Nerve Growth Factor and Glaucoma

The overall disappointing results of neuroprotective studies thus far should not halt promising research.

BY MICHAEL BELKIN, MA, MD

Bernard Becker, MD, tested the oral administration of diphenylhydantoin for restoring the visual field in glaucoma almost 40 years ago.[1] In doing so, he opened a burgeoning field of research—later termed *neuroprotection*—aimed at finding a treatment modality that will prevent or reverse neurodegeneration in patients with glaucoma and other retinal and neural diseases. The ability to treat glaucomatous neuropathy rather than IOP would be of great benefit to patients, because the latter does not always eliminate glaucoma-induced visual incapacitation and blindness.

More than 35 years of research on neuroprotection and huge expenditures of resources, however, have yielded few, if any, clinical benefits to patients. This unfortunate truth is in spite of the fact that neuroprotection, in its various forms, has repeatedly proven effective in tissue culture experiments and that hundreds of compounds have been successfully tested on animal disease models. Nevertheless, more than 100 neuroprotective drug candidates have failed phase 2 and 3 clinical trials. Only two have been approved thus far by the FDA, and both agents have limited efficacy. Riluzole for amyotrophic lateral sclerosis prolongs patients' lives by 2 to 3 months.[2] Memantine is approved for moderate-to-severe Alzheimer's disease. It slightly benefits the areas of cognition, global assessment, and behavior, but the effects are not consistently significant.[3] In the largest neuroprotective trial in ophthalmology to date—an extensive glaucoma clinical trial—memantine failed to show a benefit.

Growth factors are a heterogeneous group of endogenous proteins secreted by the body to control the growth, division, maturation, and proliferation of various cells and tissues. These factors, it was hoped, would permit the therapeutic manipulation of diseases and healing processes. Nerve growth factor (NGF) induces the differentiation and survival of particular target neurons. After this protein's discovery, for which Rita Levi-Montalcini and Stanley Cohen received a Nobel Prize in 1986, research began to harness NGF for clinical applications in inducing neuroprotection and regeneration. Like the majority of growth factors (with the notable exception of erythropoietin and colony stimulating factor for anemia treatment), however, NGF has not yet found a proven and approved clinical application.

Investigators attempted to use NGF, either directly or by the delivery of its gene, for many indications in animal models and patients as a treatment for both Alzheimer's and Parkinson's diseases with some degree of success. In ophthalmology, researchers studied the intravitreal administration of NGF in experimental models of retinal ganglion cell (RGC) degeneration and found the protein to be effective, as it was for the topical treatment of neurotrophic keratitis. An apparently unique feature of NGF,[4] with obvious clinical implications, is its ability to penetrate to the retina when administered topically, in spite of its being a large protein with a molecular weight of 30,000.

A very promising article was recently published in the *Proceedings of the Natural Academy of Sciences* on a series of experiments using NGF for the treatment of glaucoma. The research team from Rome has been studying the protein for many years. The investigators induced glaucoma in rats by injecting hypertonic saline into episcleral veins, and they measured the survival of RGCs with and without NGF eye drops administered four times daily for 7 weeks. Significantly more RGCs survived in the treated group. Three patients with advanced glaucoma received similar treatment for 3 months. All of them experienced an improvement in visual acuity, contrast sensitivity, perimetry, and electrophysiological functions.[5] Being uncontrolled and from an insignificant number of patients, these unprecedented clinical results cannot be construed as anything but an indication of a path for future research.

Contrary to most previous attempts at glaucoma neuroprotection, this study raises the possibilities that glaucomatous neuropathy may be reversed and that glaucoma can therefore actually be treated, whereas currently, clinicians can only slow or prevent visual deterioration by reducing IOP. Testing the efficacy of NGF treatment should not be as

complicated, prolonged, and expensive as other phase 3 neuroprotective trials such as the memantine glaucoma trial. The reason is that improvement in visual function such as visual fields, if any, should be easily measured and proven. In contrast, glaucoma neuroprotective trials take years to show the advantages of the treatment over the control group in delaying the slow process of RGCs' degeneration. An advantage of testing NGF in glaucoma versus neurological diseases is the robust numerical endpoints characterizing ophthalmological clinical trials compared with the rather nebulous ones used in neurology.

Nonetheless, clinicians should not become overly optimistic regarding the future of NGF in glaucoma therapy. First, similarly successful animal experiments were performed with NGF and other modalities, such as carotid occlusion,[6] but none reached clinical success. Second, the short-term clinical study on three patients treated with NGF is far too small to permit any conclusions. Third, the study was performed using murine, rather than human, NGF. Still, the remarkable results of this study call for its advance into a proper, randomized, controlled glaucoma clinical trial. Human NGF exists for this purpose.

Why isn't such a trial being conducted? Is it because of economic reasons and the lack of a patent covering NGF and its potential uses? It seems that the obstacle is not the cost of a clinical trial but the registration process of NGF as a drug, which will be expensive and will, if successful, result in a generic drug with all the economic implications associated with such an entity. If NGF is effective, however, will not the market in glaucoma and other retinal and neurological diseases be so enormous that competition will be commercially endurable? The author is aware of the naïveté of these ideas, but will someone rise to the challenge? ❑

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