Therapeutic Strategies for Glaucoma

An overview of the available treatments.

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The treatment of glaucoma has progressed significantly over the past 10 years, but the basic tenets remain the same. The only treatment proven to lower IOP and to slow the progression of visual field loss is the administration of topical eye drops. Hypotensive agents therefore remain the predominant first-line treatment for glaucoma. Although surgery can also lower IOP effectively, this option is usually reserved for patients who do not respond to medical therapy. This article reviews the current state of medical and surgical therapy for glaucoma and discusses how clinicians are using available resources to preserve patients' vision.

MONOTHERAPY

Primary monotherapy with prostaglandin analogues has enhanced patients' ability to control their IOPs with a single dose of medication at bedtime. In addition, this class of drugs is less likely to induce systemic side effects than other hypotensive drugs. For example, beta-blockers are contraindicated in patients who have cardiac or respiratory conditions. Nevertheless, physicians can still prescribe monotherapy with once- or twice-daily beta-blockers to control the IOP of patients who cannot tolerate prostaglandin analogues or who have conditions (eg, uveitic glaucoma) that contraindicate the use of this class of drugs.

ALTERNATIVE AGENTS

If patients do not respond to monotherapy, a variety of medications are available to help control their IOP. Adjunctive agents include twice- or thrice-daily doses of alpha-agonists and carbonic anhydrase inhibitors. Miotic agents are used less frequently and are reserved for patients who can tolerate the drugs' ocular side effects. Finally, oral carbonic anhydrase inhibitors such as acetazolamide and methazolamide fill a therapeutic niche, particularly when used to resolve acute angle closure and other conditions that cause IOP spikes.

Most recently, the introduction of fixed-combination agents such as Combigan (timolol-brimonidine; Allergan, Inc., Irvine, CA) and a generic version of Cosopt (timolol-dorzolamide; Merck & Co., Whitehouse Station, NJ) has changed how physicians use and prescribe IOP-lowering drugs. Compared with concomitant treatment with brimonidine and a beta-blocker, Combigan causes fewer side effects.[1] In addition, patients benefit from the convenience of instilling one drop versus two separate ones.

The availability of a generic fixed combination of timolol and dorzolamide has raised some concerns among clinicians. In some cases, insurance plans and pharmacies substitute Cosopt for the generic formulation, often without consulting the patient or the prescribing ophthalmologist. Although the generic version is usually less expensive than but chemically equivalent to Cosopt, its therapeutic equivalence remains untested. Anecdotal reports suggest that the generic fixed combination controls IOP less effectively than the branded formulation and that it may be associated with a higher incidence of side effects. In many cases, however, patients who use both versions appear to have equivalent IOPs during office examinations.

Unfortunately, the FDA holds generic ophthalmic drugs to a lower formulary standard, and the agency does not require manufacturers to test for therapeutic equivalency to the branded product. Despite the requirement that a drug's active ingredient and formulation meet specific standards to be considered a formulary equivalent, the approved formulation may still differ from the branded product. How these differences affect the efficacy of the generic product and the incidence of adverse events is generally unknown until the drug has been used widely. Physicians must ensure that all the ocular hypotensive medications they prescribe, even alternative formulations, lower IOP effectively. At the same time, clinicians must continually weigh the costs and benefits of different drugs for individual patients.

The continued development of generic IOP-lowering medications (Table 1) provides greater flexibility in the cost of drugs that may translate into improved adherence. Given a choice, patients may purchase and administer medications that are less burdensome on their financial resources.

