional pressure reduction. The choice depends on how far away the patient is from achieving the target pressure.

When monitoring treatment progress, careful clinical examination of the optic nerve is most important. Everything else, including visual field testing and optical coherence tomography (OCT), should be an adjunct rather than a substitute. That said, visual field testing is valuable because it is the only way for us to see what the patients see and do not see. For the most part, I rely on clinical examination and visual field testing—in addition to IOP measurements—to assess disease status and the effect of treatment.

LOOKING AHEAD

One of the most challenging obstacles to successful medical glaucoma therapy is adherence. Even with once-a-day, well-tolerated prostaglandins, adherence is significantly suboptimal among glaucoma patients.\(^{19}\) There is an enormous, unmet need for therapies that can be administered less often than once a day, which again lends substantial support to the usefulness of SLT as first-line treatment. The laser procedure takes only minutes to accomplish; its duration of action, however, lasts for months to years,\(^{20}\) and is repeatable when its effect wanes.
After years of research and development, the pharmaceutical pipeline for glaucoma now has several new medications on the verge of entering the market. Among these, latanoprostene bunod (Bausch + Lomb) is the only one that has produced statistically significantly greater IOP reduction than latanoprost in patients with OAG in clinical studies, showing great potential for use as a first-line treatment.20 The nitric oxide-donating PGA is anticipated to be available in early 2017. Another new drug that will probably come out in 2017 is netarsudil mesylate (Aerie), a Rho kinase inhibitor. Since netarsudil mesylate was shown to be effective only in patients with relatively low baseline pressures in one of its pivotal trials,21 its place in glaucoma therapy is somewhat unclear in the absence of any clinical experience with it. A third new compound, trabodenoson (Inotek), is an adenosine A1 receptor agonist currently in phase 3 clinical trials.

Another valuable addition to the treatment options for glaucoma would be devices that provide sustained-release of a PGA or some other agent over a longer period of time. There are several types of such sustained-release systems that are being evaluated in phase 2 and 3 clinical trials. These include punctal plugs, a polymer conjunctival insert, and injectable depts. Important questions remain regarding how effective these devices are, how long their effects last, and eventually what their role in glaucoma management might be. Presumably sustained-release therapy could provide better diurnal pressure control and help overcome adherence issues.

Tony Realini, MD, MPH, is professor of ophthalmology at West Virginia University in Morgantown, WV. Dr. Realini has received grant/research support from Alcon and Aerie Pharmaceuticals. He is also a consultant for Alcon, Bausch + Lomb, Inotek Pharmaceuticals, and Smith & Nephew. Medical writer Ying Guo, MBBS, assisted in the preparation of this manuscript.

REFERENCES
The Association Between Myopia and Glaucoma

Terri L. Young, MD, MBA

More than just an optically correctable inconvenience, myopic refractive error is increasingly being considered an ocular disorder. A greater understanding of the risk this highly prevalent condition presents—including for glaucoma—has led to an increased need for clinicians to monitor myopes more closely for early pathologic changes.

Myopia is the most common form of ocular refractive error ( ametropia), in which alterations in the curvature and thickness of the cornea and lens, depth of the anterior chamber, and axial length of the globe cause convergence of light anterior to the retinal plane and thus “nearsighted” vision. This condition affects approximately 1.6 billion people globally (representing approximately 22% of the population) and is anticipated to increase in prevalence to 2.5 billion by 2020. Myopia typically accelerates during the teenage years. There is a notably higher prevalence in children of East and Southeast Asian ethnicity (42.7% and 59.1% in 12- and 17-year-old children, respectively) compared to children of European Caucasian ethnicity (8.3% and 17.7%, respectively). Near-work activities—such as reading, writing, computer use, and playing video games—were thought to contribute to the development of myopia by leading to constant ciliary muscle contraction and hindrance of correct accommodation, to which the eye responds by elongating at a higher rate. More recently, less time spent outdoors has also been implicated (the “light-dopamine theory”) since increased light intensity stimulates dopamine release, which in turn reduces axial elongation of the eye.

Teenage and adult-onset myopia is typically characterized by an axial length of <26 mm and milder refractive errors of up to ~5 diopters (D). These forms are distinguished from the more severe condition of high (or pathologic) myopia, accounting for 27-33% of all myopic patients, in which extreme refractive errors of ≥ –6.00D and an axial length of >26 mm are associated with progressive degenerative changes of the fundus, optic disc deformation, retinal thinning, and choroidal atrophy. These clinical manifestations predispose greater risk to the individual of developing ocular morbidities, notably macular degeneration, retinal detachment, cataract, and glaucoma. It is concerning that the prevalence of myopia ≥ –8.00D has risen eightfold over the last 30 years.

