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Safety Profile of MLC601 (Neuroaid®) in Acute Ischemic Stroke Patients: A Singaporean Substudy of the Chinese Medicine Neuroaid Efficacy on Stroke Recovery Study

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Key Words
Acute stroke · Chinese medicine, safety · Clinical trials · Stroke recovery

Abstract
Background: Previous clinical trials have shown that Neuroaid® (MLC601), a traditional Chinese medicine, shows good tolerability and superiority over another traditional Chinese medicine in terms of neurological disability and functional outcome and thus may be beneficial as part of a poststroke rehabilitation program. The safety of MLC601 on hemostasis, hematology and biochemistry has been established in normal subjects and patients with nonacute stroke over a short treatment period. We assessed the safety of Neuroaid in patients with acute stroke treated for 3 months in a substudy of an ongoing randomized placebo-controlled trial. ***Methods:*** Laboratory tests (biochemical, hematological and electrocardiogram) were conducted at the month 3 follow-up, in addition to baseline tests. A total of 114 patients were recruited. As there were 13 dropouts, a total of 52 patients on MLC601 and 49 on placebo were available for analysis. Serious adverse events (SAEs) were also analyzed. ***Results:*** There were no statistically or clinically significant differences between treatment groups in biochemical, hematological or electrocardiogram tests at month 3, nor any statistically or clinically significant differences in the absolute and relative changes of the various parameters between baseline and 3 months. SAEs were similar and were those commonly seen in stroke patients. ***Conclusions:*** Longer-term laboratory safety data show no differences between MLC601 and placebo, confirming the safety of MLC601 in acute stroke patients receiving a 3-month treatment.

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Stroke is a major cause of death and disability [1]. Neuroaid® (MLC601), previously referred to as DJ [2] or Danqi Piantan Jiaonang [3], is a traditional Chinese medicine which has been used extensively in China as a drug to facilitate recovery after stroke. It combines 9 herbal (radix astragali, radix salviae mitorrhizae, radix paeoniae rubrae, rhizoma chuanxiong, radix angelicae sinensis, *Carthamus tinctorius, Prunus persica,* radix polygalae and rhizoma acori tatarinowii) and 5 animal components (*Hirudo, Eupolyphaga* seu *Steleophaga,* calculus bovis artifactus, *Buthus martensii* and cornu saigae tataricae) [4]. The neuroproliferative and neuroprotective effect of MLC601 and hence its potential role in neuroplasticity after stroke have been recently established in animal models of stroke and ischemia [5].

A meta-analysis of traditional Chinese proprietary medicines in stroke reported few adverse events of which none were severe and only 10 trials reported any deaths [6]. However, most of these trials were not compliant with the International Conference of Harmonization/Good Clinical Practice, and such an unexpectedly low frequency of serious adverse events (SAEs) could be due to bias in the admission, selection, reporting or publication processes or from the shorter treatment period.

A pooled analysis of 2 trials of MLC601 showed good tolerability and superiority of MLC601 over another traditional Chinese medicine also approved for stroke recovery [2]. Hence, a large-scale academic multicenter randomized controlled trial, the Chinese Medicine Neuroaid Efficacy on Stroke Recovery (CHIMES) study, is testing the hypothesis that MLC601 is superior to placebo in reducing neurological deficit and improving functional outcome (modified Rankin Scale at 3 months) after acute ischemic stroke in patients with cerebral infarction with an intermediate range of severity (NIHSS between 6 and $\leq$14) [4] enrolled into the study within 72 h of stroke onset.

Previous studies reported no SAEs and only 2 adverse events – 2 cases of nausea and vomiting – in 405 subjects receiving MLC601 [2]. The safety of MLC601 on hemostasis, hematology and biochemistry has already been established in normal subjects and stroke patients in earlier studies [2, 3]. However, these studies were performed in patients with nonacute stroke (between 7 days and 6 months after stroke), and these patients had experienced a relatively short treatment period of 1 month.

Hence, although we anticipated few adverse events related to MLC601, given the limitations of previous studies, we aimed to assess the safety of MLC601 in acute stroke patients receiving a 3-month treatment in a substudy of an ongoing trial performed in accordance with Good Clinical Practice guidelines.

Methods

Patient Accrual

This was a multicenter study involving 4 sites in Singapore: Changi General Hospital, National Neuroscience Institute, Tan Tock Seng Campus, National Neuroscience Institute, Singapore General Hospital Campus and National University Hospital. All sites had received local ethics approval.

