Efficacy and Safety of MLC601 (NeuroAiD®), a Traditional Chinese Medicine, in Poststroke Recovery: A Systematic Review

Fahad Javaid Siddiqui a, b  Narayanaswamy Venketasubramanian c
Edwin Shih-Yen Chan a, b  Christopher Chen c

a Duke-NUS Graduate Medical School, b Singapore Clinical Research Institute, and c National University Hospital, Singapore, Singapore

Meta-analysis was conducted using a random effects model. Results: This review included 6 studies with overall low risk of bias but some clinical heterogeneity. MLC601 increased the chances of achieving functional independence after stroke compared to control treatments (risk ratio, 2.35; 95% CI, 1.31–4.23). No deaths and 4 serious adverse events were reported in the MLC601 group, although detail was sparse with inconsistent reporting. Conclusions: There is evidence that MLC601 as an add-on to standard treatment could be effective in improving functional independence and motor recovery and is safe for patients with primarily nonacute stable stroke.

Key Words
MLC601 · Danqi Piantang Jiaonang · NeuroAiD · Stroke · Recovery · Functional independence · Barthel Index · Randomized · Trial · Systematic review · Meta-analysis

Introduction

Stroke is a leading cause of disability and mortality globally. There are a few effective stroke-specific treatment options that improve functional outcome after stroke, including thrombolytic therapy, use of early aspirin, decompression craniectomy, stroke unit care, and constraint-induced movement therapy [1]. Some of these may be offered only to a limited group of patients. Traditional Chinese medicine (TCM) is used extensively in
Asia to facilitate recovery after stroke [2]. Pharmacological studies have demonstrated some TCM to have antioxidant, anti-inflammatory, and antiglutamate effects [3]. In addition, various TCMs have also been shown to dilate blood vessels, suppress platelet aggregation, protect against ischemic reperfusion injury and enhance the tolerance of ischemic tissue to hypoxia [4].

MLC601 (NeuroAiD®; Moleac Pte. Ltd., Singapore) is a TCM derivative and combines extracts from 9 plants (radix astragali, radix salviae miltiorrhizae, radix paeoniae rubrae, rhizoma chuanxiong, radix angelicae sinesis, Carthamus tinctorius, Prunus persica, radix polygalae and rhizoma acori tatarinowii) and 5 animal components (Hirudo, Eupolyphaga seu Stelephaga, calculus bovis artifactus, Bathus martensii and cornu saigae tataricae). The demonstration of neuroprotective and neuroregenerative effects of MLC601 and MLC901 in focal and global brain ischemia in exploratory studies [5, 6] makes MLC601/MLC901 an appropriate therapeutic candidate for ischemic stroke in the clinical setting.

Since the publication of the pooled analysis of 2 trials evaluating the effects of MLC601 in stroke [7], more studies have been published. A large multicenter, randomized, double-blind, placebo-controlled study of MLC601 in acute ischemic stroke patients is currently underway [8]. It is timely to conduct an update of the previous analysis to frame the interpretation of the results of the ongoing trial. Therefore, we conducted this updated systematic review of the efficacy of MLC601 in improving the recovery of stroke patients.

**Methods**

All studies that evaluated the effect of ML601 by a randomized controlled trial design were included in this review. Participants must have had an ischemic stroke; otherwise there were no other restrictions on participant characteristics. MLC601 (NeuroAiD) must have been one of the interventions evaluated. The comparator could be either placebo or standard therapy.

**Types of Outcomes**

The primary outcome was whether or not a patient achieved a functional independence as represented by a score of ≥85 on the Barthel Index (BI) [9] or a score of 0 on item 8 of the Diagnostic Therapeutic Effects of Apoplexy (DTER) scoring system [7, 10] (equivalent to modified Rankin scale of 0–1) by the end of the study period.

The secondary outcomes were: (a) Functional Independence Measure [11], BI or DTER scores; (b) Fugl-Meyer Assessment scores [12]; (c) surface area of visual field defect; (d) middle cerebral artery blood flow velocity, and (e) survival, all measured at the end of the study period.

The 2 Chinese studies reported the score of DTER item 8 (score 0 = able to take care of oneself and speak freely) as a cutoff for functional independence. One study only reported the mean difference of BI scores without categorizing them as ‘functionally independent’ or otherwise. Therefore, raw BI scores, obtained from study investigators, were used to categorize patients using a BI cutoff of ≥85 to make it consistent with item 8 of the DTER before conducting the pooled analysis.

