Current Therapeutic Options and Treatments in Development for the Management of Primary Open-Angle Glaucoma

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Glaucoma: Definition and Associated Risk Factors

Glaucoma comprises a heterogeneous group of chronic, progressive, optic neuropathies characterized by loss of retinal ganglion cells and their axons. Glaucoma results in visual impairment and is the second leading cause of irreversible blindness worldwide.[1,2] Primary open-angle glaucoma (POAG) is the most common type of glaucoma, and is estimated to account for approximately 90% of cases of glaucoma in North America.[3,4] Because symptoms of POAG do not manifest until the disease process is already in advanced stages, and because the progression of disease occurs gradually over the course of many years, POAG is sometimes referred to as the "silent thief of sight."[5]

Current management guidelines from the American Academy of Ophthalmology Preferred Practice Pattern cite several important risk factors for POAG, including advanced age, African American and Latino/Hispanic ethnicity, elevated intraocular pressure (IOP), family history of glaucoma, low ocular perfusion pressure (OPP), type 2 diabetes, myopia, and having a thinner central cornea.[2]
OPP is defined as the difference between arterial blood pressure and the IOP. Although further investigation is needed, it is thought that low OPP alters blood flow at the optic nerve head, contributing to glaucomatous damage to the optic nerve.[2] Importantly, while glaucoma is associated with several risk factors that contribute to damage and disease progression, IOP is the only proven modifiable risk factor at this time.[3]

Burden of Glaucoma

Disease Burden

Globally, glaucoma affects 3.5% of adults 40 to 80 years of age (POAG 3.1% plus angle closure glaucoma [ACG] 0.5%).[4] With the average age increasing worldwide, the incidence of glaucoma in this population of adults is projected to increase by 74% from 2013 to 2040.[4] With this increase in prevalence of glaucoma, the consequences of glaucoma in terms of vision loss are also expected to grow. Worldwide, the number of people experiencing bilateral blindness from primary glaucoma is expected to reach 11.1 million by 2020.[6]

The increasing burden of glaucoma has important implications for the United States health care system. The CDC estimates that in 2015, 2.2 million Americans 40 years and older (about 2% of the population) had

40 years and older is expected to increase to 7.32 million individuals, a nearly 3-fold increase from the incidence of POAG from 2011.[8]

The prevalence of POAG is highest among individuals of Latino/Hispanic and African heritage.[8] In a 2016 meta-analysis by Kapetanakis et al, researchers estimated the prevalence of POAG among those aged 65 years to be 6.4% and 4.0% in patients of African descent and Latino patients, respectively, versus a prevalence of 2.0% among those of European descent.[9] Moreover, in an adjusted analysis, the risk of developing POAG increases by a factor of 2.3 with each advancing decade among Hispanic patients versus a factor of 1.6 among patients of African descent, and a factor of 2.0 among those of European descent.[9] The Hispanic/Latino population is estimated to contribute to the greatest number of individuals with POAG in the United States over the next 4 decades.[8]

POAG is characterized by an asymptomatic onset, where patients do not present with symptoms until significant visual loss occurs in late stages of the disease. As patients do not have symptoms until visual damage has already occurred, many cases remain undiagnosed and untreated.[2] The National Health and Nutrition Examination Survey published in 2014 found approximately 2.4 million individuals in the United States (2.9% of the US population) had undiagnosed and untreated glaucoma, suggesting that 78% of glaucoma was untreated and undiagnosed.[10] The rate of undiagnosed and untreated glaucoma is estimated to be 85% for blacks, 81% for Hispanics, and 73% for non-Hispanic whites.[10]

Economic Burden

As a chronic and progressive disease, glaucoma poses a substantial burden to the healthcare system. Management of glaucoma has direct medical costs (eg, visits to providers, tests, medications, and surgery), direct nonmedical costs (eg, home healthcare, and transportation), and indirect costs (eg, loss of productivity for both patient and caregiver).[2]

According to a Prevent Blindness study, the $6 billion spent annually in 2014 on the direct costs of glaucoma care is expected to reach $12 billion by 2032, and exceed $17 billion by 2050.[11,12]

Medicare beneficiaries with glaucoma had higher mean annual total healthcare costs compared with those without glaucoma, and more severe cases of glaucoma in Medicare beneficiaries are associated with higher direct annual costs. One study found that the mean annual total cost of healthcare per patient was $16,760 among Medicare beneficiaries aged 65 years and older with glaucoma versus $13,094 for Medicare beneficiaries without glaucoma. The cost increased by severity of disease. Those with visual disability had costs of $18,073, while those without visual disability had costs of $15,829. In this population, the primary drivers of cost were physician services, inpatient care, and prescription medications.[13]