MYOPIA: A GLAUCOMA RISK FACTOR

Glaucoma is a heterogeneous group of progressive blinding disorders that result from pressure-induced stresses within the lamina cribrosa and peripapillary sclera at the optic nerve head, causing optic nerve cupping, atrophy of the retinal ganglion cells (RGC), and retinal nerve fiber layer (RNFL) loss. The ocular risk factors for developing glaucoma include increased intraocular pressure (IOP), exfoliation syndrome, pigment dispersion, myopia, reduced central corneal thickness, larger optic disc diameter, and increased visibility in disc crescents. The association between myopia and glaucoma is well established, with 6% to 29% of primary open-angle glaucoma (POAG) patients reporting concurrent myopia. Population-based studies have shown that the odds of developing glaucoma rise with increasing severity of myopia. The pooled odds ratio (OR) for glaucoma and low myopia (≤ 3.00D) association is 1.65; for glaucoma and moderate-to-high myopia (>3.00D), the association is 2.46. Increased axial length (>26 mm) is cited as the most important contributing factor for the development of glaucoma in myopes. A recent study by Shen et al noted that myopia was associated with an increased prevalence of all forms of open-angle glaucoma and ocular hypertension whereas hyperopia was associated with a substantially increased prevalence of progressive angle closure glaucoma. Although high myopia is a strong risk factor for glaucoma subtypes, low and moderate myopia also have a significant effect on glaucoma risk. Additionally, there were moderate racial differences in the association of myopia with the risk of POAG and normal tension glaucoma. However, animal studies confirm that a complexity of factors relating to thickness, composition, and biomechanical behaviour of the sclera may influence risk, particularly the differential ability of circumferentially orientated collagen and elastin fibers to protect against IOP-induced expansion of the scleral canal within the optic nerve head-associated peripapillary sclera.
MECHANISMS OF MYOPIC GLAUCOMA

The mechanisms by which a myopic condition predisposes to glaucomatous development are not completely understood. However, two principal theories attempt to explain the progressive damage to RGC. The mechanical theory purports that damage to the lamina cribrosa, where RGC axons exit the eye, leads to RCG atrophy and glaucomatous optic neuropathy, whether induced by increased IOP and a tensile sclera or by exacerbated shearing forces due to a longer axial eye length (in the absence of elevated IOP).

The vascular theory considers glaucomatous optic neuropathy as a consequence of insufficient ocular perfusion secondary to increased IOP or other risk factors. One important factor implicated in the vascular theory is the diminished ability of the retina, as a result of myopia-associated retinal pigment epithelium (RPE) and choroid atrophy, to access molecules fundamental for its functioning, thus causing oxidative stress. Certainly, increased generation of reactive oxygen species and/or reduced antioxidant protection mechanisms are known to play a pathogenic role in POAG; and the high oxygen demands of the retina coupled with its high polyunsaturated fatty acid content make this tissue susceptible to oxidative stress.

Animal studies are unravelling the implication of genotype in myopia-associated glaucoma. Five main growth factors are important in high myopia, namely transforming growth factor-β, basic fibroblast growth factor, insulin-like growth factor, vascular endothelial growth factor, and hepatocyte growth factor. The low-density lipoprotein receptor-related protein 2 (LRP2), which is an endocytic receptor for a wide variety of signalling molecules active in developmental pathways and expressed in RPE cells and ciliary epithelial cells, has also been implicated. The zebrafish mutant bugeye, which exhibits nonsense mutations in LRP2, exhibits a phenotype that includes increased IOP, enlarged eye globes with significant refractive errors, decreased retinal neuron density, activation of RGC stress genes and distinct axon pathology at the optic nerve head (Figure 1).

MYOPIA VS EARLY GLAUCOMA

While the association between myopia and glaucoma is unrefuted, there are inherent challenges in differentiating between early stage glaucoma and “normal” myopia.