**Literature Search Methods**

A literature search was conducted of PubMed® (1900 to date), the Cochrane Database of Systematic Reviews (2005 to date), the Cochrane Central Register of Controlled Trials (1898 to date) and the Database of Abstracts of Reviews of Effects (1994 to date) for published reports. References of eligible articles and review articles were also searched for relevant citations. There was no restriction on the language. In addition, we also contacted authors of identified articles for any publications they were aware of. Search terms used included ‘Danqi Pian tang Jiao nan’, ‘DPJ’, ‘MLC601’, ‘NeuroAiD’ and ‘MLC 901’. The last search was conducted in September 2012.

**Study Selection, Critical Appraisal and Data Extraction**

Two review authors (F.J.S. and N.V.) screened the title and abstracts of potentially eligible trials independently. The full texts of short-listed papers were obtained and assessed in detail. Disagreements were resolved by consensus. Two reviewers (F.J.S. and N.V.) assessed eligible studies for risk of bias using the domain-specific instrument of the Cochrane Collaboration [13]. The domains assessed were randomization procedure, allocation concealment, blinding (patient, caregivers and outcome assessors), loss to follow-up, and selective reporting. Any disagreement was resolved by consulting a third review author (C.C.). Data extraction was done (F.J.S.) using a standardized data extraction form. Missing information on outcome measures were obtained by contacting the authors.

**Assessment of Heterogeneity**

Prior to data pooling, studies were assessed for clinical homogeneity based on the characteristics of the patients studied and similarity of the trial procedures (table 1). The following areas of heterogeneity were considered to be important when it came to deciding on data pooling: (a) patient age and severity of stroke; (b) comparator used; (c) outcome measurement tools, and (d) time of outcome assessments. Statistical heterogeneity was assessed by calculating the $I^2$ value.

**Data Synthesis**

All data analysis was done using RevMan 5.1 [13]. The decision to pool was based on a judgment of clinical homogeneity and an $I^2 <75%$. When it was judged to be inappropriate to pool, forest plots without pooled estimates were shown to present individual study treatment effects.

**Sensitivity Analysis**

Robustness of the results was ascertained through sensitivity analyses. $I^2$ value >75%, number of patients lost to follow-up greater than observed outcomes or unbalanced lost to follow-up between two arms of a study dictated the decision whether or not to carry out the analyses.
### Table 1. Characteristics of studies included in the systematic review of NeuroAiD in ischemic stroke

