Reviewer’s report

Title: Free radical scavenger, edaravone, reduces the brain ischemic damage especially in the white matter.

Version: 3 Date: 23 June 2010

Reviewer: Hedley Emsley

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Based on a recent review article (Lapchak, Expert Opinion Pharmacother. 2010; 11(10):1753-1763, edaravone is a free radical scavenger, marketed in Japan to treat acute ischemic stroke (AIS) patients presenting within 24 h. Efficacy of edaravone ranges from large significant clinical improvements to only modest improvements in clinical function measured using standard stroke scales when administered 6-72 h following an ischemic stroke. The conclusion of this review was that edaravone may be a useful neuroprotective agent but that additional clinical studies are necessary to verify the efficacy of edaravone.

There do appear to be some more recent data to have emerged in an experimental setting, for instance, Kubo et al. 2009;1279:139-146. These findings of mitigation of grey and white matter in a rat model are clearly relevant to the present paper and I'm surprised that the authors' discussion of the literature is not more comprehensive.

The authors have investigated edaravone, primarily with imaging rather than clinical endpoints, at longer time points than previously studied, in ischaemic stroke patients. The design appears to be a retrospective observational study of two successive cohorts of patients.

I do have considerable reservations.

Introduction

Firstly, as alluded to above, a much more comprehensive albeit brief summary of edaravone, and its position as a potential neuroprotectant in the context of accepted standard criteria (eg STAIR), is necessary.

Materials and methods

Stroke appears to have been defined by MRI appearances rather than clinically. We certainly need reassurance that patients fulfilled clinical criteria for definition of stroke (eg WHO criteria). We can't rely solely on a tissue injury MRI definition as clinicians. Limited clinical outcome data have been recorded - only mRS. This obviously severely limits the assessment of clinical outcome. The appropriateness of the statistical analysis would need to be assessed by a statistician. However, no reference is made to sample size considerations. This is required.
Results

There is no adequate description of the patients. Baseline characteristics need to be properly described/tabulated to describe the study population, demonstrate an absence of significant differences between the treatment epochs etc.

In respect of the presentation of the data, the figures are currently difficult to interpret. The y axes bear no labels. The ratio is difficult to interpret (I understand the rationale but this needs clearer explanation). What appears to be the only significant finding (ie the apparent difference in lesion volume at the earliest time point in the lacunar group) much more detail in terms of distribution of lesions is necessary. The title of the manuscript asserts ‘....especially in the white matter’ but of course we do not know what the distribution of lesions was - were they predominantly deep grey matter (basal ganglia etc) or were they mainly in white matter. Greater detail is required as this is the pivotal finding. The proposed difference in the lacunar group at 7-12 months is unconvincing.

Discussion

No reference is made to potential effects on endothelial/blood brain barrier function of edaravone - and given the likely relevance of endothelial dysfunction to small vessel disease pathophysiology I don't think this can be omitted.

The discussion in relation to the need for an RCT, which is obviously needed, is quite weak. Ethical considerations would not be so insurmountable as the authors suggest if there is truly an absence of convincing effect on clinical outcome thus far.

Level of interest: An article of importance in its field

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

To my knowledge I have no competing interests