Effects of MLC601 on Early Vascular Events in Patients After Stroke

The CHIMES Study

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Background and Purpose—Early vascular events are an important cause of morbidity and mortality in the first 3 months after a stroke. We aimed to investigate the effects of MLC601 on the occurrence of early vascular events within 3 months of stroke onset.

Methods—Post hoc analysis was performed on data from subjects included in the CHInese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES) study, a randomized, placebo-controlled, double-blinded trial that compared MLC601 with placebo in 1099 subjects with ischemic stroke of intermediate severity in the preceding 72 hours. Early vascular events were defined as a composite of recurrent stroke, acute coronary syndrome, and vascular death occurring within 3 months of stroke onset.

Results—The frequency of early vascular events during the 3-month follow-up was significantly less in the MLC601 group than in the placebo group (16 [2.9%] versus 31 events [5.6%]; risk difference=−2.7%; 95% confidence interval, −5.1% to −0.4%; P=0.025) without an increase in nonvascular deaths. Kaplan–Meier survival analysis showed a difference in the risk of vascular outcomes between the 2 groups as early as the first month after stroke (Log-rank P=0.024; hazard ratio, 0.51; 95% confidence interval, 0.28–0.93).

Conclusions—Treatment with MLC601 was associated with reduced early vascular events among subjects in the CHIMES study. The mechanisms for this effect require further study.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00554723.

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Key Words: clinical trial ■ Neuroaid ■ secondary prevention ■ stroke ■ vascular diseases

Early vascular events after stroke are important causes of morbidity and mortality with 90% of mortality within 30 days after a stroke being related to stroke progression, recurrent stroke, or cardiovascular disease.[1,2] Although stroke progression most commonly occurs soon after stroke, the risk for recurrent stroke was 7.4% at 90 days in a hospital-based cohort and 17.3% at 3 months after a transient ischemic attack or minor stroke in a population-based study.[3,4]

Treatments to prevent early vascular events include antiplatelets[5] and management of underlying conditions such as carotid stenosis, sources of embolism, and dissection. Clinical studies on patients with nonacute stroke showed that MLC601 (NeuroAiD™) improved recovery with a good safety profile.[6] Because MLC601 has been reported to improve cerebral blood flow velocity in patients with subacute stroke[7] and potentially induce ischemic preconditioning by activating ATP-dependent potassium channels,[8] we hypothesized that MLC601 may have an effect on preventing occurrence of early vascular events within 3 months of stroke onset.

Methods

The CHInese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES) study is a randomized, double-blinded, placebo-controlled trial comparing MLC601 with placebo in patients with acute ischemic stroke of intermediate severity in the preceding 72 hours.[9] Subjects were allocated to either MLC601 or placebo for 3 months, in addition to standard stroke care, for example, antiplatelet therapy, control of vascular risk factors, and appropriate rehabilitation. Subjects were assessed on 3 follow-up visits when occurrence of any adverse events was recorded. Information ascertained for all adverse events included diagnosis for the event, date of onset/resolution, severity, action taken concerning study treatment, relatedness to study drug, treatment given, seriousness criteria, causality, expectedness, and outcome. All serious adverse events were adjudicated by a blinded committee.

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Table 1. Concomitant Therapies of Subjects During the CHIMES Study

	MLC601 (n=550)	Placebo (n=549)
Antiplatelet medication	525 (95.5)	518 (94.4)
Statin	505 (91.8)	502 (91.4)
Antihypertensive treatment	427 (77.6)	437 (79.6)
Angiotensin converting enzyme inhibitor	182 (33.1)	169 (30.8)
Angiotensin receptor blocker	165 (30.0)	163 (29.7)
Antidiabetic treatment	151 (27.5)	166 (30.2)
Rehabilitation	412 (74.9)	414 (75.4)

Data in number, %. CHIMES indicates the CHInese Medicine Neuroaid Efficacy on Stroke recovery study.

Study End Points

The primary analysis for this study was on a composite vascular outcome consisting of nonfatal recurrent stroke (ischemic or hemorrhagic; transient ischemic attack was excluded), nonfatal acute coronary event (ST–elevation myocardial infarction, non-ST–elevation myocardial infarction, or unstable angina), or vascular death (death from stroke or cardiac causes including sudden death) within 3 months after randomization. Vascular outcome events were reported by the subject or proxy (eg, relative, caregiver, nurse, physician) at occurrence or during study follow-up. On notification, detailed information was obtained and recorded; furthermore, medical records or death certificates were reviewed whenever available. All components of the composite outcome were serious adverse events and were hence blindly adjudicated.