TABLE 1. AVAILABILITY OF GENERIC GLAUCOMA DRUGS

Class	Brand Name	Generic Available
Alpha-2 agonists (AA)	Alphagan P	Yes[a]
Beta-blockers (BB)	Betagan/Timoptic	Yes
Carbonic anhydrase inhibitors (CAI)	Azopt/Trusopt	Yes[b]
Prostaglandin analogues	Lumigan/Travatan/Xalatan	No
Fixed-combination BB and CAI	Cosopt	Yes
Fixed-combination AA and BB	Combigan	No

Abbreviation: AA; alpha-2 agonist; BB, beta-blockers; CAI, carbonic anhydrase inhibitor.
[a]Generic brimonidine 0.2% currently available; brimonidine 0.15% pending; brimonidine 0.1% not under development.
[b]Generic dorzolamide (Trusopt) currently available; brinzolamide (Azopt) not available.
Note: Azopt and Travatan (Alcon Laboratories, Inc., Fort Worth, TX); Alphagan P, Betagan, Lumigan, and Combigan (Allergan, Inc., Irvine, CA); Timoptic, Trusopt, and Cosopt (Merck & Co., Inc., Whitehouse Station, NJ); Xalatan (Pfizer, New York, NY).

SURGICAL THERAPY

When patients do not respond to medical therapy, physicians face difficult decisions about how to proceed. In recent years, ophthalmologists have increasingly treated glaucoma with selective laser trabeculoplasty. The Glaucoma Laser Trial showed that argon laser trabeculoplasty and medical therapy lowered IOP with similar efficacy over the term of the study. The median treatment effect of 2 years, however, has limited trabeculoplasty's role as a primary treatment in the minds of most glaucoma specialists.[2,3] Nonetheless, selective laser trabeculoplasty is an effective treatment option for patients whose glaucoma is rapidly advancing despite maximally tolerated medical therapy. Of course, maximally tolerated medical therapy is really maximally optimized medical therapy, as clinicians consider side effects, cost, adherence, convenience, and other factors.

Should medical and laser therapy be insufficient, additional treatment options include trabeculectomy and the placement of a tube shunt, with or without the adjunctive use of mitomycin C or 5-fluorouracil. Research has shown that other antifibrotic agents such as p38, as well as antibodies to transforming growth factor and vascular endothelial growth factor (eg, bevacizumab), are promising for preventing fibrosis and bleb failure.[4,5]

Additionally, alternative surgical interventions such as canaloplasty, the Ex-Press mini glaucoma shunt (Optonol Ltd., Neve Ilan, Israel), the Trabectome (NeoMedix Corporation, Tustin, CA), and endoscopic cyclophotocoagulation are available for patients whose disease is refractory to medical therapy. By focusing on the outflow and production of aqueous, these procedures lower IOP while avoiding some of the complications that commonly occur with trabeculectomy and tube shunts.

CONCLUSION

Although the field of glaucoma has not changed fundamentally in the past decade, the available options for medical and surgical treatment have grown tremendously. An expanded armamentarium will allow physicians to offer care that meets patients' specific needs. ■

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1. Sherwood MB, Craven ER, Chou C, et al. Twice-daily 0.2% brimonidine-0.5%/timolol fixed-combination therapy vs. monotherapy with timolol or brimonidine in patients with glaucoma and ocular hypertension: a 12-month randomized trial. Arch Ophthalmol. 2006;124:1230-1238.
2. Glaucoma Laser Trial Research Group. The Glaucoma Laser Trial (GLT). 2. Results of argon laser trabeculoplasty vs. topical medicines. Ophthalmology. 1990;97:1403-1413.
3. Glaucoma Laser Trial Research Group. The Glaucoma Laser Trial (GLT) and Glaucoma Laser Trial Followup Study: 7. Results. Am J Ophthalmology. 1995;120(6):718-731.
4. Grewal DS, Jain R, Kumar H, Grewal SP. Evaluation of subconjunctival bevacizumab as an adjunct to trabeculectomy: a pilot study. Ophthalmology. 2008;115(12):2141-2145.
5. Myer-ter-Ven T, Gebhardt S, Sebald W. et al. P38 inhibitors prevent TGF-beta-induced myofibroblast transdifferentiation in human tenon fibroblasts. Invest Ophthalmol Vis Sci. 2006;47:1500-1509.