In total, 114 patients (Singapore General Hospital: 3, National University Hospital: 6, Tan Tock Seng Hospital: 31, and Changi General Hospital: 74) were randomized in Singapore between November 5, 2007, and December 1, 2008. Of these 114 patients, 58 were allocated to the MLC601 group, and 56 were allocated to the placebo group. While primary and secondary outcome data were collected for all patients in this intention-to-treat trial, laboratory data for 13 patients were not available at month 3; in the MLC601 group, 3 patients were lost to follow-up, 1 patient was withdrawn by the investigators due to SAEs, and 2 patients withdrew their consent; in the placebo group, 1 patient died, 3 patients were withdrawn by the investigators due to SAEs, and 3 patients withdrew consent. Reasons for consent withdrawal were available for 4 out of 5 subjects and did not show any specific pattern. These included improvement of symptoms, hematuria, loss of trial medication and depression. This left 101 patients, 52 on MLC601 and 49 on placebo, whose laboratory data at month 3 were available for analysis.

Tests

Hematology, biochemistry and electrocardiogram (ECG) tests were performed at baseline and at 3 months.

Hematology tests included levels of hemoglobin, red blood cell count, white blood cell count, hematocrit, platelet count, lymphocytes, monocytes, eosinophils and basophils.

Biochemistry tests included levels of sodium, potassium, chloride, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, alkaline phosphatase, total bilirubin, total protein, albumin, globulin, urea, creatinine and uric acid.

Whether a result was determined to be 'clinically significant' was decided by the investigators based on the laboratory test values and whether this led to a change in medical management.

Unblinded SAEs were also analyzed.

Statistical Analysis

Demographic data were summarized by descriptive statistics and presented by treatment groups. Analysis was based on the intention-to-treat principle. A 2-sample t test was used separately for each comparison of continuous laboratory tests. In case of nonnormality confirmed by the Kolmogorov-Smirnov test, the nonparametric Mann-Whitney U test was performed. For comparison of categorical outcomes, Fisher's exact test was used. Multiple logistic regression was also carried out to adjust for baseline characteristics.

Table 1. Trial profiles and patient demographics

	MLC601	Placebo	p value	All patients
Total number of subjects	58	56		114
Incomplete follow-up at month 3	6	7	0.95	13
Died	0	1	0.99	1
Lost to follow-up	3	0	0.25	3
Withdrawn by investigator due to SAE	1	3	0.59	2
Withdrew consent	2	3	0.97	7
SAEs				
Number of SAES	8	10	0.74	18
Number of patients	7	9	0.73	16
Mean age ± SD, years	60.7 ± 10.0	62.4 ± 11.1	0.39	61.5 ± 10.6
Gender, n				
Male	44 (75.9%)	40 (71.4%)	0.75	84 (73.7%)
Female	14 (24.1%)	16 (28.6%)	0.75	30 (26.3%)
Race, n				
Chinese	42 (72.4%)	40 (71.4%)	1	82 (71.9%)
Malay	7 (12.1%)	14 (25.0%)	0.12	21 (18.4%)
Indian	3 (5.2%)	1 (1.8%)	0.64	4 (3.5%)
Filipino	1 (1.7%)	0 (0.0%)	1	1 (0.9%)
Others	5 (8.6%)	1 (1.8%)	0.22	6 (5.3%)

Results

Patient Demographics

Demographics of the 114 patients whose baseline data were available are presented in table 1. The treatment groups are largely similar, and there was no difference in the baseline laboratory data of those who were lost to follow-up and those who were followed up to 3 months.

Severe Adverse Events

During the study period, there were 8 SAEs reported in 7 patients in the MLC601 group while 10 SAEs were reported in 9 patients in the placebo group. In particular, there was 1 death, 7 life-threatening events in 6 patients and 5 patients whose study treatments were permanently discontinued due to SAEs. Only 1 SAE was deemed possibly related to the trial medication by the investigators. All SAEs observed were common for stroke patients and included stroke progression, recurrent stroke and cardiac events.

Laboratory Investigations at 3 Months

Hematology Tests

Results of hematology tests are summarized and presented in table 2. There was 1 patient in the placebo group in whom no hematology tests were performed. Based on a significance level of 0.05, there was no statistically significant difference between both groups in all the hematology tests at 3 months. Additionally, when examining the absolute and relative changes between baseline and 3 months, no statistically significant difference between the two groups was observed.