| Studies            | Methods                                      | Participants                                                                 | Interventions                                                                 | Outcomes                                                                 |
|--------------------|----------------------------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| China 01 [7]      | Multicenter, randomized, double-blind, active controlled trial conducted in China from 1999 to 2000 | Inclusion criteria: Age 18–70 years, diagnosed with ischemic stroke according to Western medicine diagnosis standards in China, met requirements of TCM standards for diagnosis of apoplexy, DTER score ≥10, at the restoration stage according to TCM criteria (i.e. 15 days to 6 months after stroke onset, provided informed consent) | Intervention group: MLC601, 0.4 g, 4 capsules 3 times a day for 4 weeks Control group: Buchang Naoxintong Jiaonang, 4 capsules 3 times a day for 4 weeks | Primary outcome: Functional and neurological function as assessed on DTER Comprehensive functions score was dichotomized into 0 vs. 2–8 (which may be compared with a 0–1 vs. 2–5 dichotomy on mRS) The neurological/motor function was assessed by adding the first 7 subscores of the DTER |
| China 02 [7]      | Multicenter, randomized, double-blind, active controlled trial conducted in China from 1999 to 2000 | Inclusion criteria: Age 18–70 years, diagnosed with ischemic stroke according to Western medicine diagnosis standards in China, met requirements of TCM standards for diagnosis of apoplexy, DTER score ≥10, at the restoration stage according to TCM criteria (i.e. 15 days to 6 months after stroke onset, provided informed consent) | Intervention group: MLC601, 0.4 g, 4 capsules 3 times a day for 4 weeks Control group: Buchang Naoxintong Jiaonang, 4 capsules 3 times a day for 4 weeks | Primary outcome: Functional and neurological function as assessed on DTER Comprehensive functions score was dichotomized into 0 vs. 2–8 (which may be compared with a 0–1 vs. 2–5 dichotomy on mRS) The neurological/motor function was assessed by adding the first 7 subscores of the DTER |
| Kong et al. [15]  | Single-center, randomized, double-blind, placebo-controlled, phase II pilot study conducted in a rehabilitation facility in Singapore | Inclusion criteria: Age 21–80 years, within 1 month of ischemic stroke, motor power of grade <5/5 on the Medical Research Council Scale in at least 1 limb, presroke mRS ≤1, nonchild-bearing potential, cerebral infarction compatible with CT or MRI. Exclusion criteria: Recent thrombolysis, ICH, full-dose or long-term anticoagulation, significant nonischemic brain lesion, coexisting systemic diseases (cancers, renal/liver failure, dementia, psychosis, cirrhosis), previous stroke, craniootomy or seizures, aphasia or other cognitive disabilities, hemoglobin <10 mg/dl | Intervention group: MLC601, 4 capsules 3 times a day for 1 month plus standard care Control group: Placebo, 4 capsules 3 times a day for 1 month plus standard care | Primary outcome: Motor impairment as assessed on FMA at 4 weeks Secondary outcomes: Functional status at 4 and 8 weeks as assessed on FIM; FMA scores and subscores at 4 and 8 weeks; stroke severity as assessed on NIHSS scores and subscores at 4 and 8 weeks Patients were also analyzed by severity category as severe (0–55), moderate (56–80) and mild (81–100) based on FMA scores |
| Harandi et al. [14]| Single-center, randomized, double-blind, placebo-controlled trial conducted in a tertiary care center in Iran from July 2009 to Feb 2010 | Inclusion criteria: Age 30–72 years, within 1 month of ischemic stroke as assessed by CT or MRI Exclusion criteria: Treatment with thrombolytic, ischemic stroke with hemorrhage, severe renal or liver failure, dementia, psychosis, history of seizure disorder, previous stroke and hemoglobin <10 mg/dl | Intervention group: MLC601, 400 mg, 4 capsules 3 times a day for 3 months plus standard care Control group: Placebo, 4 capsules 3 times a day for 3 months plus standard care | Motor impairment as assessed on FMA at baseline, 4, 8 and 12 weeks Patients were also categorized as having severe (0–55), moderate (56–80) and mild (81–100) motor limitation based on FMA scores |
| Shahripour et al. [16]| Single-center, randomized, double-blind, placebo-controlled study conducted in a tertiary hospital in Iran from April 2009 to March 2010 | Inclusion criteria: Age 60–80 years, acute brain infarct in MCA territory within a week confirmed by CT or MRI, hospitalized within 24 h of stroke Exclusion criteria: ICH, history of stroke, inability to swallow, significant systemic diseases, brain tumors or infections | Intervention group: MLC601, 4 capsules 3 times a day for 3 months plus standard treatment Control group: Placebo, 4 capsules 3 times a day for 3 months plus standard treatment | Primary outcome: MCA blood flow velocity as measured by transcranial Doppler at baseline and 3 months done by single operator Secondary end points: Barthel Index and mRS |
| Ghandehari et al. [17]| Single-center, randomized single-blind, active-control trial conducted in a tertiary care hospital in Iran from 2009 to 2010 | Inclusion criteria: Age- and sex-matched, ≥18 years old, within 1 week of presentation with pure homonymous hemianopia, due to PCA territory ischemic stroke confirmed on CT or MRI and confirmed by perimetry Exclusion criteria: Recent thrombolysis, ICH, rapidly improved neurological deficit, GCS <5, tumors or demyelinating lesions, coexisting ophthalmic and/or systemic diseases, lacunar infarction in posterior cerebral artery territory, aphasia, epilepsy, craniootmy, previous stroke with visual field defects, stroke recurrence during 3-month follow-up affecting visual field, requiring rehabilitation or speech therapy | Intervention group: MLC601, 400 mg, 4 capsules 3 times a day for 3 months plus standard care Control group: Piracetam, 800 mg, 2 tablets 3 times a day for 3 months plus standard care | Outcome: Visual field defect as measured by point grid perimetry at baseline and 3 months; surface area of each visual field defect was manually calculated in mm² |