Assessment of IOP alone can prove ambiguous for identifying glaucoma in high myopic patients due to the fact that IOP is significantly dependent on corneal thickness. Corneal thickness varies according to ethnic group, and is characteristically thin in myopic eyes (making them more likely to test negative for IOP elevation). Differences in biomechanical properties of the cornea conferred (in part) by corneal thickness may have an impact on IOP measurement (and thus accuracy of using IOP when screening for glaucoma). The optic disks of many high myopia patients are accompanied by tilt, torsional or pale appearance, or peripapillary atrophy leading to pseudo-glaucomatous visual field defects. The need for a systematic approach to estimate association between myopia and glaucoma will be addressed with consensus use of the Disc Damage Likelihood Scale, a new system for estimating the relationship between optic disc size, neuroretinal rim, and cup/disc ratio and assessing glaucomatous damage of the optic disc in correlation with the degree of visual field loss.

High-definition spectral-domain optical coherence tomography (SD-OCT) is a valuable aid for detection of early glaucomatous changes, as it provides visualization of a thinning circumpapillary retinal nerve fiber layer (cp-RNFL), a traditional indicator of glaucoma. However, a thin cp-RNFL is also a clinical feature of the enlarged eyes and stretched retinas implicit in high myopia. Since retinal thinning typically occurs in the peripheral but not central areas, assessment of macular

FIGURE 1 Adult bugeye zebrafish have enlarged eye globes with significant refractive error, thinned retinas, and elevated intraocular pressure without iridocorneal angle obstruction or malformation. A,C Dorsal views of adult wild-type (A) and bugeye (C) zebrafish. B,D Histology of central retina sections at 6 months in wild-type (B) and mutant (D) eyes. E–H Histology of wild-type (E,F) and bugeye mutant (G,H) iridocorneal angles in the dorsal region (E,G) or at the ventral canaliculair aqueous humor drainage region (F,H). I Intraocular pressures (IOP) in adult wild-type and bugeye zebrafish. IOPs in bugeye fish were elevated compared to age and size matched fish from TL wild-type stain (p<0.0001, t-test). Scale bars: A,C=4 mm; B,D=50 mm; EH=40 mm. (From: Veth KN, Willer JR, Collery RF, et al. Mutations in Zebrafish lrp2 Result in Adult-Onset Ocular Pathogenesis That Models Myopia and Other Risk Factors for Glaucoma. PLoS Genet. 7(2): e1001310.)
measurements such as the ganglion cell complex and ganglion cell inner plexiform layer, which are not influenced by myopic thinning of the cp-RNFL, are proving to have superior diagnostic value for identifying glaucomatous changes in high myopic eyes. 17

FUTURE DIRECTIONS

Early detection of any pathology provides the greatest potential for prevention; this pertains equally to myopia and myopia-related glaucoma. Interventions to control excessive ocular growth and limit myopic progression are under investigation. One approach involves ocular strategies such as varifocals, bifocals, and novel contact lens design, as it appears eye growth responds to optical cues. Another approach is based on behavioral strategies such as modified ergonomics in the classroom, in which curbed computer monitors/work stations recreate the optics of outside viewing. The use of atropine has been shown to reduce the rate of axial elongation; however, in view of rebound growth once treatment ceases and concerns of long-term side effects, further studies are investigating lower-dose formulations of atropine and other muscarinic antagonists. Consideration is also being given to the combination of interventions such as medicated contact lenses. 18

One of the most important approaches for monitoring early glaucoma changes in high myopes is to perform routine visual field testing, a relatively simple test that is arguably underused in current clinical practice. At present, ophthalmologists may err on the side of performing visual field tests only when excessive optic nerve cupping or asymmetry in the optic nerve cupping between two eyes is apparent. Similarly, the initial response to visual changes may be to provide a new glasses or contact lens prescription rather than proceeding with glaucoma testing.

Therapeutic approaches for myopic patients who have early glaucomatous changes do not necessarily differ from what would be advised for glaucoma in non-myopic patients. While administration of topical IOP-lowering medications or surgery would be indicated, there may be consideration given to taking an earlier, more invasive surgical approach than for non-myopes; however, there are no studies available at present to support this course of action. Future approaches will likely be based upon a better understanding and subsequent control of scleral biomechanics. Influencing the synthesis and organization of collagen and elastin fibers in the posterior sclera may provide a therapeutic avenue to distend the peripapillary sclera and prevent further optic nerve cupping and RGC loss.

