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Interleukin-1 receptor antagonist in animal models of stroke: a fair summing up?

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Letter to the Editor

Interelukin-1 Receptor Antagonist in Animal Models of Stroke: A Fair Summing Up?

To the Editor:

We read with interest Banwell et al's systematic review and stratified meta-analysis of the efficacy of interleukin-1 receptor antagonist (IL-1RA) in animal models of stroke recently published in the *Journal*.[1] IL-1RA fares quite well, demonstrating a 38% reduction in infarct volume overall. This compares favorably to the 24% reduction reported in a meta-analysis of preclinical data for tissue plasminogen activator.[2] In contrast to other similar meta-analyses,[3,4] in which the efficacy detected in individual studies declined with higher "quality scores," the reported efficacy of IL-1RA increases when more of the 10 "quality items" are reported in the study's methods.

We welcome the authors' thorough analysis of much of the current knowledge regarding the efficacy of IL-1RA in animal models of stroke, and agree that there is room for improvements in the conduct of preclinical studies in stroke. Meta-analysis is clearly a very powerful tool in both preclinical and clinical studies; however, data other than histological or functional outcome, such as pharmacokinetics, should be considered as well.[5]

We feel that some aspects of the design and execution of this meta-analysis may weaken the authors' conclusion that "the animal data supporting IL-1RA as a candidate drug for stroke are limited, and that further experiments are required before proceeding to clinical trial." The factors chosen for inclusion in the quality score are vital to conducting high- quality preclinical stroke research, but nonetheless we feel that some items, and their application, require further study or refinement. First, the 10 quality score factors are given equal weighting in the analysis, even though some factors (eg, avoidance of anaesthetics with marked intrinsic neuroprotective properties, control of temperature) will have a far greater potential to introduce error and bias than others (eg, peer-reviewed publication, statement of compliance with animal regulations). This issue was discussed in an earlier article cowritten by one of the authors in 2004,[6] and we agree that a weighted score would be a useful refinement. Second, studies in comorbid animals are included in the quality score, but there is no evidence that studying the effects of treatments in such animals is of any more value than doing so in young, healthy animals, a point also discussed in the original article describing this methodology.[6] There is little evidence of a penumbra in comorbid animals,[7] even though one is frequently identified in stroke patients.[8] Third, not making a statement regarding any potential conflict of interest scores "0," but the score given for a reported conflict of interest is not clear. Given the binary nature of the scoring system, it could only either have no impact on the quality score (relative to not making a statement) or improve it. This also may require some modification.

Despite the authors' comprehensive search strategy and hand-searching of conference abstracts, the quality score for one study was taken from an abstract,[9] even though the full article has been available online since 2007.[5] The information required to calculate the quality score for this study could not have been included in a short abstract, and thus this study received a quality score of 1 out of 10, whereas we believe that the score would have been 4 had it been based on the full publication. This highlights the importance of distinguishing between "not done" and "not reported," and the consequent impact on the score. Although we certainly advocate the reporting of all such factors in future studies, some of the 10 quality items (eg, statement of compliance with animal welfare regulations) have not previously been routinely reported, but this does not equate to "not done." The systematic review highlights the need to improve experimental procedures and addresses the issue of differences between preclinical and clinical studies. However, it seems appropriate to recognize the limitations of the meta-analysis methodology, and it would be incorrect to assume that this article is a definitive account of IL-1-RA's potential as a treatment for clinical stroke. The blanket application of this methodology to potential stroke treatments could even be potentially damaging to the field of stroke research, and, as with the experimental methodology that it addresses, further refinement is probably needed to improve its value.

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