Current Management Options and Unmet Needs

Within the eye, the balance between the production of aqueous humor in the ciliary tissue and outflow of

the unconventional (ie, uveoscleral) pathways functions to maintain an IOP of approximately 10 to 21 mm Hg.[14-18] Current therapies are aimed at either enhancing the outflow of aqueous humor via the unconventional or uveoscleral pathway, or by decreasing the production of aqueous humor.[19] Although muscarinic cholinergic agonists may enhance outflow of aqueous humor through the trabecular meshwork by contracting the ciliary muscle, these agents are used infrequently as they may cause blurry vision and myopia and are subject to adherence challenges (they may be administered up to 4 times daily).[3,14,20] As a result, in practice, there is a lack of agents that target the conventional pathway.[3,20] Existing mechanisms are illustrated in Figure 1.[19] Although several mechanisms for IOP-lowering are available, no treatment is available to repair or regenerate optic nerve damage in patients with glaucoma. The goal of POAG management is to lower IOP, since elevated IOP is the only known modifiable risk factor for progressive disease leading to blindness.[20,21] However, lowering IOP may not be sufficient to prevent vision loss, highlighting the need for new agents with new mechanisms of action and perhaps more effective IOP lowering.[1]

Management of glaucoma includes control of IOP to a target pressure of at least a 25% reduction which has been shown to slow progression of POAG. However, an IOP target sufficient to reduce IOP by more than 25% may be selected if there is more severe optic nerve damage, damage is increasing rapidly, or the patient has the risk factors indicated previously. A higher IOP target may be acceptable for patients who do not tolerate treatments or have a limited life expectancy.[2] Of note, approximately one-third to one-half of patients with POAG do not have elevated IOP—a condition known as normal tension glaucoma (NTG).[1,22] NTG is characterized by ocular damage and vision loss at statistically normal intraocular pressure levels (maximum IOP <21 mm Hg). Treatment for patients with NTG also aims to reduce IOP; a 30% reduction of IOP in patients with NTG was shown to slow the rate of visual field progression.[23,24] However, patients with NTG may have difficulty achieving substantial IOP reductions given their low baseline IOP. Additional IOP-lowering is a challenge for patients with NTG in comparison to patients with elevated IOP.[23]

The usual steps for treating glaucoma include the use of instilled medications (eye drops). If pharmacologic treatment is not sufficiently effective, surgical procedures may be required; these include laser surgery (trabeculoplasty or cycloablation), traditional surgery (trabeculectomy), or other procedures (eg, shunts or canaloplasty).[25] As indicated previously, available instilled ophthalmic preparations used in clinical practice are limited to agents that reduce IOP either through reduction of aqueous humor production or by facilitating aqueous humor drainage (uveoscleral outflow). Although muscarinic agonists indirectly target the conventional outflow pathway by contracting the ciliary muscle to widen and promote outflow through the trabecular meshwork/Schlemm's canal, as of this writing, there are no agents directly targeting the conventional outflow pathway or agents that impact both conventional and unconventional pathways.[3,14,20] As of this writing, there are no available agents targeting both conventional and unconventional outflow pathways for IOP lowering.[3,14]

Management With IOP-Reducing Therapy

onset in patients with ocular hypertension (OHT) and use of pharmacologic and surgical therapies reduces the risk of disease progression and vision loss in patients with glaucoma.[20] In the 1636-patient Ocular Hypertension Treatment Study (OHTS), topical ocular hypotensive medication was effective in delaying or preventing onset of POAG over 60 months of follow-up (POAG incidence was 4.4% in the treatment group vs 9.5% in the observation group; HR 0.40; 95% CI, 0.27-0.59; P <.001).[26] Similarly, 48-month results of the Early Manifest Glaucoma Treatment study demonstrated a 49% risk of visual field progression in the control group versus a 30% risk of progression in the treatment group, corresponding with a treatment difference of 19% (95% CI, 7%-23%; P = .004).[27] Results of the Ocular Hypertension Treatment Study and the Early Manifest Glaucoma Treatment study suggested a 10% risk reduction for every 1 mm Hg reduction in IOP.[28,29] More recently, in a follow-up analysis of data reported by Garway-Heath et al, it was estimated that each 1 mm Hg reduction in IOP reduced the risk of visual field deterioration by approximately 19%.[30,27] Results of several landmark randomized multicenter clinical trials demonstrating effects of IOP lowering in patients with POAG are summarized in Table 1.[20,23,26,27,30-33]