TIA = Transient ischemic attack; AF = atrial fibrillation; mRS = modified Rankin Scale; CT = computed tomography; MRI = magnetic resonance imaging; ICH = intracerebral hemorrhage; FMA = Fugl-Meyer Assessment; FIM = Functional Independence Measure; NIHSS = National Institutes of Health Stroke Scale; MCA = middle cerebral artery; PCA = posterior cerebral artery; GCS = Glasgow Coma Scale.
The treatment effect on the primary outcome (binary measure) was summarized as a relative risk and pooled using the Mantel-Haenszel method. All the secondary outcomes (continuous measures) were summarized as mean differences of change scores and pooled using the inverse variance method.

Results

Search Results

In total, we identified 30 citations. Through PubMed we identified 14 citations. In this set, 5 articles were found to be relevant; the rest were rejected as they were either basic science studies, stroke epidemiology studies or uninformative. Through the Cochrane Library search we identified 15 citations. Of these, 6 were the same as those found in PubMed, 2 were trial registry entries (1 published and 1 ongoing), 4 were conference presentations of results of the trials for which full reports had been published and identified in both sets of citations, 1 was a webpage of the company that markets the drug outside China, and 2 were duplicate publications (1 trial and 1 update of progress of an ongoing trial). None of the citations that were uniquely identified through the Cochrane database were found to be eligible for full text evaluation. Another study was identified through personal contact of the author (C.C.). In total, 5 studies were short-listed for full text evaluation. The included studies involved a total of 915 patients, 580 randomized to MLC601 and 335 randomized to the control arm. The age of the patients ranged between 18 and 80 years. Table 1 provides details of the characteristics of the individual studies.

Characteristics of the Included Studies

All 6 included trials compared MLC601 to placebo [14–16] or another treatment, i.e. piracetam [17] and Bucchang [7]. Two trials (China 01 and 02) [7] were multicenter studies, while the rest were single-center studies conducted in three countries: Iran, Singapore and China. The included studies involved a total of 915 patients, 580 randomized to MLC601 and 335 randomized to the control arm. The age of the patients ranged between 18 and 80 years. Table 1 provides details of the characteristics of the individual studies.

Impact of Risk of Bias

We were able to obtain additional information on the key domains of risk of bias for 4 of the included clinical trials (fig. 2). We found that in general there was low risk of bias in the included studies for the domains that were important for our objectives. Nevertheless, 1 study [16] had incomplete outcome data assessment (for BI). In the ‘worst-case scenario’ the pooled effect became statistically insignificant and heterogeneity increased to 65% (analysis not shown). In another study [17] where the outcome assessment involved unblinded patients, the risk of bias was also high. However, this was a single study that reported visual field defect as outcome.

Outcomes – Functional Independence and Motor Recovery

Functional Independence

We combined the results reported by studies China 01, China 02 [7] and Shahripour et al. [16]. The Chinese studies reported outcomes based on DTER (item 8), whereas Shahripour et al. [16] used BI. The pooled analysis is presented in figure 3. Results show the pooled relative risk of
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias

| Study       | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|-------------|----------------------------|------------------------|----------------------------------------|------------------------------|------------------------|---------------------|------------|
| China 01    | ?                          | ?                      | ?                                     | ?                            | ?                      | ?                   |            |
| China 02    | ?                          | ?                      | ?                                     | ?                            | ?                      | ?                   |            |
| Ghandehari  | +                          | +                      | +                                     | +                            | +                      | +                   | +          |
| Harandi     | +                          | +                      | +                                     | +                            | +                      | +                   | +          |
| Kong        | +                          | +                      | +                                     | +                            | +                      | +                   | +          |
| Shahripour  | +                          | +                      | +                                     | +                            | +                      | +                   | +          |

**Fig. 2.** Risk of bias: judgments of the review authors for each risk of bias item for each included study and presented as percentages across all included studies.
2.35 (95% CI, 1.31–4.23) in favor of MLC601. The effect was consistent at 1 and 3 months.

