CHIMES-I: sub-group analyzes of the effects of NeuroAiD according to baseline brain imaging characteristics among patients randomized in the CHIMES study

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Rationale The clinical effects of neuroprotective and/or neurorestorative therapies may vary according to location and size of the ischemic injury. Imaging techniques can be useful in stratifying patients for trials that may be beneficial against particular ischemic lesion characteristics.

Aim To test the hypothesis that the efficacy of NeuroAiD compared with placebo in improving functional outcome and reducing neurological deficit in patients with cerebral infarction of intermediate severity varies between sub-groups of patients randomized in the main Chinese Medicine Neuroaid Efficacy on Stroke study when categorized according to baseline imaging characteristics.

Design This is a retrospective cohort sub-group analysis of patients who participated in the main Chinese Medicine Neuroaid Efficacy on Stroke study, a multicenter, double-blind, placebo-controlled trial that recruited 1100 patients within 72 h of ischemic stroke onset with National Institutes of Health Stroke Scale 6–14 and were randomized to either NeuroAiD or placebo taken four capsules three times daily for three months. Review of the baseline images to classify the acute stroke lesions in terms of size, location, and extent of involvement will be performed retrospectively by two readers who will remain blinded as to treatment allocation and outcomes of the subjects.

Study outcomes The primary efficacy end-point in the main Chinese Medicine Neuroaid Efficacy on Stroke study is the modified Rankin Scale grades at three-months. Secondary efficacy end-points are the National Institutes of Health Stroke Scale score at three-months; difference of National Institutes of Health Stroke Scale scores between baseline and 10 days and between baseline and three-months; difference of National Institutes of Health Stroke Scale sub-scores between baseline and 10 days and between baseline and three-months; modified Rankin Scale at 10 days, one-month, and three-months; Barthel index at three-months; and Mini Mental State Examination at 10 days and three-months. Analysis of these primary and secondary end-points will be performed for sub-groups defined in this study after review of the baseline brain imaging: nonlacunar and lacunar, cortical and sub-cortical, hemispheric vs. brainstem, Alberta Stroke Program Early CT score <7 and 7–10, and score <8 and 8–10.

Key words: cerebral infarction, imaging, ischemic stroke, stroke, therapy, treatment

Introduction

NeuroAiD combines 14 natural ingredients indicated as treatment for poststroke recovery in China. In Singapore, NeuroAiD is listed as a Chinese Proprietary Medicine since 2006. It is widely available in China and in many countries in Asia. In Europe, a simplified formulation (MLC901) consisting of the nine herbal components is available.

NeuroAiD was first registered with the Sino Food and Drug Administration in 2001 after being evaluated in two randomized, double-blind, positive-controlled clinical trials (1). Pooled analysis of data from these studies that included 605 patients with ischemic stroke within two-weeks to six-months of onset has shown that NeuroAiD improved functional outcome and was safe in patients with ischemic stroke (2). Other studies further supported the efficacy and safety of NeuroAiD in different phases after ischemic stroke (3–9).

The protocol of a double-blind, placebo-controlled, randomized trial to investigate Chinese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES study) was previously published in this journal (10). Chinese Medicine Neuroaid Efficacy on Stroke is the first large-scale multicenter clinical trial to assess the efficacy and safety of a traditional Chinese medicine in the management of acute ischemic stroke conducted according to GCP guidelines and has recently completed recruitment of the target 1100 patients [Clinicaltrials.gov Identifier: NCT00554723 (http://clinicaltrials.gov)].

The properties of NeuroAiD have more recently been elucidated in animal and in vitro models (11,12). NeuroAiD has been shown to have both neuroprotective and neuroproliferative properties. It reduces infarct size and protects against glutamate-induced neuronal injury. It also protects the hippocampal CA1 cells from global ischemia, partly via reducing lipid peroxidation (as indicator of oxidative stress) and the role of Akt. More remarkable is the effect of NeuroAiD on neurogenesis beyond mere neuronal protection. In vivo and in vitro experiments showed how NeuroAiD increases cell proliferation, neuritic outgrowth, and synaptogenesis.

A long series of failed neuroprotection clinical trials in stroke has been reported, analyzed, and debated (13–16). Lessons were learned and rethinking the designs of trials was imperative. Looking at a more homogenous study, population and brain pathology may improve the chances of success. Furthermore, rather than addressing one specific target in the ischemic cascade,