Current Management of Glaucoma and the Need for Complete Therapy

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Abstract

Glaucoma is a long-term ocular neuropathy defined by optic disc or retinal nerve fiber structural abnormalities and visual field abnormality. Primary open-angle glaucoma is the most common type of glaucoma. Currently available treatments, initiated in a stepwise process, focus on intraocular pressure (IOP) reduction, and initially include topical drug therapy (single then multidrug combinations), followed by laser then surgical treatment. Topical prostaglandin analogues or beta-adrenergic receptor blockers are first used, followed by alpha-agonists or topical carbonic anhydrase inhibitors, and infrequently, cholinergic agonists and oral therapy. Limitations to existing topical IOP-reducing medications include continued disease progression in glaucoma patients with normal IOP, treatment failure, and low rates of compliance and persistence. Therapeutic agents under investigation include neuroprotectants, which target the disease process manifested by death of retinal ganglion cells, axonal loss, and irreversible loss of vision. Neuroprotectants may be used alone or in combination with IOP-reducing therapy (a treatment strategy called *complete therapy*). Memantine, an *N*-methyl-D-aspartate receptor blocker currently approved for dementia, is the neuroprotectant farthest along in the process seeking regulatory approval for glaucoma treatment and has a favorable safety profile because of its selective mechanism of action. Several other neuroprotectants are in early stage investigation. Complete therapy provides hope for improved outcomes by reducing the significant morbidity and economic consequences that occur as a result of neurodegeneration and disease progression.

(Am J Manag Care. 2008;14:S20-S27)

The definition and management of glaucoma have changed substantially over the past 3 decades, but several evolving treatment paradigms have not yet moved into clinical practice.[1] These include a widespread recognition that glaucoma is a neuropathy of the optic nerve rather than a disease of elevated intraocular pressure (IOP) as well as a diminishing reliance on a minimum IOP as the primary treatment goal.[2] Advances in the study of glaucoma neuroprotectants have made these issues more clinically relevant.

Significance of Glaucoma to Managed Care

About one half of the 2.2 million Americans with open-angle glaucoma are unaware of their disease, since they do not have ocular or systemic symptoms.[3-5] The visual impairment resulting from progressive glaucoma is irreversible.[6] Loss of peripheral vision, depth perception, and contrast sensitivity associated with this optic neuropathy can have a major effect on an individual's life.[7-12] For example, injuries from automobile accidents and falls because of visual impairments are greater in patients with glaucoma.[13-15] End-stage glaucoma is associated with appreciable resource utilization and costs because of the need for both vision rehabilitation and ophthalmology care.[16] Glaucoma patients may also be at increased risk for depression.[17] These factors may lead to increased costs of care for managing glaucoma as well as for concomitant morbidities.

Despite abundant evidence that early detection and optimal management of glaucoma are the best ways of preserving sight and reducing economic consequences,[18,19] the National Committee for Quality Assurance (NCQA) reports that approximately 40% of Medicare beneficiaries enrolled by participating plans do not undergo screening for glaucoma.[20] Moreover, as agents used to treat ocular conditions constitute a relatively small proportion of overall pharmaceutical spending, ocular conditions and ophthalmic products remain one of the least managed areas of pharmaceutical care.[21]

To address these disparities, several health policy and quality-of-care initiatives have recently been implemented. These include the 2005 Health Plan Employer Data and Information Set measure for glaucoma screening[22]; expanded glaucoma-specific preventive benefits for Medicare beneficiaries[23]; and specific glaucoma prevention, detection, and management objectives in *Healthy People 2010*.[24]

Glaucoma is primarily a disease of aging,[6] and this population is increasingly being covered under managed care plans as a result of the advent of the Medicare Modernization Act of 2003 (known as Medicare Part D). Therefore, managed care decision-makers are reprioritizing glaucoma as a disease that is being actively managed for their covered population.