Functional independence was also assessed by change scores of the functional improvement scales in 2 studies [15, 16]. One study reported an effect favoring control treatment, though not achieving statistical significance, both at 1 and 2 months (–0.45; 95% CI, –1.08 to 0.18 and –0.55; 95% CI, –1.18 to 0.08, respectively) while the other reported a statistically significant effect favoring MLC601 at 3 months (1.0; 95% CI, 0.50–1.51). Due to high statistical heterogeneity (I² = 93%), no pooling of results was undertaken.

Motor Recovery

Two Chinese studies [7] along with the studies by Kong et al. [15] and Harandi et al. [14] assessed motor recovery. The Chinese studies used the motor items of DTER, while the other 2 studies used the Fugl-Meyer Assessment motor score. The pooled analysis is presented in figure 4. The result was directionally in favor of MLC601 though not statistically significant (0.27; 95% CI, –0.02 to 0.55). Harandi et al. [14] showed a much stronger effect at both time points of 1 and 2 months. However, all studies showed beneficial effect in favor of MLC601.

Visual Field Defect Recovery

One study on visual field recovery [17] showed that there was a reduction of defect area in both left and right eyes in favor of MLC601 as measured by difference in changed scores from baseline. The results of right and left eyes were 148.10 (95% CI, –112.19 to 408.39) and 204.60 (95% CI, –39.99 to 449.19), respectively, although this was not statistically significant.

Cerebral Blood Flow Improvement

One study evaluated cerebral blood flow velocity in the territory of the middle cerebral artery [16] and showed...
a significant increase in the velocity in the treatment group (6.36; 95% CI, 3.29–9.43).

Safety

The included studies provided sparse information on the adverse effects of the MLC601. Table 2 presents the distribution of adverse and serious adverse effects. Overall side effects were uncommon in both groups though nonserious ones were more frequent in the MLC601 group. The Chinese trials reported no serious adverse events [7]. Nonserious adverse events included nausea and vomiting in 2 patients receiving MLC601. No adverse event was reported for the control group. Ghandehari et al. [17] reported no serious adverse event in the MLC601 group, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches. Mild abdominal discomfort in 2 patients receiving MLC601 and headache, drowsiness and dizziness in 2 patients in the control group were reported. Harandi et al. [14] reported no serious adverse event, while 1 patient was withdrawn from the control group due to severe headaches.
that occurred in 15 patients, 12 were mild and 4 were moderate. No further description of adverse events was available. Shahripour et al. [16] reported that 6 patients experienced adverse effects and all withdrew from the study, 2 (nontraumatic epistaxis) from the MLC601 and 4 (upper gastrointestinal upset) from the control group.

**Discussion**

The included studies in this systematic review evaluated the treatment effect on various clinical and surrogate outcomes. Functional independence even when measured on different scales shows little heterogeneity and the chance of being functionally independent is more than twice as high in those patients receiving MLC601 compared to those receiving standard therapy. These results are from 3 studies of which 2 are of uncertain quality. However, effect size from the third study in this pooled analysis, which was judged as at low risk of bias, was consistent with the other 2 studies with regard to the direction of effect. Due to the small sample size the confidence interval of this estimate is wide and crosses the null value. When additional heterogeneity was modeled by using a random effects model, the treatment effect remained statistically significant.

Motor recovery is a more objective measure of neurological recovery, although baseline comparability of the study arms was not available for 2 of the 4 contributing studies. Motor recovery after stroke was assessed using different scales and at different times. Both these factors were taken into account while conducting the analysis and, therefore, standardized mean differences were computed and pooled with a random-effect model. The results showed some heterogeneity. Nevertheless, all the point estimates favored MLC601. The pooled estimate marginally crossed the line of no difference.

Visual field defects are an important sensory defect resulting from stroke. The only study that reported this outcome showed a large effect that did not achieve statistical significance. The fact that patients were not blinded to the treatment allocation and were part of the outcome assessment procedure might have contributed to bias in the outcome measurements. However, since any improvement in vision may be clinically important and the observed difference in improvements is relatively large, the possibility of statistically significant results in post-stroke hemianopsia with MLC601 cannot be excluded and further study should be encouraged.

In a study evaluating the effect of MLC601 on the surrogate endpoint of cerebral blood flow velocity, it was found that mean arterial blood flow velocity significantly normalized when measured as a change from baseline. In the same study, there was a corresponding improvement in BI in the MLC601 group which may have implications on perfusion demand by surviving neurons, vasodilatory effects of MLC601, and neurovascular coupling that is important in neurorepair.