Statistical Analysis

Post hoc intention-to-treat analysis was performed. Odds ratio and risk difference (RD) between the 2 groups, with the corresponding 95% confidence intervals (CIs) and *P* values, were computed for the composite vascular outcome and individual components. An ordinal logistic regression model was fitted with recurrent vascular events and month-3 modified Rankin Score (mRS), adjusting for treatment, age, sex, and baseline National Institutes of Health Stroke Scale. Kaplan–Meier curves for time from randomization to the first occurrence of any vascular event or vascular death were plotted for both groups and compared by Log-rank test and hazard ratio. Patients who did not experience any vascular event or death were censored on the day of last visit, which was the 3-month follow-up for most patients.

Results

Baseline characteristics of the 1099 subjects included in the primary analysis were described previously.[9] Poststroke use of secondary prevention treatments and rehabilitation were similar between the 2 groups (Table 1). The numbers of at-risk subjects, that is, those who had not experienced events and were not lost to follow-up, at each time point are shown in the Figure.

Overall, the composite vascular outcome occurred in 47 (4.3%) subjects during the 3-month follow-up period: 16 (2.9%) subjects in the MLC601 group and 31 (5.6%) subjects in the placebo group (odds ratio, 0.50; 95% CI, 0.27–0.93; RD, −2.7%; 95% CI, −5.1% to −0.4%]; Table 2). Although not always reaching statistical significance attributable to the small numbers of events in each subgroup, each individual vascular event was consistently fewer in the MLC601 group. The ordinal logistic regression model showed a statistically significant relationship between recurrent vascular events and mRS (cumulative odds ratio, 0.25; 95% CI, 0.13–0.50; $P<0.001$). Sensitivity analyses assuming that all subjects with incomplete follow-up had a vascular event showed an RD of −2.6% (95% CI, −6.4% to 1.2%), whereas removing subjects with incomplete follow-up from the cohort showed an RD of −3.0% (95% CI, −5.5% to −0.4%).

Subjects who experienced an early vascular event were older ($P=0.033$) and more likely to have a history of hyperlipidemia ($P=0.016$) and myocardial infarction (Log-rank $P=0.053$). A multivariable logistic regression was fitted by adding these factors as covariates, and the results were not affected.

Kaplan–Meier curves for the composite vascular outcomes showed divergence in the rates of occurrence of vascular events and vascular deaths between the treatment groups as early as the first month after the stroke ($P=0.024$; hazard ratio, 0.51; 95% CI, 0.28–0.93; Figure).

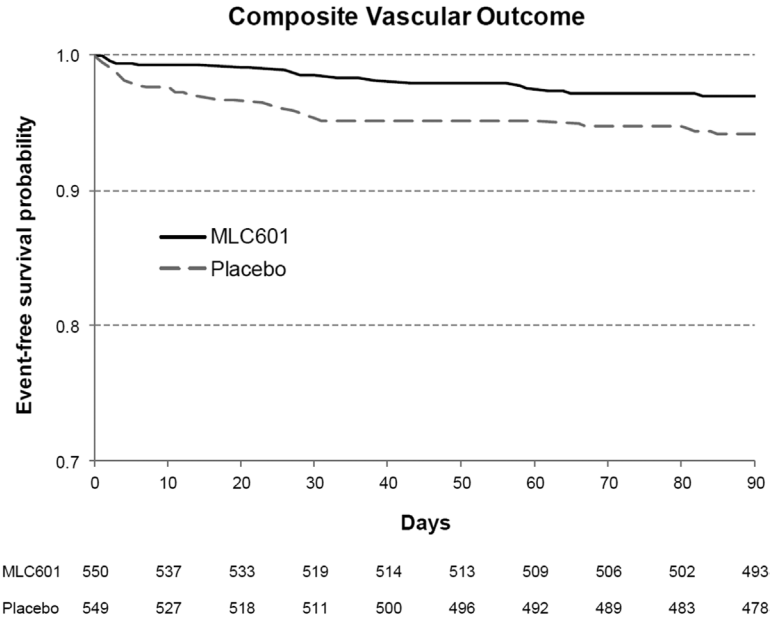

Figure. Kaplan–Meier curve of composite outcome of recurrent stroke, acute coronary event, or vascular death. Log-rank test: $P=0.024$, hazard ratio, 0.51; 95% confidence interval, 0.28–0.93.

