

Author Response: Phenytoin for neuroprotection in acute optic neuritis: a randomised, placebo-controlled, phase 2 trial

Raju Kapoor FRCP^{1,2,3}, Rhian Raftopoulos MRCP^{1,2,3}, Daniel R Altmann PhD^{3,4}, David H Miller FMedSci^{1,2,3} and Simon J Hickman FRCP⁵

National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK¹

University College London Institute of Neurology, Queen Square, London WC1N 3BG, UK²

Queen Square Multiple Sclerosis Centre, Queen Square, London WC1N 3BG, UK³

Medical Statistics Department London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK⁴

Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK⁵

Corresponding author: Dr Raju Kapoor

National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK

Email: r.kapoor@nhs.net

Phone: +44 203 448 4719

Author Response

We are grateful to Asadi-Pooya and Martinez-Lapiscina et al for their thoughtful responses to our paper. We believe they raise important considerations for developing the work to deliver better neuroprotection for persons with multiple sclerosis.

We used phenytoin to inhibit voltage-gated sodium channels. Asadi-Pooya suggests that a drug with a better side effect profile and fewer drug interactions would be preferable. While these are attributes of an ideal drug, we stress that this was a proof of concept study in which the overriding requirement was for a sodium channel inhibitor which could be loaded to achieve therapeutic concentrations within hours. Our positive findings should encourage development of an alternative to phenytoin which (unlike presently available alternatives) can be loaded quickly, and which is better tolerated. Importantly, they reinforce the emerging concept of a narrow window of opportunity for sodium channel inhibition to provide neuroprotection as an attack of multiple sclerosis begins¹.

Asadi-Pooya and Martinez-Lapiscina et al both comment that treatment had no significant effect on vision. We stress again that this was a proof of concept study without the statistical power to evaluate clinical benefit. Using a biomarker of neurodegeneration (thickness of the retinal nerve fibre layer, RNFL) for the primary outcome enabled a realistic sample size. Lack of power meant that we did not dwell on the results of colour vision and low contrast acuity (LCVA), which were actually better (albeit non-significantly) in the group treated with phenytoin. To establish significance, we calculate that the effect size on LCVA we found in our study (0.15 for 2.5% LCVA vs 0.45 for the RNFL) would require a trial involving 630 participants, underlining the need to identify a more sensitive, meaningful vision outcome for future work². However, we would urge caution in using the binary outcome suggested by Martinez-Lapiscina et al: i) the clinical meaningfulness of their 7-letter cutoff of inter eye asymmetry of LCVA remains unproven³; ii) the relationship between loss of vision and tissue atrophy depends on threshold effects and is unlikely to be linear⁴; iii) outcomes should be adjusted for measurements at baseline, whereas their proposed outcome involves measurement of vision post-treatment in the unaffected eye, which is vulnerable both to treatment effects and to intercurrent optic neuritis in that eye; and iv) regardless of any correlation between inter eye asymmetry of vision and atrophy of the RNFL, a binary outcome of the kind they suggest cannot demonstrate a between-group difference with greater statistical power than an adjusted comparison of the continuous variable upon which the binary dichotomy is based⁵. Binary classifications are useful for distinguishing 'normal' from 'abnormal' in a clinical setting, but they are less powerful and often unnecessary in trial settings. However, for interest, we report the results using the suggested binary measure on our data: the proportions of subjects with 6-month unaffected LCVA >7 more than 6-month affected are: active 64% (25/39) vs placebo 71% (30/42), $p=0.480$ for 1.25% LCVA, and active 62% (24/39) vs placebo 74% (31/42), $p=0.237$ for 2.5%.

Finally, Martinez-Lapiscina et al refer to possible methodological limitations of our study⁶, mostly to do with the use of the RNFL to measure outcome, rather than the ganglion cell plus inner plexiform (GCIP) layers, in turn requiring us to measure the unaffected eye for baseline adjustment. There are advantages in comparing the GCIP measurements in the same eye, and we welcome further work in which this outcome is assessed prospectively. However, cellular heterogeneity of the GCIP,

especially after optic neuritis⁷, may limit the interpretation of changes of its thickness, and in our preliminary comparison, adjusted changes in the RNFL remained more sensitive to treatment effects⁸.

Contributors

RK wrote the first draft, and all the authors contributed to and approved the final version.

Declaration of interests

We declare no conflicts for the Author Response

Funding

There was no funding source for the Author Response

References

1. Al-Izki S, Pryce G, Hankey DJ, et al. Lesional-targeting of neuroprotection to the inflammatory penumbra in experimental multiple sclerosis. *Brain* 2014; **137**:92-108.
2. Mowry EM, Loguidice MJ, Daniels AB, et al. Vision related quality of life in multiple sclerosis: correlation with new measures of low and high contrast letter acuity. *J Neurol Neurosurg Psychiatry* 2009; **80**: 767-72.
3. Balcer LJ, Miller DH, Reingold SC, Cohen JA. Vision and vision-related outcome measures in multiple sclerosis. *Brain* 2015; **138**:11-27.
4. Costello F, Coupland S, Hodge W, et al. Quantifying axonal loss after optic neuritis with optical coherence tomography. *Ann Neurol*. 2006; **59**:963-9.
5. Altman DG, Royston P. The cost of dichotomising continuous variables. *BMJ* 2006; **332**: 1080.
6. Saidha S, Calabresi PA. Phenytoin in acute optic neuritis: neuroprotective or not? *Lancet Neurol* 2016; **15**: 233-5.
7. Green AJ, McQuaid S, Hauser SL, et al. Ocular pathology in multiple sclerosis: retinal atrophy and inflammation irrespective of disease duration. *Brain* 2010; **133**:1591-601.
8. Raftopoulos RE, Rangarajan A, Chen C-L, et al. Sodium channel blockade with phenytoin has a neuroprotective effect on the ganglion cell complex after acute optic neuritis. *Multiple Sclerosis* 2015; **23(S11)**: 273-4.