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Short communication

Sex and the treatment effect in the Chinese Medicine NeuroAiD Efficacy on Stroke recovery (CHIMES) trial

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ABSTRACT

In the randomized controlled trial of NeuroAiD versus placebo following ischemic stroke, there was a trend for sex influencing the treatment effect of NeuroAiD in improving functional outcome following ischemic stroke ($p = 0.075$).

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1. Introduction

There is growing evidence that sex influences the effects of some stroke treatments. Compared to men, women have greater benefit from stroke thrombolysis in some studies [1,2], but poorer response to carotid endarterectomy surgery [3]. We investigated whether sex influenced the treatment effect of NeuroAiD (MLC601) on stroke recovery at 3 months in the Chinese Medicine NeuroAiD Efficacy on Stroke Recovery (CHIMES) trial.

2. Methods

The multicenter, randomized, placebo-controlled CHIMES trial investigated the efficacy of a Traditional Chinese Medicine (TCM) NeuroAiD in improving functional outcome following ischemic stroke [4]. Participating hospitals' institution review boards approved the trial. Informed consent was obtained from subjects. We employed the secondary endpoint measure in the CHIMES trial of month-3 modified Rankin Scale (mRS) dichotomy 0–1 (good outcome) versus 2–6. Statistical testing using the Statistical Analysis Software 9.3 (SAS Institute, Cary, NC, USA) included interaction analyses between treatment effect with sex with adjustment for age, stroke-onset-to-first-dose of NeuroAiD duration, hemoglobin,

smoking, habitual drinking, hyperlipidemia and angiotensin-receptor blocker use.

3. Results

Of the 1096 participants, 1009 (92%), 639 men, 370 women (Table 1) had complete mRS data. Women were less likely to have good functional outcome than men ($p < 0.002$). Among women, a higher proportion had good functional outcome with NeuroAiD treatment versus placebo (adjusted $p = 0.056$). There was no such treatment difference among men (adjusted $p = 0.803$). In a multivariable logistic regression model, a trend for the interaction between sex and treatment effect was detected (odds ratio 1.13, adjusted $p = 0.075$; Table 2).

4. Discussion

We found a strong trend of an interaction between sex and treatment effect of NeuroAiD influencing functional status following ischemic stroke. In the study's placebo arm, and consistent with other data [5], women had poorer outcome following ischemic stroke. Thus, women may have a greater propensity to benefit from stroke recovery strategies, which may explain the sex interaction observed. This is consistent with observed treatment effect of NeuroAiD in subgroups with poorer anticipated prognosis in the CHIMES trial including older age and higher

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Table 1
Baseline characteristics and concomitant therapies between men and women

	Men n = 639	Women n = 370	p value
Mean age (years)	60 ± 11	64 ± 11	<0.001
Baseline modified Rankin Scale ≤ 1	91.6%	94.1%	0.173
Mean baseline National Institute of Health Stroke Scale	8.6 ± 2.6	8.7 ± 2.4	0.455
Stroke-onset-to-first-dose ≥ 48 h	46.9%	54.1%	0.031
Mean hemoglobin (g/dL)	14.7 ± 1.7	13.3 ± 1.4	<0.001
Smoking	65.7%	11.1%	<0.001
Habitual drinking	43.2%	3.5%	<0.001
Hyperlipidemia	54.2%	41.4%	<0.001
Hypertension	79.5%	84.6%	0.114
Previous stroke	12.5%	11.4%	0.617
Myocardial infarction	4.2%	1.9%	0.133
Angina	3.8%	2.4%	0.327
Diabetes	31.9%	33.0%	0.727
Peripheral vascular disease	1.1%	0.3%	0.446
Cortical involvement	36.0%	36.5%	0.892
<i>Concomitant therapies</i>			
Antiplatelet	95.9%	93.8%	0.131
Statin	91.2%	93.5%	0.227
Antihypertensive	78.9%	82.7%	0.163
Angiotensin-converting enzyme inhibitor	33.2%	31.4%	0.577
Angiotensin-receptor blocker	27.1%	36.5%	0.002
Antidiabetic	28.3%	31.1%	0.389
Rehabilitation	78.1%	76.0%	0.437

Table 2
Treatment effect at 3 months and treatment-sex interaction of MLC601

Model	Effect	Unadjusted analysis			Adjusted analysis ^a		
		OR	95% CI	p value	OR	95% CI	p value
Men only	Treatment	0.98	(0.72–1.34)	0.916	0.96	(0.69–1.33)	0.803
Women only	Treatment	1.59	(1.05–2.42)	0.030	1.54	(0.99–2.40)	0.056
All participants	Treatment	1.15	(0.90–1.47)	0.269	1.11	(0.97–1.27)	0.129
	Sex Interaction				0.80	(0.67–0.95)	0.012
					1.13	(0.99–1.30)	0.075

^a Adjusted for age, stroke-onset-to-first-dose of NeuroAiD, hemoglobin, smoking, habitual drinking, hyperlipidemia and angiotensin-receptor blocker. CI = confidence interval, OR = odds ratio.

baseline National Institute of Health Stroke Scale [6]. To our knowledge, there is no published report of a sex interaction in treatment response to TCM. Further studies are needed to verify this trend observed in post hoc analyses and to better understand the possible mechanisms underlying this sex difference.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication. The authors received funding for the trial and/or accommodation and transportation support for meetings from the CHIMES Society. Moleac (Singapore) provided grants to the CHIMES Society of which the society had sole discretion on use. Other than CHIMES funding for the trial, the other authors and investigators have no conflict of interest to declare.

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