This article will review the current treatment options for the most common type of glaucoma, known as primary open-angle glaucoma (POAG), explore the rationale for new therapies directed at preventing vision loss (neuroprotectants), and describe a new paradigm in managing POAG using complete therapy directed at the full pathophysiology of the disease.

Clinical Controversy: Beyond IOP

POAG is a long-term ocular disease process that is generally bilateral and often asymmetric.[2] It is defined by optic disc or retinal nerve fiber structural abnormalities and visual field abnormality as detected by optic disc examination and visual field testing.[1,2] The most definitive evidence of glaucoma is documented, progressive change in optic disc appearance and reproducible worsening in automated visual field testing.[1] Structural alterations of the optic nerve or nerve fiber layer more frequently occur prior to visual field abnormalities or visual defects, although the opposite may be seen.[25]

There is strong evidence that IOP plays an important role in the neuropathy of POAG,[2,26-28] and it has been shown that a reduction in the level of IOP lessens the risk of visual field progression in open-angle glaucoma.[29-32] Previously, an IOP of more than 21 mm Hg in adults was generally accepted as being significantly raised.[33,34] In the Advanced Glaucoma Intervention Study associative analysis, patients with 100% of their visits with IOPs less than 18 mm Hg over 6 years had mean changes from baseline in visual field defect score close to zero during follow-up, whereas patients with less than 50% of visits with IOPs less than 18 mm Hg had an estimated worsening over follow-up of 0.63 unit of visual field defect score (P = .083).[35] More recently, a minimum IOP target level has been replaced by the goal to lower IOP by a percentage reduction from baseline, typically 25% to 30%, or even greater when there is substantial damage already present in the visual field.[36] Therefore, there is no IOP maximum level criterion used in the definition of open-angle glaucoma.[2]

The relationship between elevated IOP and glaucomatous optic neuropathy is highly variable,[2] and there are unresolved questions regarding the relationship between IOP control and visual field damage. Up to 10% of patients with elevated IOP show signs of visual field loss,[37] and up to 61% of patients with low IOP (≤21 mm Hg) show glaucomatous disc and vision field changes.[26,37-39] Additionally, there is an ongoing controversy regarding which aspect of IOP is most important in progression: mean IOP over time, fluctuation (diurnal vs visit-to-visit) of IOP over time, or peak pressure over a designated level.[29,35,40-43] Further challenging reliance on IOP levels is the fact that population-based screening for glaucoma using IOP measurement is not clinically or cost-effective because of low sensitivity and specificity of the test.[44] About half of all individuals with POAG have IOP levels less than 22 mm Hg, the usual screening cutoff.[45]

However, the practice of glaucoma screening routinely combines direct examination with IOP measurement.[2,46] A Netherlands-based Markov cost-effectiveness simulation model of patients aged at least 40 years visiting an ophthalmic practice (where all patients were subject to ophthalmoscopy, but tonometry was performed on (1) all initial patients, (2) high-risk patients only, or (3) no one) found it most cost-effective to routinely perform tonometry to all initial ophthalmic patients to prevent blindness as a result of glaucoma.[47] Moreover, a US-based cost-effectiveness model of screening at-risk members demonstrated a positive return on investment for commercial and Medicare managed care populations.[48] These cost-effectiveness data further support the rationale for the Medicare glaucoma screening benefit and the NCQA biannual requirement of glaucoma screening for Medicare members aged 65 years and older.[22,46]

Current Treatment Options

These clinical debates have led to a reassessment of the role of the current treatment options for glaucoma directed at lowering IOP as well as consideration of the need for glaucoma therapies that address

the optic neurodegenerative disease processes. Clinical practice guidelines for POAG have been developed by the American Academy of Ophthalmology (AAO),[2] although several recent studies have indicated low compliance with these guidelines in various practice sites.[49,50] The treatment goals, according to the AAO practice guidelines (2005), include achieving stable optic nerve or retinal fiber layer status, controlled IOP, and stable visual fields while maintaining quality of life.[2] Treatment plans are often difficult to implement because the disease is frequently asymptomatic, long term, and typically requires multiple medications.[51]