IOP-lowering therapy is also effective at delaying progression of disease in patients without elevated IOP (NTG). NTG is characterized by ocular damage and vision loss at statistically normal IOP levels.[23,24] In the Collaborative Normal Tension Glaucoma Study, 140 patients with NTG received IOP-lowering medical or surgical treatment in 1 eye. When IOP was lowered by 30% (the treatment target in this study), the treated eyes had a slower rate of visual field progression than untreated eyes.[23]

Unmet Needs in Glaucoma Therapy

As indicated above, most pharmacologic agents that lower IOP act by either reducing aqueous humor production or by increasing outflow/drainage of aqueous humor from the eye primarily through the uveoscleral pathway.[2,14] There is an unmet need for tolerable treatments that target the conventional (trabecular meshwork/Schlemm's canal) outflow pathway, and for therapies that target both conventional and unconventional outflow pathways. The trabecular meshwork tissue is diseased in glaucoma presenting increased resistance to aqueous outflow, and is therefore responsible for elevated IOP in POAG.[17,34] Current therapies do not target the conventional outflow pathway, leaving a potentially important modality for IOP reduction largely unused.[34]

Evaluation and treatment of IOP can be complicated by variability of IOP between eyes as well as diurnal and nocturnal variations. IOP tends to rise at night when individuals are supine, and peaks around 5:30 am. Therefore, daytime office measurements may underestimate IOP levels, and may miss spikes in IOP.[24] With treatments administered during the morning hours, nocturnal IOP elevations may be uncontrolled, which may result in overestimation of treatment efficacy, uncontrolled IOP elevation, and an increased risk of glaucomatous damage.

Another unmet need is the challenge of adherence in patients receiving complex glaucoma treatment regimens.[35]

decreased.[36,37] Adherence is expected to be better for simple regimens.[36] In one study of patients newly initiating prostaglandin therapy for glaucoma, 25% of patients received 1 or 2 prescription fills of adjunctive therapy added on to prostaglandin therapy. Of these patients, slightly more than one-fourth (26%) continued therapy with a different agent, and the remaining 74% discontinued therapy entirely.[38] In order to improve adherence to IOP-lowering therapy, there is a need for novel effective agents with simple treatment regimens (ie, once-daily dosing and single agent) for the management of glaucoma, especially in the population ineffectively managed with combination therapies.[36] Patients may potentially achieve more consistent effects of treatment, and overall greater effectiveness in glaucoma management with convenient regimens.[35]

Pharmacologic Options for Glaucoma Management

A reasonable objective for initial treatment of patients with POAG is to reduce IOP by 20% to 30% below baseline. This target IOP is an estimate of treatment needed to lower the risk of disease progression and protect vision. An IOP may be adjusted up or down, as indicated by risk factors present, stage of glaucomatous damage or disease severity, and progression or aggressiveness during long-term monitoring. Therefore, management in IOP reduction should be individualized to patient needs over the course of disease and is subject to change.[2]

Prostaglandin analogs are considered first-line therapy for POAG. They increase uveoscleral outflow, effectively lower IOP, are usually well-tolerated, can be dosed once a day, and also act during the night when IOP levels may be more elevated.[39] These agents bind to prostaglandin receptors; they alter the expression of matrix metalloproteinases (MMPs) and increase uveoscleral outflow, lowering IOP.[14]

Currently, latanoprost is the most prescribed prostaglandin analog in the United States.[40] In pivotal phase 3 trials of latanoprost conducted in the United States, the United Kingdom, and Scandinavia, latanoprost reduced baseline diurnal IOP over 6 months of treatment by a mean of 6.7 mm Hg, 8.5 mm Hg, and 8.0 mm Hg, respectively.[41] In a later trial evaluating the efficacy of latanoprost compared with placebo in lowering IOP and preserving vision, the treatment was evaluated in 516 patients with newly diagnosed open-angle glaucoma (OAG). At baseline, 44% of the treatment group and 49% of the control group had IOP levels ≥20 mm Hg. At 24 months, the mean reduction in IOP was 3.8 mm Hg in the latanoprost-treated group and 0.9 mm Hg in the placebo group. At 24 months, visual field preservation was significantly better in patients treated with IOP-lowering therapy compared with placebo (HR 0.44; 95% CI, 0.28-0.69; $P = .0003$). None of the 18 serious adverse events observed in the latanoprost-treated group were attributed to the drug.[30]

The IOP lowering activity of prostaglandin analogs and other important classes of therapies used as single agents in the treatment of glaucoma is summarized in Table 2.[2,19] These agents include the following:

Prostaglandin analogs act by increasing outflow through the uveoscleral (unconventional) pathway. Adverse events may include conjunctival hyperemia, hyperpigmentation of the iris and eyelashes, increased eyelash

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