Published in final edited form as:
Am J Ophthalmol. 2011 November ; 152(5): 715–716. doi:10.1016/j.ajo.2011.06.015.

Clinical Evidence for Neuroprotection in Glaucoma

M. Francesca Cordeiro, MBBS, PhD[1,2] and **Leonard A. Levin, MD, PhD**[3,4,*]

[1]Institute of Ophthalmology, University College London, UK

[2]Western Eye Hospital, Imperial College Healthcare NHS Trust, London, UK

[3]Maisonneuve-Rosemont Hospital Research Center and Department of Ophthalmology, University of Montreal, Canada

[4]University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Glaucoma is treated by lowering intraocular pressure (IOP). However, numerous laboratory studies have shown that experimental glaucoma can be helped by therapies that act by mechanisms other than lowering IOP. Such therapies are termed “neuroprotective” because the targets are the neurons affected in glaucomatous optic neuropathy. Until recently there has been no level I evidence that any neuroprotective therapy is effective in patients with glaucoma.[1] With the recent online publication of the results of the Low Pressure Glaucoma Treatment Study[2] (LoGTS), there are now data that the α_2 agonist brimonidine, a drug previously shown to be neuroprotective in the laboratory, may also have a beneficial effect on visual function independent of IOP lowering. This commentary analyzes the implications of LoGTS for our understanding of neuroprotection.

LoGTS was a randomized double-masked, multicenter study comparing visual field progression in normal-tension glaucoma patients treated with brimonidine or timolol. Subjects had visual field and optic nerve head evidence of glaucomatous optic neuropathy and a diurnal IOP < 21 mm Hg. Randomization was in a 4:3 (brimonidine:timolol) ratio to account for an expected increased dropout in the brimonidine group from ocular allergy. The primary outcome measure was visual field progression at 3 or more points by pointwise linear regression and confirmed on 3 successive fields. Sample size was based on an 80% power to detect a 25% difference in visual field progression at α=0.05. Follow-up was up to 4 years with visual fields every 4 months.

*Correspondence: Leonard A. Levin, MD, PhD, 5415 boul de l’Assomption, Montréal, QC H1T 2M4, Canada.

FINANCIAL DISCLOSURES

Dr. Cordeiro has served as a paid consultant and received honoraria for lectures relating to neuroprotection with respect to Allergan (the sponsor of the LoGTS) and several other pharmaceutical companies. She has patents related to diagnostic technologies which may be relevant to assessing neuroprotection, assigned to University College London.

Dr Levin has served as a paid consultant and received honoraria for lectures relating to neuroprotection with respect to Allergan (the sponsor of the LoGTS) and several other pharmaceutical companies. He has patents issued or pending on neuroprotective therapies, which are assigned to the Wisconsin Alumni Research Foundation, and a financial interest in a start-up company developing radioprotective drugs.

CONTRIBUTION OF AUTHORS

Conception and design of editorial, analysis and interpretation of data (MFC, LAL); drafting the article and revising it critically for important intellectual content (MFC, LAL); and final approval of the version to be published (MFC, LAL).

Mean (±SEM) follow-up was 30±2 months. Of the 178 analyzed patients, 9.1% of the brimonidine group and 39.2% of the timolol group progressed (p=0.001). Comparable visual field progression results were seen when analyzed by glaucoma change probability mapping or the 3-omitting method for pointwise linear regression. IOP decrease was similar in the two groups, implying that the difference in progression might be unrelated to effects on IOP.

This impressive difference in visual field progression in two therapies with similar IOP lowering profiles is tempered by several issues. First, the higher incidence of ocular allergy in the brimonidine group (20%) led to significant drop-out in the first year, and could have masked a subgroup of progressing patients that were not subsequently analyzed. If so, this would imply that visual field progression and incidence of ocular allergy are highly associated, which is uncommonly observed. Nonetheless, the apparent neuroprotective effects of brimonidine may only be applicable to patients who do not develop ocular allergy. Ocular allergy insufficient to cause a subject to drop-out could unmask group assignment to the treating ophthalmologist, although this is less concerning because the visual field analysis was masked.

Second, the diurnal effects of brimonidine and timolol could have differed, with less nocturnal IOP reduction with timolol compared to brimonidine. Against this are studies demonstrating almost identical IOP lowering over 24 hours with the two drugs[3] and insignificant nocturnal IOP lowering with brimonidine.[4] Ocular perfusion pressure (diastolic blood pressure minus IOP) in the first study was even lower with brimonidine than timolol, implying that changes in ocular perfusion were not responsible for the apparent neuroprotective effects observed in LoGTS.