The AAO Preferred Practice Pattern notes that laser trabeculoplasty is an appropriate initial therapeutic alternative (Evidence A-I) to topical medications.[2] However, most clinicians initiate with medical therapy, followed by laser, filtering, and cyclodestructive surgery (alone or in combination), and the stepwise process reflects the safety and efficacy of the treatments for the individual patient.[2,52]

Conventional treatment within typical clinical practice usually begins with the use of topical antiglaucoma medications, with an initial trial in the eye with higher IOP. Pressure measurements are taken, and the clinician attempts to distinguish between therapeutic impact and normal IOP fluctuation.[53] Multiple drug classes may be used, generally added sequentially for their complementary contribution to IOP reduction.[2] Examples of eyedrops for first-line therapy include topical cardioselective, $beta_1$-adrenergic (eg, betaxolol) or noncardioselective beta-adrenergic (eg, timolol, levobunolol, metipranolol, carteolol) receptor blockers, or topical prostaglandin analogues (eg, latanoprost, bimatoprost, travoprost, unoprostone).[2] Beta-blockers, which reduce IOP by decreasing aqueous humor formation in the eye, are used as first-line treatment because they have relatively few ocular adverse effects, can be used once or twice daily, and do not affect pupil size or accommodation. They may have ocular, respiratory, cardiac, and certain central nervous system side effects.[53] Prostaglandin analogues are highly potent at reducing IOP by increasing aqueous humor outflow in the eye. They have few systemic side effects, can be used once daily while maintaining good 24-hour control, and do not affect pupil size or accommodation, although they do have certain adverse ocular effects (eg, iris pigmentation changes, eyelash hypertrichosis, and ocular inflammation). Prostaglandin analogues (specifically bimatoprost, latanoprost, and travoprost) have been shown to be superior, or at least as effective, in reducing IOP as timololol, the gold standard (2003).[54-60] In addition, they are theoretically more effective for prevention of acute IOP spikes because of their mechanism for increasing aqueous humor outflow rather than suppressing production.[61]

Second-line treatments include alpha-agonists (eg, brimonidine) and topical carbonic anhydrase inhibitors (eg, dorzolamide, brinzolamide). They are typically administered 2 to 3 times daily and have few systemic side effects, but they may cause ocular irritation. Alpha-agonists work by increasing uveoscleral outflow of aqueous humor,[61] and the newer, more specific $alpha_2$ agonists (eg, brimonidine, apraclonidine) have fewer systemic hypotensive side effects than earlier alpha-adrenergic agonists. Brimonidine is used for long-term sustained therapy, whereas apraclonidine is most useful for short-term adjunctive use.[61] Carbonic anhydrase inhibitors decrease aqueous humor production via enzymatic inhibition.[61] These may replace or be added to beta-blocker or prostaglandin analogue therapy to further lower IOP.[2,52] Combination drugs (eg, beta-blockers with a carbonic anhydrase inhibitor, alpha-agonists, or a prostaglandin analogue) may be used to improve compliance.[62]

Third- or fourth-line treatments include cholinergic agonists, most commonly pilocarpine or carbachol. These miotic agents lower IOP by increasing conventional trabecular outflow.[61] Although efficacious, these parasympathomimetic agents have certain side effects, such as induced myopia and headache, difficulty in evaluating optic disk and visual field because of pupillary constriction and possible cataract formation, cystoid macular edema, or retinal tears or detachments. In addition, these need to be administered 3 or 4 times daily.[52] Systemic (orally administered) agents, such as the carbonic anhydrase inhibitors acetazolamide and methazolamide, may be added to the regimen if the IOP is uncontrolled with topical agents or if acute elevations of IOP occur, such as in acute angle-closure glaucoma. Oral carbonic anhydrase inhibitors also have untoward side effects, such as lethargy, loss of appetite, periph-

eral paresthesias, nephrolithiasis, and potentially fatal aplastic anemia or autoimmune reactions. Epinephrine, a nonspecific adrenergic agonist, is rarely used today, although it has a long history for glaucoma use.[61]

