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ARTICLE

The value of patient selection in demonstrating treatment effect in stroke recovery trials: lessons from the CHIMES study of MLC601 (NeuroAiD)

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Abstract

Objective: The CHIMES Study compared MLC601 to placebo in patients with ischemic stroke of intermediate severity in the preceding 72 hours. We aimed to verify if patient selection based on two prognostic factors (ie, stroke severity and time to treatment) improves detection of a treatment effect with MLC601.
Methods: Analyses were performed using data from the CHIMES Study, an international, randomized, placebo-controlled, double-blind trial comparing MLC601 to placebo in patients with ischemic stroke of intermediate severity in the preceding 72 hours. Three subgroups, that is, onset to treatment time (OTT) ≥48 hours; baseline National Institute of Health Stroke Scale (NIHSS) ≥10; both OTT ≥48 hours and baseline NIHSS ≥10, were analyzed using modified Rankin Scale (mRS) ≤1 and a composite endpoint of mRS ≤1, Barthel Index ≥95, and NIHSS ≤1 at month 3.
Results: Placebo response rates were lower (ie, worse natural outcome) among subgroups with prognostic factors. Conversely, MLC601 treatment effects were significantly higher in the subgroups with prognostic factors than for the entire cohort, being highest among patients with both OTT ≥48 hours and baseline NIHSS of 10 to 14: odds ratios of 2.18 (95% CI 1.02 to 4.65) for month 3 mRS ≤1 and 3.88 (95% CI 1.03 to 14.71) for the composite endpoint.
Conclusions: : Patients who have moderately severe strokes and longer OTT demonstrate better treatment effects with MLC601. These factors can guide patient selection in future trials.

Introduction

MLC601 (NeuroAiD), a product combining herbal and non-herbal extracts, has been shown to have neuroprotective and neurorestorative properties in cellular and animal ischemic models (1). Early clinical trials in patients with non-acute stroke have shown benefits in improving neurological and functional outcomes (2). In the Chinese Medicine Neuroaid Efficacy on Stroke recovery Study (CHIMES), we investigated the use of MLC601 in acute stroke within 72 hours of onset (3). We recently published a preplanned analysis which showed larger treatment effects of MLC601 in both primary and secondary outcomes in the Philippine cohort compared to the treatment effects in the overall CHIMES study cohort (4). We hypothesized that this may have been due to inclusion of more women, relatively more severe strokes, and longer delays from stroke onset to treatment time (OTT) among Filipino patients than those included from other countries. Increasing age, female sex, stroke severity and OTT ≥48 hours were found to be predictive factors of poorer outcome, the presence of which may enhance the detection of treatment effect in the CHIMES Study (5).

In this analysis, we aimed to verify if selection of patients according to two important prognostic factors, that is, baseline stroke severity and delay in treatment, would show larger treatments effects of MLC601 in the CHIMES cohort. We focused on these two particular factors because they can reasonably be incorporated in selection criteria of clinical trials, as well as due to their plausible effects on outcome after stroke.

Methods

Analyses were performed using data from the CHIMES Study, an international, randomized, placebo-controlled, double-blind trial that compared MLC601 to placebo in 1099 patients with ischemic stroke of intermediate severity (National Institute of Health Stroke Scale, NIHSS, 6 to 14) in the preceding 72 hours (clinicaltrials.gov NCT00554723) (3). Patients 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 study was approved by the Ethics Committee of each site and all subjects gave informed consent prior to participation.

Subjects with actual month 3 outcomes were included in the analyses of the overall cohort and three subgroups according to the presence of two prognostic factors of poorer outcome: OTT ≥48 hours, baseline NIHSS 10 to 14, and both OTT ≥48 hours and baseline NIHSS 10 to 14. The primary outcome measure used was the modified Rankin score (mRS) at month 3. Since the CHIMES study included patients with relatively less severe stroke (3), we also used a composite endpoint of mRS ≤1, Barthel Index (BI) ≥95, and NIHSS ≤1 to define excellent outcome representing minimal or no poststroke deficit which was used in other acute stroke trials (6–8).

Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were used to estimate treatment effects (mRS of 0 or 1 and composite outcome) in a logistic regression model after adjusting for age and sex which were also predictors of poorer outcomes in the CHIMES cohort (3–5). The numbers needed to treat (NNT) to achieve mRS 0 to 1 at month 3 were calculated for each group using the inverse of absolute differences to estimate the clinical benefit of MLC601.