Third, in retrospect, subjects in both groups were undertreated. The proportion with a ≥ 20% decrease in IOP at the time of progression was only 44% in the brimonidine group and 39% in the timolol group. In comparison, target reduction of IOP was 30% in the Collaborative Normal Tension Glaucoma Study.[5] The baseline diurnal IOP in progressing brimonidine subjects was higher than timolol subjects (16.9±2.4, n=9 vs. 15.4±2.5, n=31), indicating that there was still a role for further IOP lowering in addition to neuroprotection. Additional IOP lowering would likely have made it more difficult to detect a neuroprotective effect due to brimonidine.

Fourth, the perceived lower progression rate in brimonidine-treated subjects could be the result of a paradoxically higher progression rate in timolol-treated subjects. Timolol may have effects on neural or vascular physiology that theoretically could be deleterious to the optic nerve. On the other hand, there is no reason to believe that timolol is actually harmful in patients with glaucoma, even though it could explain the results obtained. This could be explored further by comparing progression rates in CNTGS between timolol-treated normal-tension glaucoma subjects and untreated subjects.

The apparent neuroprotective effect observed in the LoGTS trial should be placed in the context of clinical trials that did not demonstrate neuroprotective efficacy, including those in other neurologic diseases.[6,7] These trials were preceded by laboratory studies demonstrating potent neuroprotective effects in animals, yet translation to the clinic did not occur. Some reasons for this “Loss in Translation” are discussed elsewhere.[8,9]

The results of the LoGTS are encouraging, and one interpretation is that the drug studied was associated with a neuroprotective effect. Why this result differed from other studies of neuroprotection is unknown, and could reflect study design, the disease studied, the drug used, our inability to measure neuroprotection directly, or a combination thereof. However, confirmation of the neuroprotection paradigm by other randomized clinical trials is

necessary to increase confidence that this and other non-IOP lowering approaches are viable therapies for glaucoma and other optic neuropathies.

Acknowledgments

FUNDING/SUPPORT

NIH R21 EY017970 and P30EY016665, CIHR, Retina Research Foundation, and an unrestricted departmental grant from Research to Prevent Blindness, Inc.

OTHER ACKNOWLEDGMENTS

None

References

1. Chua B, Goldberg I. Neuroprotective agents in glaucoma therapy: Recent developments and future directions. Expert Rev Ophthalmol. 2010; 5(5):627–636.
2. Krupin T, Liebmann JM, Greenfield DS, Ritch R, Gardiner S. A randomized trial of brimonidine versus timolol in preserving visual function: Results from the Low-pressure Glaucoma Treatment Study. Am J Ophthalmol. Mar. in press.
3. Quaranta L, Gandolfo F, Turano R, et al. Effects of topical hypotensive drugs on circadian IOP, blood pressure, and calculated diastolic ocular perfusion pressure in patients with glaucoma. Investigative ophthalmology & visual science. Jul; 2006 47(7):2917–2923. [PubMed: 16799034]
4. Liu JH, Medeiros FA, Slight JR, Weinreb RN. Diurnal and nocturnal effects of brimonidine monotherapy on intraocular pressure. Ophthalmology. Nov; 2010 117(11):2075–2079. [PubMed: 20663566]
5. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol. Oct; 1998 126(4):487–497. [PubMed: 9780093]
6. Sena DF, Ramchand K, Lindsley K. Neuroprotection for treatment of glaucoma in adults. Cochrane database of systematic reviews (Online). 2010; (2):CD006539. [PubMed: 20166085]
7. Baltmr A, Duggan J, Nizari S, Salt TE, Cordeiro MF. Neuroprotection in glaucoma - Is there a future role? Exp Eye Res. Nov; 2010 91(5):554–566. [PubMed: 20800593]
8. Danesh-Meyer HV, Levin LA. Neuroprotection: extrapolating from neurologic diseases to the eye. Am J Ophthalmol. Aug; 2009 148(2):186–191. [PubMed: 19464671]
9. Levin LA, Danesh-Meyer HV. Lost in translation: Bumps in the road between bench and bedside. JAMA. Apr 21; 2010 303(15):1533–1534. [PubMed: 20407063]