Biochemistry Tests

The results of biochemistry tests are summarized and presented in table 3. There was 1 patient on placebo in whom no biochemistry tests were performed. In addition, there were 15 patients on MLC601 and 16 patients on placebo, in whom no chloride tests were performed, and 6 patients on MLC601 and 4 patients on placebo in whom no uric acid tests were performed. Based on a significance level of 0.05, there were no statistically significant differences between both groups on all the biochemistry tests. Additionally, when examining the absolute and relative changes between baseline and at 3 months, no statistically significant difference between the two groups was observed.

ECG Test

Results of the ECG test are summarized and presented in table 3. There was 1 patient in the placebo group in whom no ECG test was performed. Based on a significance level of 0.05, no statistically significant difference was found between the two groups in the ECG test at 3 months, even after adjusting for baseline ECG status.

Table 2. Hematology tests at month 3

	MLC601 (n = 52)	Placebo (n = 48)	p value	All patients (n = 100)
Hemoglobin, g/dl	13.6 ± 1.5	13.6 ± 1.5	0.834	13.6 ± 1.5
Change from baseline	–1.1 ± 1.4	–1.4 ± 1.2	0.280	–1.2 ± 1.3
Percentage change	–6.9 ± 9.5	–8.9 ± 7.3	0.241	–7.9 ± 8.6
Clinically significant, n	5 (9.6)	8 (16.7)	0.295	13 (13.0)
RBCs, n × 10^{12}/l	4.7 ± 0.6	4.6 ± 0.5	0.401	4.7 ± 0.5
Change from baseline	–0.4 ± 0.5	–0.4 ± 0.4	0.559	–0.4 ± 0.5
Percentage change	–7.2 ± 9.3	–8.4 ± 7.4	0.447	–7.8 ± 8.4
Clinically significant, n	3 (5.8)	4 (8.3)	0.708	7 (7.0)
WBCs, n × 10^9/l	7.9 ± 2.9	7.6 ± 2.3	0.820	7.8 ± 2.6
Change from baseline	–1.2 ± 2.6	–1.8 ± 2.2	0.157	–1.5 ± 2.4
Percentage change	–11.9 ± 24.1	–16.3 ± 23.3	0.191	–14.0 ± 23.7
Clinically significant, n	2 (3.9)	0 (0.0)	0.496	2 (2.0)
Hematocrit, %	40.4 ± 6.6	40.9 ± 4.1	0.972	40.7 ± 5.5
Change from baseline	–3.7 ± 6.5	–3.9 ± 3.6	0.276	–3.8 ± 5.3
Percentage change	–8.0 ± 14.9	–8.4 ± 7.6	0.286	–8.2 ± 11.9
Clinically significant, n	1 (2.0)	3 (6.3)	0.352	4 (4.0)
Platelet count, n × 10^9/l	296.3 ± 79.7	294.2 ± 84.3	0.956	295.3 ± 81.5
Change from baseline	14.7 ± 51.9	6.9 ± 40.8	0.715	11.0 ± 46.9
Percentage change	6.8 ± 20.0	4.0 ± 16.2	0.671	5.5 ± 18.2
Clinically significant, n	1 (1.0)	2 (4.2)	0.606	3 (3.0)
Neutrophils, n × 10^9/l	5.1 ± 2.6	4.4 ± 1.5	0.276	4.8 ± 2.2
Change from baseline	–1.3 ± 2.6	–1.7 ± 2.0	0.391	–1.4 ± 2.3
Percentage change	–15.7 ± 31.2	–22.4 ± 27.3	0.258	–18.9 ± 29.5
Clinically significant, n	1 (1.9)	0 (0.0)	1.000	1 (1.0)
Lymphocytes, n × 10^9/l	1.9 ± 0.6	2.2 ± 0.8	0.069	2.1 ± 0.7
Change from baseline	–0.1 ± 0.8	–0.2 ± 1.1	0.860	–0.1 ± 0.9
Percentage change	10.5 ± 42.5	7.0 ± 39.1	0.964	8.8 ± 40.7
Clinically significant, n	0 (0.0)	0 (0.0)	1.000	0 (0.0)
Monocytes, n × 10^9/l	0.5 ± 0.2	0.6 ± 0.2	0.807	0.5 ± 0.2
Change from baseline	–0.0 ± 0.2	–0.1 ± 0.2	0.492	–0.1 ± 0.2
Percentage change	1.1 ± 46.4	–4.0 ± 39.3	0.791	–1.4 ± 43.0
Clinically significant, n	0 (0.0)	0 (0.0)	1.000	0 (0.0)
Eosinophils, n × 10^9/l	0.3 ± 0.3	0.4 ± 0.5	0.639	0.3 ± 0.4
Change from baseline	0.1 ± 0.2	0.1 ± 0.5	0.905	0.1 ± 0.4
Percentage change	260.8 ± 581.8	247.1 ± 552.7	0.574	253.9 ± 564.3
Clinically significant, n	1 (2.0)	0 (0.0)	1.000	1 (1.0)
Basophils, n × 10^9/l	0.07 ± 0.05	0.07 ± 0.04	0.967	0.07 ± 0.04
Change from baseline	0.0 ± 0.0	–0.0 ± 0.0	0.338	–0.0 ± 0.0
Percentage change	4.4 ± 54.3	3.0 ± 60.9	0.503	3.7 ± 57.2
Clinically significant, n	0 (0.0)	0 (0.0)	1.000	0 (0.0)