Table 2. Vascular Outcomes in the CHIMES Study at 3 Months

Events	MLC601 (n=550) n	MLC601 (n=550) %	Placebo (n=549) n	Placebo (n=549) %	Risk Difference (95% CI), %	*P* Value
Recurrent stroke, acute coronary event, or vascular death	16	2.9	31	5.6	−2.7 (−5.1, −0.4)	0.025
Nonfatal recurrent stroke	10	1.8	16	2.9	−1.1 (−2.9, 0.7)	0.232
Nonfatal acute coronary event	1	0.2	6	1.1	−0.9 (−1.8, 0.0)	0.057
Vascular death	5	0.9	9	1.6	−0.7 (−2.1, 0.6)	0.280
Fatal acute coronary event	5	0.9	5	0.9	0 (−1.1, 1.1)	0.998
Fatal stroke	0	0	4	0.7	−0.7 (−1.4, −0.0)	0.045

CHIMES indicates the CHInese Medicine Neuroaid Efficacy on Stroke recovery study; and CI, confidence interval.

Discussion

Our study shows that the rate of early vascular events in the MLC601-treated subjects was half that of placebo-treated subjects. In absolute terms, ≈27 fewer patients had an early vascular event per 1000 patients treated for 3 months. There was no increase in nonvascular deaths.[9] Although early vascular events were associated with poorer mRS, and a reduction in such vascular events with treatment should improve functional outcome, this was not detected statistically in the primary analysis of the CHIMES study, presumably because of dilution by other factors.[9]

Only a limited number of treatments have been shown to reduce early recurrent vascular events after acute stroke. Aspirin produced a small but important reduction of ≈10 deaths or recurrent strokes per 1000.[5] Recently, it was reported that addition of clopidogrel to aspirin started within 24 hours from stroke onset resulted in a 3.5% absolute reduction in recurrent stroke compared with aspirin alone during the next 90 days.[10]

The risk of early vascular events was associated with hypertension, atrial fibrillation, diabetes mellitus, infarct size, and underlying mechanism.[1–4] The CHIMES study included only patients with moderately severe acute strokes on antiplatelet therapy and excluded patients with severe stroke and atrial fibrillation requiring anticoagulation. Furthermore, all patients received standard medical management and treatments for secondary stroke prevention as necessary, including statins and antihypertensive drugs. Hence, this may account for the lower 3-month vascular event rate in the CHIMES study.

The present results are hypothesis generating. Because treatment was given for 3 months in the CHIMES study, in contrast to other acute stroke trials wherein treatments were given for a few days to weeks, the longer treatment duration may have played a role. Previous studies of MLC601 in normal subjects and patients with stroke showed neither antiplatelet effects nor interaction with aspirin. Moreover, because no difference in hemorrhagic events between MLC601 and placebo was detected in the CHIMES study,[9] it seems unlikely that an antithrombotic effect of MLC601 can be an explanatory mechanism, nor does MLC601 have any known effect on blood pressure or lipids. It is possible that the effect of MLC601 on ATP-dependent potassium channel activation may provide myocardial and cerebral preconditioning and hence chronic cytoprotection.[8,11] It is also plausible that the beneficial effect may be attributable to putative pleiotropic actions of MLC601 on the vasculature or other tissue targets.

There were some limitations in this study. The analysis was post hoc, and the trial was not originally powered to investigate vascular outcomes. Furthermore, the number of vascular events overall was small. Although the study required that all subjects receive standard stroke care, including antiplatelet therapy, control of vascular risk factors, and appropriate rehabilitation, the choice of specific therapies to control medical and social risk factors in each subject was left to the treating physician. Nevertheless, the CHIMES study was a well-monitored, large, double-blinded, randomized trial in which vascular outcomes were ascertained prospectively, blinded to subject treatment allocation. The composite vascular outcome is commonly used for similar analyses. Finally, there was no difference in the use of concomitant therapies and rehabilitation between the 2 groups during the study period.

In summary, this study suggests a potentially important effect of MLC601 in reducing early vascular events and deaths, which may complement observations from previous clinical trials. This warrants further investigation of MLC601 both for confirmation of this effect and elucidation of mechanism(s) of action.

Appendix

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For a complete list of the CHInese Medicine Neuroaid Efficacy on Stroke recovery study contributors, see Reference 9.

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Disclosures

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