Several clinical trials have evaluated the use of laser first[63,64] or incisional surgery first,[43] and results were comparable to initiating with medical therapy. The selected approach should be based on the risks and benefits of the antiglaucoma medications for a particular patient.[2] Laser therapy (trabeculoplasty) may be used to reduce resistance to the outflow of aqueous humor. Surgical therapy includes filtering or cyclodestructive surgery.[2] The failure rate of filtering surgery is 20% to 30%, and many patients may require re-operation.[2] Cyclodestructive surgery is often reserved for eyes with reduced visual acuity and patients who are poor candidates for incisional surgery, although it is being performed more commonly and does have certain advantages over laser filtration surgery.[2]

Therapy Failure Leads to Unmet Need

The existing medications for glaucoma lead to a significant unmet need because of therapy failure, which may lead to disease progression. For many, particularly those taking topical eyedrops, therapy fails because of poor compliance and persistence, although simplified regimens with once- or twice-daily administration provides improved compliance. Recent research in a managed care organization indicated that more than 50% of patients in a health maintenance organization did not refill their initial eyedrop prescription by 1 year after diagnosis.[51] Among participants in a US government health plan, with minimal cost to obtain drugs, 25% of newly diagnosed open-angle glaucoma subjects never filled the second prescription.[65] Another study showed that patients received their eyedrop glaucoma therapy only 7 of 10 days on average.[66] Persistence of therapy is also a significant concern.[67] Other causes of therapy failure include delayed efficacy and systemic side effects of IOP-reducing treatments[68] as well as lack of diurnal control.[42,69]

It is known that early diagnosis and treatment can reduce vision loss in some patients, but there is a significant unmet need in glaucoma management because of the risk of disease progression in patients with normal IOP. Treated patients undergo visual field worsening (4% per year).[1,70,71] The risk of blindness in 1 eye is as high as 27%,[72] and up to 13% of patients with glaucoma continue to manifest progressive optic nerve atrophy and concomitant visual field loss on a permanent basis.[29,41,70,73,74]

Future Treatment Options: Complete Therapy

As an optic neuropathy, glaucoma is manifested by death of retinal ganglion cells (RGCs), axonal loss, and an irreversible loss of vision.[75] The evolving definition of glaucoma from one of elevated IOP to one characterized by an IOP-sensitive, progressive optic neuropathy has brought a focus on the role of neuroprotectants in the management of the disease process. Such neuroprotectants would not replace but rather would be used in conjunction with IOP-reducing therapy to provide a complete therapy for glaucoma management. Complete therapy including a neuroprotectant would provide doubly targeted treatment for patients with IOP-dependent glaucoma. It would also potentially reduce the rate of disease progression in patients with uncontrolled IOP or when progression occurs even with IOP at acceptable levels. If the deleterious consequences of glaucoma progression can be minimized by complete therapy, then the economic and clinical burden of the disease[16,76,77] to the patient and payer will be reduced.

Neuroprotectants in Development

Neuroprotection strategies include preventing or slowing the death of RGCs and/or enhancing blood flow to the optic nerve, thereby reducing the development of glaucomatous optic neuropathy. No medications have been approved for neuroprotection. However, several oral neuroprotective drugs that block *N*-methyl-D-aspartate (NMDA)-sensitive glutamate receptors have been investigated. These include memantine, an NMDA receptor blocker currently approved for the treatment of dementia, and riluzole, a glutamate regulator approved for amyotrophic lateral sclerosis.[75] Another possibility is dextromethorphan, a weakened form of a main narcotic ingredient used in cough syrups. Memantine is in the final stage (phase 3) of the required clinical trial sequence that leads to US Food and Drug Administration (FDA) review for possible approval, whereas riluzole and

dextromethorphan have yet to move beyond preclinical investigation.