Figures in parentheses indicate percentages. Change from baseline: data at month 3 – data at baseline; percentage change: (data at month 3 – data at baseline) × 100/data at baseline. RBCs = Red blood cells; WBCs = white blood cells.

Discussion

Longer-term laboratory safety data conducted at 3 months on 101 patients showed no statistical and clinical differences between the MLC601 and placebo groups across a range of biochemical and hematological parameters as well as ECG and SAE reports. Further analysis of the absolute and relative changes of these parameters between baseline and at 3 months showed no statistical and clinical differences between the MLC601 and placebo groups either. These results confirm the safety of MLC601 in acute stroke patients undergoing 3 months of treatment.

Safety data on MLC601 have previously been reported [2, 3]. These reports were on blood, urine and stool pa-

Table 3. Biochemistry and ECG tests at month 3

	MLC601 (n = 52)	Placebo (n = 48)	p value	All patients (n = 100)
Sodium, mmol/l	139.0 ± 2.3	138.6 ± 2.4	0.444	138.8 ± 2.3
Change from baseline	1.5 ± 3.2	1.0 ± 2.7	0.624	1.3 ± 3.0
Percentage change	1.1 ± 2.4	0.7 ± 2.0	0.611	0.9 ± 2.2
Clinically significant, n	0 (0.0)	0 (0.0)	1.000	0 (0.0)
Potassium, mmol/l	4.0 ± 0.4	4.1 ± 0.4	0.391	4.1 ± 0.4
Change from baseline	0.1 ± 0.6	0.0 ± 0.5	0.874	0.0 ± 0.6
Percentage change	3.2 ± 16.5	0.9 ± 10.5	0.823	2.1 ± 13.9
Clinically significant, n	1 (2.0)	1 (2.1)	1.000	2 (2.0)
Chloride, mmol/l	104.1 ± 2.7	104.0 ± 2.6	0.971	104.0 ± 2.6
Change from baseline	0.8 ± 3.7	0.6 ± 3.6	0.960	0.7 ± 3.6
Percentage change	0.8 ± 3.7	0.7 ± 3.5	0.970	0.8 ± 3.6
Clinically significant, n	0 (0.0)	0 (0.0	1.000	0 (0.0)
SGOT, U/l	22.4 ± 7.0	23.1 ± 7.1	0.333	22.7 ± 7.0
Change from baseline	–2.4 ± 10.3	–1.6 ± 9.4	0.718	–2.0 ± 9.8
Percentage change	–2.6 ± 34.5	0.1 ± 29.5	0.709	–1.3 ± 32.0
Clinically significant, n	0 (0.0)	0 (0.0)	1.000	0 (0.0)
SGPT, U/l	22.2 ± 11.0	23.4 ± 10.9	0.277	22.8 ± 10.9
Change from baseline	–0.7 ± 14.1	1.0 ± 9.2	0.472	0.1 ± 11.9
Percentage change	9.2 ± 53.9	14.1 ± 48.2	0.442	11.6 ± 51.0
Clinically significant, n	0 (0.0)	0 (0.0)	1.000	0 (0.0)
Alkaline phosphatase, U/l	69.0 ± 17.7	68.4 ± 18.4	0.863	68.7 ± 17.9
Change from baseline	–3.3 ± 15.6	–1.5 ± 14.2	0.559	–2.4 ± 14.9
Percentage change	0.1 ± 24.6	–0.2 ± 22.7	0.956	–0.1 ± 23.6
Clinically significant, n	0 (0.0)	0 (0.0)	1.000	0 (0.0)
Serum bilirubin (total), μmol/l	13.5 ± 3.9	15.0 ± 5.6	0.180	14.2 ± 4.8
Change from baseline	–4.8 ± 6.5	–3.7 ± 6.2	0.645	–4.2 ± 6.3
Percentage change	–20.0 ± 26.2	–11.4 ± 35.2	0.439	–15.7 ± 31.1
Clinically significant, n	0 (0.0)	0 (0.0)	1.000	0 (0.0)
Serum protein (total), g/l	67.1 ± 4.1	68.1 ± 4.7	0.252	67.6 ± 4.4
Change from baseline	–0.4 ± 4.7	–0.8 ± 6.1	0.759	–0.6 ± 5.4
Percentage change	–0.2 ± 6.8	–0.5 ± 9.0	0.885	–0.4 ± 7.9