The application of genome-wide association studies such as the International Glaucoma Genetics Consortium (IGGC) 19 and Consortium for Refractive Error in Myopia (CREAM) 20 show great potential for increasing our understanding of the genetic associations between refractive errors and risk for glaucoma development. The ultimate aim of these and other studies is to provide a platform for identifying genetic markers that identify those at most risk for developing these conditions and to also provide information as to which therapeutic strategies are most likely to be effective in thwarting myopic development, or preventing its co-morbidities such as glaucoma.

Terri L. Young, MD, MBA, is the department chair of ophthalmology and visual science and Peter A. Duehr Professor of ophthalmology, pediatrics, and medical genetics at the University of Wisconsin, Madison. She states that in the past 12 months, due to increased central corneal thickness. Graefes Arch Clin Exp Ophthalmol. 1999;237(3):229-4.


This CME program is sponsored by the University of Florida College of Medicine and supported by an unrestricted educational grant from Bausch + Lomb, Inc. DIRECTIONS: Select the one best answer to each question in the exam (Questions 1–10) and in the evaluation (Questions 11–16) below by circling one letter for each answer. Participants must score at least 80% on the questions and complete the entire Evaluation section on the form below. The University of Florida College of Medicine designates this enduring material for a maximum of 1 AMA PRA Category 1 Credit™. There is no fee to participate in this activity. You can take the test online at http://cme.ufl.edu/self-study/tig/.

1. Which statement is correct regarding glaucoma diagnosis in myopic eyes?
   A. A thin circumpapillary retinal nerve fibre layer is the most reliable indicator of glaucomatous changes
   B. The ganglion cell complex is influenced by myopic thinning of the cp-RNFL
   C. The ganglion cell-inner plexiform layer alone is the best indicator of myopic thinning
   D. Macular measurements have superior diagnostic value over cp-RNFL

2. According to Dr. Realini, which of the following is most important for monitoring treatment progress in glaucoma patients?
   A. Clinical evaluation of the optic nerve
   B. IOP measurements
   C. Visual field testing
   D. OCT

3. Compared with medical therapy, SLT is:
   A. Equally effective in lowering IOP
   B. Insusceptible to nonadherence
   C. More cost-effective
   D. All of the above

4. What are potential future interventions for preventing myopia-associated glaucoma?
   A. Therapeutics to target collagen and elastin fiber organization in the sclera
   B. High-dose atropine
   C. Anti-vascular endothelial cell growth factor monoclonal antibodies
   D. Minimally invasive glaucoma devices to decrease aqueous outflow

5. High (pathologic) myopia predisposes individuals to which ocular pathologies?
   A. Development of refractive errors ≤ –6D and an axial length of >26 mm
   B. Optic disc deformation, retinal thinning, and choroidal atrophy
   C. Age-related macular degeneration, retinal detachment, cataract, and glaucoma
   D. Thinning circumpapillary retinal nerve fiber layer, POAG, and uveitis

6. Which of the following should be taken into consideration when choosing a first-line prostaglandin agent?
   A. Preservative intolerance
   B. Ocular surface health
   C. Insurance coverage
   D. All of the above

7. Which of the following is a result of the Early Manifest Glaucoma Trial?
   A. IOP-lowering therapy reduced the risk of glaucoma progression by half
   B. More than a third OAG patients did not progress without treatment
   C. SLT was as effective as medical therapy in patients with OAG
   D. Both A and B

8. Increased axial eye length may cause which of the following?
   A. Damage to the lamina cribrosa and RGC loss
   B. Decreased scleral tension
   C. Atrophy of the corneal epithelium
   D. Increased synthesis of collagen and elastin fibers in the peripapillary sclera

9. What is the current and projected prevalence of myopia worldwide?
   A. ~1.6 million (22% of the population) and 2.6 billion by 2020
   B. ~22% of the population
   C. ~1.6 million and 2.6 billion by 2030
   D. ~22% of the population and 2.6 billion by 2030

10. Which method does Dr. Realini recommend for determining the magnitude of IOP reduction in glaucoma therapy?
    A. Calculate with the established formula based on global risk assessment
    B. Estimate based on stage of the disease and risk of progression
    C. Aim for an initial 25% IOP reduction for all new patients
    D. None of the above

If you wish to receive credit for this activity, please fill in the following information. Retain a copy for your records.

PLEASE PRINT CLEARLY

FIRST NAME     LAST NAME   DEGREE

ORGANIZATION/INSTITUTE

ADDRESS LINE 1

ADDRESS LINE 2

CITY     STATE    ZIP

PHONE     FAX

E-MAIL ADDRESS