Disease Progression and the Need for Neuroprotection in Glaucoma Management

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Abstract

Glaucoma, the second leading cause of worldwide blindness, is a progressive optic neuropathy characterized by a loss of retinal ganglion cells and their axons beyond typical age-related baseline loss. Diagnosis is defined by optic disc and visual field changes, and the primary goal of glaucoma treatment is to preserve vision. Proven existing therapies (ie, pharmacotherapy, laser, and surgical) focus on reduction of intraocular pressure (IOP), although elevated IOP is no longer a diagnostic feature of glaucoma. New neuroprotectant drugs are being investigated, with the goal of reducing retinal ganglion cell loss, either prophylactically or after the insult has occurred. Various treatment strategies are being evaluated, and include a neuroprotectant only, or a complete therapy approach comprised of both a neuroprotectant supplemented by an IOP-lowering therapy. Dually targeted complete therapy may directly preserve the optic nerve, decrease the risk factors that cause glaucoma damage, and reduce glaucoma-related morbidities. Neuroprotectant therapy outcomes should include functional and structural effects of disease progression and neuroprotectant therapies, as well as patient functioning and economic impact.

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Glaucoma is a multifactorial, progressive optic neuropathy with a characteristic loss of retinal ganglion cells (RGCs) beyond typical age-related baseline loss and the second leading cause of blindness in the world.[1] Prevalence models estimate that 8.4 million individuals will suffer from glaucoma-induced bilateral blindness in 2010, rising to 11.1 million in 2020.[2] In the United States, blindness from glaucoma has been estimated to cost $1.5 billion annually in benefits, lost tax revenues, and health expenses.[3] Glaucoma-related vision loss, particularly in field of vision, is asymptomatic in the early stages and irreversible.[4] As a result, a significant proportion of patients are undiagnosed; thus, economic and clinical scopes are larger than the numbers suggest.[5] Population-based screening is not recommended,[6] and although there are no known ways to prevent glaucoma, early detection in high-risk individuals and treatment help prevent progression and vision loss.[6,7]

Elevated intraocular pressure (IOP) is an important risk factor for glaucoma that has remained a clinical focus for several reasons, including ease of measurement, the number of available IOP-reducing therapies, and the relationship of elevated IOP to disease progression.[8] However, the relationship between IOP reduction and glaucoma damage is less clear,[9-11] and such ambiguities suggest that factors other than IOP may be responsible for some of the long-term damage from glaucoma. Further complicating the issue is the current debate over which measurement of IOP (diurnal, peak, visit-to-visit) is the most significant contributor to disease progression and subsequent vision loss.[12-14] In particular, central corneal thickness has also been shown to be associated with disease progression in open-angle glaucoma,[15] which accounts for 90% of glaucoma cases.[16]

Glaucoma is no longer diagnosed by elevated IOP levels,[7,17] and it is now recognized as a neuropathy defined by characteristic optic disc and visual field change.[18] The absence of reliance on IOP level as a diagnostic criterion has occurred because 20% to 30% of glaucoma patients have IOP in the normal range (typically 10-21 mm Hg).[19,20] Furthermore, the annual progression rate is 9% to 10% even in patients treated with IOP-lowering medical, laser, or surgical therapy.[21-27] The Early Manifest Glaucoma Trial[28,29] found that although the mean IOP during follow-up was significantly associated with the risk of progression, this risk was highly variable, and several other

baseline factors were significant independent predictors whose combined effect might be as important as IOP. These additional independent predictors included presence of bilateral disease, worse mean deviation, degree of baseline exfoliation, age older than 68 years, presence of frequent disc hemorrhages, and duration between follow-up visits.[28-30] The Ocular Hypertension Treatment Study found a relationship between IOP reduction and glaucoma incidence[10]; however, progression was not confirmed in 85% of cases.[31] The Collaborative Normal-Tension Glaucoma Study found that visual field progression could occur in both treated and untreated normal tension glaucoma patients, and no study analyses detected a relationship between a change in the IOP and visual field progression.[32,33] This clinical evidence of continued disease progression despite IOP management has provided the basis for proposed alternative risk factors and treatment approaches that could modify the clinical course of glaucoma.

The primary goal of glaucoma treatment is to preserve vision.[7] However, because current knowledge of the factors causing optic nerve damage and visual loss is limited, the predominant focus of therapy is to reduce IOP while maintaining patient quality of life.[7,17] Currently, IOP-lowering therapies (ie, pharmacotherapy, laser, or surgical) are the only proven treatment available. Recent advances in topical medications that more effectively control IOP have diminished the need for surgical intervention.[34] Despite these improvements, multiple medications are often needed to control the disease,[34] and disease progression continues to occur. A multidrug approach may be useful, which includes agents targeted toward lowering IOP as well as an agent directed at preserving and protecting the optic nerve from glaucomatous damage.