Clinically significant, n	0 (0.0)	0 (0.0)	1.000	0 (0.0)
Serum albumin, g/l	38.0 ± 3.6	38.4 ± 3.3	0.589	38.2 ± 3.4
Change from baseline	1.1 ± 3.1	1.0 ± 3.3	0.977	1.1 ± 3.2
Percentage change	3.2 ± 8.6	3.4 ± 9.4	0.924	3.3 ± 8.9
Clinically significant, n	0 (0.0)	0 (0.0)	1.000	0 (0.0)
Serum globulin, g/l	29.2 ± 4.0	29.9 ± 3.7	0.224	29.5 ± 3.9
Change from baseline	–1.3 ± 3.6	–1.4 ± 4.8	0.432	–1.4 ± 4.2
Percentage change	–3.4 ± 9.5	–2.5 ± 17.8	0.477	–3.0 ± 14.2
Clinically significant, n	0 (0.0)	0 (0.0)	1.000	0 (0.0)
Blood urea, mmol/l	4.4 ± 1.6	4.5 ± 1.3	0.488	4.5 ± 1.5
Change from baseline	–0.1 ± 1.8	–0.6 ± 1.6	0.241	–0.4 ± 1.7
Percentage change	3.0 ± 38.9	–6.6 ± 27.1	0.282	–1.6 ± 33.9
Clinically significant, n	0 (0.0)	0 (0.0)	1.000	0 (0.0)
Serum creatinine, μmol/l	87.4 ± 21.3	83.8 ± 22.0	0.394	85.7 ± 21.6
Change from baseline	2.3 ± 17.9	–1.5 ± 11.3	0.317	0.5 ± 15.1
Percentage change	20.5 ± 129.6	–0.6 ± 12.9	0.293	10.4 ± 94.0
Clinically significant, n	1 (2.0)	0 (0.0)	1.000	1 (1.0)
Blood glucose (random), mmol/l	7.1 ± 2.3	7.3 ± 3.0	0.904	7.2 ± 2.7
Change from baseline	–1.0 ± 4.2	–1.4 ± 4.2	0.521	–1.2 ± 4.1
Percentage change	–1.7 ± 42.8	–4.0 ± 30.5	0.795	–2.9 ± 36.9
Clinically significant, n	2 (3.9)	5 (10.4)	0.256	7 (7.0)
Serum uric acid, μmol/l	356.5 ± 96.5	352.9 ± 76.2)	0.978	354.8 ± 86.7
Clinically significant, n	2 (4.4)	2 (4.8)	1.000	4 (4.4)
ECG test Abnormal, n	20 (38.5)	24 (50.0)	0.246	44 (44.0)
Clinically significant, n	2 (3.9)	2 (4.2)	1.000	4 (4.0)

Figures in parentheses indicate percentages. Change: data at month 3 – data at baseline; percentage change: (data at month 3 – data at baseline) × 100/data at baseline. SGOT = Serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase. Change analysis was not performed for serum uric acid as it was not conducted at baseline for most of the patients.

rameters, liver and renal functions and ECG. However, in the earliest study [2], the results were based on a shorter treatment and assessment period (1 vs. 3 months) and in less acute stroke patients (from 2 weeks to 6 months vs. within 48 h of the stroke onset). In a later study [3], the results were observed only for a shorter treatment and assessment period (1 vs. 3 months), in less acute stroke patients (within 7 days vs. within 2 days of the stroke onset) and in a smaller cohort (10 patients vs. 100 patients). Our present results confirm the safety profile of MLC601 observed in those initial reports.

This is a planned substudy of the main CHIMES trial, and the results from this planned analysis support the decision not to have mandatory laboratory safety tests during study follow-up in the main trial protocol. There will be further unblinded analysis of safety events conducted by the CHIMES Data Safety Monitoring Review Board.

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