Safety data were quite sparse in the included studies. There was inconsistency in the reporting of various adverse effects and in defining serious and nonserious adverse events across studies. A possible link to the intervention was also not extensively discussed in any of the studies. There is a need to record and report the adverse and serious adverse effects in a standardized format, e.g. CIOMS [18] or MedDRA [19], using current definitions [20–21].

As regards the safety of MLC601, no deaths in any of the studies have been reported. Most of the reported ad-

### Table 2. Distribution of serious and nonserious adverse events as reported in the included studies in different arms of the trials

| Study                  | n  | Adverse events | Serious adverse events |
|------------------------|----|----------------|------------------------|
|                        |    | MLC601 (n = 580) | control (n = 335) | total (n = 915) | MLC601 (n = 580) | control (n = 335) | total (n = 915) |
| China 01 and 02 [7]    | 605| 2 0 2 | 0 0 0 |
| Ghandehari [17]       | 40 | 2 2 4 | 0 1 1 |
| Harandi [14]          | 150| 7 0 7 | 0 0 0 |
| Kong [15]             | 40 | 9 7 16| 4 1 5 |
| Shahripour [16]       | 80 | 2 4 6 | 0 0 0 |
verse events appear to be nonserious and did not require discontinuation of the intervention; however, a few events in the intervention group did require withdrawal of patients from MLC601. In all studies except 1, patients were blinded to the treatment allocation; therefore, reporting is less likely to be affected by bias. Nonetheless, a study on a subgroup of patients in the ongoing CHIMES trial has confirmed the safety of MLC601 in acute stroke patients [22].

While studies did not exclude stroke patients in the acute phase following the event, they included patients from 1 week to as long as 6 months after the index ischemic stroke. This suggests that the efficacy of MLC601 may extend beyond neuroprotection and involve neurorestoration long after stroke onset. These findings in the clinical studies parallel those found in nonclinical studies which reported both neuroprotective and neuroregenerative properties of NeuroAid in animal and neuronal models of ischemia [5, 6]. The additional benefit of starting the treatment early in acute stroke is being investigated [8].

Limitations and Strengths

Our review has several limitations. The risk of bias information is not available for 2 of the largest studies. Nevertheless, results from the other smaller studies with low risk of bias remained consistent with the 2 larger studies, giving some confidence in the results. Not all studies assessed the same clinical outcomes. Hence, in any given meta-analysis only a few studies contributed. In addition, even for the studies that assessed the same outcome, different tools were used, increasing the heterogeneity between the studies and highlighting the limitations of existing evidence after a thorough search of the literature, rigorous methodological evaluation of relevant trials, explicit reporting of risk of bias and commenting on the robustness of the results.

Conclusions

The ongoing large clinical trial of MLC601 in acute stroke should help overcome the limitations of previously conducted studies. Nevertheless, our review reveals that there is some evidence that MLC601 as an add-on to standard treatment could be effective in further improving functional independence and motor recovery and is safe for patients with primarily nonacute stable stroke.

Acknowledgements

The authors would like to thank Drs. Christopher Chen, Ali Amini Harandi, Keng He Kong, Reza Bavarsad Shahripour, and Kavian Ghandehari for providing information on their respective publications reviewed in this systematic review, and Dr. Robert Gan for his help in obtaining the necessary publications and contacts of the primary authors.

Disclosure Statement

N.V. and C.C. received funding from the National Medical Research Council of Singapore, CHIMES Society and Moleac for NeuroAid research. F.J.S. and E.S.-Y.C. have no disclosures.

