Prognostic Factors and Treatment Effect in the CHIMES Study

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Background: Stroke trials often analyze patients with heterogeneous prognoses using a single definition of outcome, which may not be applicable to all subgroups. We aimed to evaluate the treatment effects of MCL601 among patients stratified by prognosis in the Chinese Medicine Neuroaid Efficacy on Stroke Recovery (CHIMES) study. *Methods:* Analyses were performed using data from the CHIMES study, an international, randomized, placebo-controlled, double-blind trial comparing MLC601 with placebo in patients with ischemic stroke of intermediate severity in the preceding 72 hours. All subjects with baseline data and the modified Rankin Scale (mRS) score at 3 months were included. *Results:* Data from 1006 subjects were analyzed. The predictive variables for mRS score greater than 1 at month 3 were age older than 60 years ($P < .001$), baseline National Institutes of Health Stroke Scale score 10-14 ($P < .001$), stroke onset to initiation of study treatment of more than 48 hours ($P < .001$), and female sex ($P = .026$). A higher number of predictors was associated with poorer mRS score at month 3 for both placebo ($P < .001$) and treatment ($P < .001$) groups. The odds ratio (OR) for achieving a good outcome increased with the number of predictors and reached statistical significance in favor of MLC601 among patients with 2 to 4 predictors combined (unadjusted OR = 1.44, 95% confidence interval, 1.02-2.03; adjusted OR = 1.60, 95% confidence interval, 1.10-2.34). *Conclusions:* Age, sex, baseline National Institutes of Health Stroke Scale score, and time to first dose are predictors of functional outcome in the CHIMES study. Stratification by prognosis showed that patients with 2 or more predictors of poorer outcome have better treatment effect with MLC601 than patients with single or no prognostic factor. These results have implications on designing future stroke trials. **Key Words:** Acute stroke—stroke recovery—MLC601—NeuroAiD—prognosis—clinical trial.

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Received November 6, 2014; accepted November 19, 2014.

The CHIMES study was supported by the CHIMES Society and grants received by C.L.H.C. from the National Medical Research Council of Singapore (NMRC/1288/2011 and NMRC/1096/2006). The authors received funding for the trial and accommodation and transportation support for meetings from the CHIMES Society. J.C.N. has minor shares in E*Chimes, the Philippine distributor of NeuroAiD. Moleac, Singapore provided grants to the CHIMES Society of which the society had sole discretion on use.

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1052-3057/- see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.11.017

Introduction

Some of the difficulties in translating acute stroke treatments from bench to bedside have been attributed to discrepancies between preclinical and clinical study designs.[1-3] Unlike preclinical studies, stroke clinical trials often include heterogeneous patients[4] who are usually analyzed together using a single definition of "good" outcome that may not be applicable to all patient subgroups.

Using a prognosis-based approach to target patient selection or define and adjust desired outcomes have been proposed by several groups.[5-9] Trials that implemented such approach have identified cohorts with specific prognostic profiles likely to benefit or be harmed by treatments.[10-12]

MLC601 has been shown to have both neurorestorative and neuroprotective properties in animal and cellular models.[13] Clinical trials suggest that MLC601, as an add-on to standard treatment, could be effective in improving functional outcome and motor recovery and is safe for patients with primarily nonacute stable stroke.[14]

In a recent publication, the favorable treatment effect of MLC601 in patients with acute ischemic stroke recruited from the Philippines in the Chinese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES) study was hypothesized to be because of inclusion of patients with poorer prognosis.[15] In this analysis, we aimed to evaluate if treatment effect of MCL601 varies among acute stroke patients with differing prognostic profiles in the CHIMES study cohort and if stratification by anticipated prognosis may identify patients more likely to benefit from MLC601.

Methods

Analyses were performed using data from the CHIMES study, an international, randomized, placebo-controlled, double-blind trial that compared MLC601 with placebo in patients with ischemic stroke of intermediate severity in the preceding 72 hours (clinicaltrials.gov NCT00554723).[16-18] Subjects were allocated to either MLC601 or placebo for 3 months as add-on to standard stroke care (ie, antiplatelet therapy, control of vascular risk factors, appropriate rehabilitation) and followed for 3 months. The primary outcome measure used in this study was the modified Rankin scale (mRS) score at 3 months. Of 1099 subjects in the CHIMES study, 1006 with complete baseline data and an mRS score at month 3 were included in this post hoc analysis. Logistic regression analyses were performed to identify predictors of mRS score greater than 1 and to assess the association between number of predictors and mRS. Sensitivity, specificity, positive predictive values, negative predictive values, and receiver operating characteristic for mRS score less than 2 versus 2 or more at month 3 were calculated. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were used to estimate treatment effects overall and according to number of predictors. ORs were also adjusted by logistic regression for baseline prognostic factors, that is, age, sex, National Institutes of Health Stroke Scale (NIHSS), prestroke mRS, and duration from stroke onset to initiation of study treatment.

Results

Baseline characteristics of patients were similar between the treatment groups as previously described.[16,18] The predictive variables for mRS score greater than 1 at month 3 were age older than 60 years ($P < .001$), baseline NIHSS score of 10-14 ($P < .001$), stroke onset to initiation of study treatment of more than 48 hours ($P < .001$), and female sex ($P = .026$). Increasing number of predictors at baseline was associated with worse mRS score at month 3 for both placebo ($P < .001$) and treatment ($P < .001$) groups (Fig 1). A high response rate in the placebo group (>50% with mRS score < 2) was seen among subjects with one or no predictor of poorer mRS. Having more than 1 predictor has a sensitivity of 72%, specificity of 61%, positive predictive value of 68%, and negative predictive value of 64% for a poorer outcome of mRS score greater than 1 at 3 months (Table 1). Receiver operating characteristic area under the curve was .7211.

The overall OR of MLC601 for achieving an mRS score less than 2 at month 3 was 1.15 (95% CI, .89-1.47). Stratification according to number of predictors of poorer outcome showed ORs increasing with the number of predictors and reached statistical significance in favor of MLC601 among subjects with 2 or more predictors (OR = 1.44, 95% CI, 1.02-2.03) and was higher in those with 3 or more predictors (OR = 2.21, 95% CI, 1.22-4.0; Fig 2). Adjustment for baseline prognostic factors generally increased the ORs.

Discussion

Age, stroke severity, sex, and time delay to treatment have been identified as predictors of outcome after a stroke in this and many previous studies.[19] Aside from sex, these factors are often eligibility criteria in stroke clinical trials. In addition to being individually predictive of outcome in the CHIMES cohort, we found a strong graded association between the number of predictors and mRS status at 3 months.

The CHIMES study showed an overall OR of achieving mRS score less than 2 in favor of MLC601, although this did not reach statistical significance.[16] This may be because of inclusion of patients with relatively good prognosis. In the CHIMES study, patients were included if they were 18 years and older, had a baseline NIHSS score of 6 to 14, and stroke onset in the preceding 72 hours. The