Glaucoma: A Neurodegenerative Disease

Neurodegenerative diseases include a variety of heterogeneous disorders such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and glaucoma.[35] All neurodegenerative diseases are characterized by excitotoxic cell death, which contributes to neuronal cell injury and death. Excitotoxicity is caused, in part, by overstimulation of *N*-methyl-D-aspartate–type glutamate receptors and excessive calcium ion influx, which cause free radical formation.[35] Most neurons and glial cells contain high concentrations of glutamate, the major excitatory neurotransmitter in the brain, and glutamate-mediated synaptic transmission is critical for normal functioning of the nervous system. If neurons or glial cells are injured and unable to properly control regulation or clearance of glutamate, secondary damage can result, even if the primary cause of the disease is not related to glutamate. Injured neurons are more vulnerable to even normal levels of glutamate, and become overstimulated and die.[35]

Glaucoma is the most common optic neuropathy. For more than 60 years, it has been known that excitotoxicity occurs in RGCs.[35] The disease is characterized by a progressive decrease in the numbers of RGCs and their axons when nerve fibers, at the point where the optic nerve exits the eye, become pinched and die. This condition leads to thinning of the neural rim and progressive enlargement of the optic nerve cup.[35,36] After loss of more than 40% of the nerve fibers, patients may notice a gradual loss of peripheral vision, or "tunnel vision."[7,16,37,38] This vision loss is permanent.[7]

Neuroprotective Therapy

Therapies directed at neuronal loss, either prophylactically or after the insult has occurred, are currently being investigated.[39] The target is RGC loss, not the elevated IOP that indirectly causes the death of the RGC.[34] By strict definition, a neuroprotectant is directed at the neuron itself.[39]

There are many treatment strategies being evaluated. One includes a neuroprotectant only, whereas a complete therapy management approach includes a neuroprotective agent supplemented by an IOP-lowering therapy. This dually targeted therapy would provide several potential benefits, including direct preservation of the optic nerve, decreasing one of the most important factors that cause glaucoma damage, and potentially reducing the significant economic[40,41] and quality-of-life[42,43] consequences associated with disease progression.

Developments in Assessing Neuroprotection Outcomes in Glaucoma

Glaucoma is a slowly progressing, long-term disease. Because of a significant amount of redundancy in the retina, particularly in the ganglion cell layer, a substantial dysfunction or loss in RGCs is

required to clinically detect reduced retinal sensitivity.[34] Glaucoma progression is currently measured by event-based progression at predefined end points, but these are limited by the fact that most patients do not reach an efficacy end point.[44] Rate-based progression defined glaucoma progression as a function of parameter-based change over time and, today, is not widely used.[44] Visual field (a functional end point) testing is limited by the variability in results,[5] but multiple tests are used to reduce the variability and increase specificity.[44] Tests such as the Short Wavelength Automated Perimetry and Frequency Doubling Technology (FDT) are available that detect abnormalities in the visual field in patients with early or mild glaucomatous damage but who have normal results on Standard Automated Perimetry.[34,45-47] The FDT may also be used as a potential screening test for early-stage glaucoma by selectively targeting the function of magnocellular ganglion cells.[34,47]

Neuroprotection therapy is fundamentally linked to neuronal death; therefore, outcomes should also assess this end point.[39,48,49] Some evaluations aim to detect ganglion cell damage at an early stage using quantitative morphologic evaluation of RGC layers,[48] nerve fiber layer and focal thickness, size of the neuroretinal rim, and number of ganglion cells or axons.[5,39]

It is also important to assess patient-reported functional outcomes as they relate to therapies for neuroprotection, including health-related quality of life (HRQOL) using vision-specific, glaucoma-specific, and generic instruments. Numerous evaluations have demonstrated that HRQOL is reduced in glaucoma as a result of visual impairment and its relationship to patient functioning.[42,50,51] Furthermore, HRQOL instruments should assess patient-reported metrics as they relate to peripheral and color vision loss, which can be used in concert with objective measures of this outcome, as well as other parameters of disease impact from glaucoma and visual loss, including psychological and social well-being.[50] It is important that these self-assessment instruments have adequate sensitivity and specificity to detect the differences between therapeutic modalities as well as changes in disease progression over time.

Economic outcomes, including cost-effectiveness analysis of interventions,[52] are important assessments for future investigative therapies directed at neuroprotection,[53] and managed care organizations will need to understand the potential costs and benefits associated with these glaucoma treatment paradigm changes. Prior research has demonstrated that more severe or progressive glaucoma has been associated with increased medical costs, as well as increased risk of depression, injury, and hospital or ancillary unit admissions.[40,41,43,54-60] Althin et al suggests that economic evaluations of glaucoma should include outcomes that are relevant and meaningful for current clinical practice, address the diversity of treatment options and practices, incorporate therapy discontinuation, and consider the variability in patient response.[53] As such, research on neuroprotectants should consider these objectives and ensure that end points are relevant for managed care decision-makers, providers, and patients.

Conclusion

The treatment of glaucoma is no longer restricted to managing vision loss related to elevated IOP. The focus has shifted to reducing disease progression and loss of visual function that result from neurodegeneration. Alternative strategies that include neuroprotectants may be useful in preventing optic nerve damage, thereby improving the structural, functional, and other patient-reported outcomes as well as reducing the economic impact of glaucoma.

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