The safety and efficacy of memantine for prevention of open-angle glaucoma progression are currently being evaluated in a phase 3, randomized, multicenter, placebo-controlled, double-blind clinical trial. Patient recruitment ended in 2001 with more than 500 patients in this study.[78] The favorable safety profile for memantine is likely because of its mechanism of action, whereby it preferentially blocks NMDA receptor activity.[78] According to the package insert for memantine,[79] side effects for use in Alzheimer's disease are low, and the most common adverse events reported (≥5% and higher than placebo) were dizziness, confusion, headache, and constipation. Memantine is also being studied in vascular dementia, diabetic neuropathic pain, and HIV-associated dementia.[80]

Other classes of drugs are also being investigated for glaucoma neuroprotection.[81] Brimonidine is a selective alpha-adrenergic agonist currently used topically to decrease IOP. It has also been examined in preclinical models and early clinical trials for its neuroprotective properties, although results are not conclusive in humans.[82-85] Glatimir, an injectable agent administered subcutaneously and approved for multiple sclerosis, is undergoing experimental research in glaucoma.[52] Other agents under investigation include erythropoietin[86]; glial cell line–derived neurotrophic factor[87]; a glaucoma vaccine with Cop-1, an FDA-approved drug for multiple sclerosis[88]; and other agents directed at lowering IOP (eg, oral carbenoxolone and cannabinoid agonists).[61]

Agents that enhance ocular blood flow being investigated include dorzolamide, a topical carbonic anhydrase inhibitor currently approved for glaucoma, which has been shown to increase retinal artery flow velocities[89]; and betaxolol, which has been shown to increase blood flow velocity in the optic nerve head tissue.[90] Improvements have been made in measuring ocular blood flow velocity, but measurement difficulties still persist.[91]

The ability to measure human neuroprotection is fundamentally linked to the clinical measurement of glaucoma progression, and there is research being conducted to identify markers that are reproducible, sensitive, specific, and valid.[92,93] New imaging and visual techniques are being developed and tested to detect ganglion cell damage at the early stages.[61] Until end points and markers are determined, measurements of the clinical utility of such neuroprotectants may not be as informative.

Conclusion

Management of POAG is moving beyond a focus on IOP reduction to a recognition that glaucoma is a neurodegenerative disease. With current treatment paradigms, a significant minority of patients experience progression and worsening of the visual field. Existing therapeutic options for glaucoma that are directed at IOP may be complemented by new neuroprotectants that focus on preventing neuronal loss, thereby reducing disease progression and blindness. Memantine is one of the most promising neuroprotectants for glaucoma because it has the most advanced clinical trial data (phase 3) required for FDA approval and has a favorable safety profile as a result of its selective mechanism of action. Complete therapy provides hope that glaucoma outcomes can be improved by reducing the significant morbidity and economic consequences that occur because of neurodegeneration and disease progression.

Acknowledgment

Laurie Kozbelt assisted in the preparation of this manuscript.

Author Affiliations: From Duke University Medical Center, Durham, NC; Goldberg, MD & Associates, Battle Ground, WA; Xcenda, Palm Harbor, FL; Allergan, Inc, Irvine, CA.

Funding Source: The research and manuscript were funded by Allergan, Inc.

Author Disclosures: The authors (SJM, LDG) received honoraria from Allergan, Inc; the author (PP) received compensation from Xcenda, which is a consultant to Allergan, Inc; the author (JGW) is employed by Allergan, Inc; the author (TJB) is employed by Xcenda.

Authorship Information: Concept and design (SJM, LDG, PP, JGW, TJB); acquisition of data (SJM, LDG, PP, JGW, TJB); analysis and interpretation of data (SJM, LDG, PP, JGW, TJB); drafting of the manuscript (SJM, LDG, PP); critical revision of the manuscript for important intellectual content (SMJ, LDG, PP) and supervision (SMJ, LDG, TJB).

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