References

1 European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee: Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25:457–450.
2 Wu B, Liu M, Liu H, Li W, Tan S, Zhang S, et al: Meta-analysis of traditional Chinese patent medicine for ischemic stroke. Stroke 2007;38:1973–1979.
3 Rausch WD, Liu S, Gille G, Radad K: Neuroprotective effects of ginsenosides. Acta Neurobiol Exp 2006;66:369–375.
4 Bei W, Peng W, Zang L, Xie Z, Hu D, Xu A: Neuroprotective effects of a standardized extract of Diospyros kaki leaves on MCAO transient focal cerebral ischemic rats and cultured neurons injured by glutamate or hypoxia. Planta Med 2007;73:636–643.
5 Heurteaux C, Gandin C, Borsotto M, Widmann C, Brau F, Lhuillier M, et al: Neuroprotective and neuroproliferative activities of NeuroAid (MLC601, MLC901), a Chinese medicine, in vitro and in vivo. Neuropharmacology 2010;58:987–1001.
6 Quintard H, Borsotto M, Veysiere J, Gandin C, Llabal F, Widmann C, et al: MLC901, a traditional Chinese medicine protects the brain against global ischemia. Neuropharmacology 2011;61:622–631.
7 Chen C, Venketasubramanian N, Gan RN, Lambert C, Picard D, Chan BP, et al: Danqi Piantang Pianong (DP), a traditional Chinese medicine, in poststroke recovery. Stroke 2009;40:859–863.
8 Venketasubramanian N, Chen CL, Gan RN, Chan BP, Chang HM, Tan SB, et al: A double-blind, placebo-controlled, randomized, multicenter study to investigate CHinese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES Study). Int J Stroke 2009;4:54–60.
9 Mahoney FI, Barthel DW: Functional evaluation: the Barthel Index. Md State Med J 1965;14:61–65.
10 Encephalopathy Emergency Scientific Research Coordination Team of the State Traditional Chinese Medicine Authority: The standards for evaluating the Diagnostic Therapeutic Effects of Apoplexy (DTER). Zhonghua Shen Jing Ke ZaZhi 1996;29:379.
11 Turner-Stokes L, Nyen K, Turner-Stokes T, Gatehouse C: The UK FIM+FAM: development and evaluation. Functional Assessment Measure. Clin Rehabil 1999;13:277–287.

12 Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S: The post-stroke hemiplegic patient. I. A method for evaluation of physical performance. Scand J Rehabil Med 1975;7:13–31.

13 Review Manager (RevMan) Computer Program, version 5.1. Copenhagen, the Nordic Cochrane Centre, the Cochrane Collaboration, 2011.

14 Harandi AA, Abolfazli R, Hatemian A, Ghragozlee K, Ghaffar-Pour M, Karimi M, et al: Safety and efficacy of MLC601 in Iranian patients after stroke: a double-blind, placebo-controlled clinical trial. Stroke Res Treat 2011;2011:721613.

15 Kong KH, Wee SK, Ng CY, Chua K, Chan KF, Venketasubramanian N, et al: A double-blind, placebo-controlled, randomized phase II pilot study to investigate the potential efficacy of the traditional Chinese medicine Neuroaid (MLC 601) in enhancing recovery after stroke (TIERS). Cerebrovasc Dis 2009;28:514–521.

16 Shahripour BR, Shamsaei G, Pakdaman H, Majdinasab N, Nejad EM, Sajedi SA, et al: The effect of NeuroAid (MLC601) on cerebral blood flow velocity in subjects’ post brain infarct in the middle cerebral artery territory. Eur J Intern Med 2011;22:509–513.

17 Ghandehari K, Mood ZI, Ebrahimzadeh S, Picard D, Zhang Y: NeuroAid (MLC601) versus piracetam in the recovery of post-infarct homonymous hemianopsia. Neural Regen Res 2011;6:418–422.

18 CIOMS: Reporting Adverse Drug Reactions. Geneva, CIOMS, 2000. http://www.cioms.ch/publications/reporting_adverse_drug.pdf.

19 MedDRA MSSO NGC: Welcome to MedDRA and the MSSO. 2010 (updated 22 Nov 2010; cited 23 Nov 2012). http://www.meddramsso.com/index.asp.

20 FDA: What Is a Serious Adverse Event? 2012 (updated 23 June 2011; cited 29 Nov 2012). http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm.

21 ICOH: Clinical safety data management: definitions and standards for expedited reporting E2A. Federal Register 1995;60:11284–11287.

22 Young SHY, Zhao Y, Koh A, Singh R, Chan BPL, CHnag HM, Venketasubramanian N, Chen C, CHIMES investigators: Safety profile of MLC601 (Neuroaid) in acute ischemic stroke patients: a Singaporean substudy on the Chinese medicine Neuroaid efficacy on stroke recovery study. Cerebrovasc Dis 2010;30:1–6.