Author's response to reviews

Title: Systematic review and stratified meta-analysis of the efficacy of RhoA and Rho kinase inhibitors in animal models of ischaemic stroke.

Authors:

Vesterinen M Vesterinen (h.m.vesterinen@googlemail.com)
Currie G (gillian.currie@ed.ac.uk)
Samantha Carter (sammylou_13@hotmail.com)
Sarah Mee (sarahmee1@googlemail.com)
Ralf Watzlawick (ralf.watzlawick@charite.de)
Egan J Egan (kieren.egan@googlemail.com)
Malcolm R Macleod (malcolm.macleod@ed.ac.uk)
Emily S Sena (emily.sena@ed.ac.uk)

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Author's response to reviews: see over
Dear Editor(s),

Re: Systematic review and stratified meta-analysis of the efficacy of RhoA and Rho kinase inhibitors in animal models of ischaemic stroke.

Vesterinen, Currie, Carter, Mee, Watzlawick, Egan, Macleod & Sena.

I am delighted to enclose this manuscript for consideration for publication in Systematic Reviews.

Ischaemic stroke is one of the most common causes of death and disability worldwide and yet thrombolysis with tissue plasminogen activator is the only pharmacological intervention in routine clinical practice. Unfortunately, its use is limited by potentially severe adverse effects at later times to treatment and therefore only suitable for a subset of patients. Novel therapies are required.

The Rho pathway is an attractive drug target for the treatment of ischaemic stroke as it is closely aligned to the pathogenesis of several CNS disorders. In particular it is inhibitors of RhoA/ROCK which are considered to have the potential to improve outcome for stroke patients. This drug class includes fasudil which has previously performed favourably in a clinical trial involving only 160 patients; both safety and efficacy were promising when administered up to 48 hours after stroke onset but follow-up was only to one-month.

Further clinical trials may now be warranted. However, clinical trials should be based on strong evidence from preclinical studies which has not always been the case. We have used systematic review and meta-analysis previously to assess rigorously the preclinical literature of a number of interventions tested in preclinical stroke models, as well as several other CNS diseases. Examples of our use of these tools include: identifying that the majority of preclinical studies testing NXY-059 lacked experimental validity, and the observed efficacy in the high quality, pragmatically designed studies were more closely aligned to the results of the failed phase two clinical trial; designing a large scale clinical trial of hypothermia to treat ischaemic stroke based on the best available evidence from animal studies; and identifying systematic weaknesses in the design of preclinical studies across a number of diseases which include using treatment...
times which are too early, or sample sizes which are too small to be adequately powered to detect significant differences between cohorts of animals.

Our aim was to assess the impact of study design characteristics and study quality on the reported measures of efficacy in a systematic review and meta-analysis of Rho inhibitors tested in animal models of focal cerebral ischaemia to inform both the design of clinical trials and, if required, further preclinical experiments.

None of the authors have a financial or any other conflict of interest to declare.

With thanks and best wishes,

Yours sincerely,

Professor Malcolm Macleod
BSc(Hons) MBChB PhD FRCP(Ed)