Results

The baseline characteristics of patients included in CHIMES were similar between MLC601- and placebo-treated groups (3). Of the 1099 patients included in the CHIMES Study, 1009 had actual month 3 outcomes assessed, 530 had OTT ≥48 hours, 363 had baseline NIHSS of 10 to 14, and 201 had both OTT ≥48 hours and NIHSS of 10 to 14 (Table 1).

Table 1 Modified Rankin scores (mRS), number-needed-to-treat (NNT), and composite endpoint in patients with onset to treatment time (OTT) ≥48 hours or more severe National Institute of Health Stroke Scale (NIHSS) in the CHIMES Study

	N	NIHSS median	Outcome (mRS ≤1 at 3 months)						Composite endpoint (mRS ≤1, Barthel Index ≥95, and NIHSS ≤1 at 3 months)
			MLC601	Placebo	Absolute difference	OR (95% CI)	P value	NNT[a]	Odds Ratio (95% CI)
Overall	1099	8	49.10%	45.60%	3.50%	1.16 (0.90, 1.49)	0.253	29	0.97 (0.71, 1.31)
OTT ≥48 hours	530	8	44.20%	35.30%	8.90%	1.47 (1.02, 2.11)	0.037	11	1.22 (0.75, 1.99)
NIHSS 10 to 14	363	12	28.00%	18.50%	9.50%	1.71 (1.01, 2.90)	0.047	10	1.26 (0.58, 2.74)
OTT ≥48 hours and NIHSS 10 to 14	201	12	25.00%	13.50%	11.50%	2.18 (1.02, 4.65)	0.044	9	3.88 (1.03, 14.71)

[a]Number needed to treat with MLC601 to achieve one additional patient with mRS ≤1 at month 3.

The odds ratio for good outcome, defined as month 3 mRS ≤1, in the entire cohort was 1.16 (95% CI: 0.90 to 1.49) after adjusting for age and sex. The OR for each of the analyzed subgroups reached statistical significance, that is, 1.47 (95% CI 1.02 to 2.11) in the OTT ≥ 48 hours subgroup and 1.71 (85% CI 1.01 to 2.90) in the NIHSS 10 to 14 subgroup, with the highest treatment effect seen among patients with both OTT ≥48 hours and NIHSS of 10 to 14 (OR = 2.18, 95% CI 1.02 to 4.65). The OR for the composite outcome of mRS ≤1, BI ≥95, and NIHSS ≤1 was similarly highest and statistically significant for patients with both prognostic factors (OR = 0.88, 95% CI 1.03 to 14.71).

The proportion of good outcome decreased with the presence of prognostic factors in the MLC601-treated group (44.2% in the OTT ≥48 hours subgroup, 28% in the NIHSS 10 to 14 subgroup) and was lowest (25%) among patients with both prognostic factors. By comparison, the reduction in good outcome was more pronounced in the placebo group (35.3% in the OTT ≥48 hours subgroup, 18.5% in the NIHSS 10 to 14 subgroup, 13.5% in the group with both prognostic factors). This led to larger absolute differences in favor of MLC601 (8.9% in the OTT ≥48 hours subgroup, 9.5% in the NIHSS 10 to 14 subgroup) and corresponding lower NNT (11 in the OTT ≥48 hours subgroup, 10 in the NIHSS 10 to 14 subgroup) which were best demonstrated in patients with both prognostic factors (absolute difference of 11.5%, NNT = 9).

Discussion

Our study used actual clinical trial data to demonstrate the importance of proper selection of patients with potential to benefit in clinical trials (9–11). The variables we analyzed, OTT and NIHSS, represent important inherent treatment-related (ie, mode of action) and disease-related (ie, prognosis) factors to consider when designing studies.

Stroke is a devastating disease. The aim of treatment is to restore as much of the resulting neurological and functional impairments as possible. Recovery from stroke, however, depends significantly on how much tissue is saved by reversing the injurious process (eg, revascularization) and severity of the deficits after the tissue damage.

To date, the only approved pharmacological treatment for acute ischemic stroke is intravenous thrombolysis by recombinant tissue plasminogen activator (rt-PA). rt-PA has been shown to improve outcomes of survival and independence (7, 8, 12–15). However, its use is limited by the very short window of opportunity for treatment and risk of bleeding, making less than 6% of stroke patients eligible for such treatment (16, 17). In a pooled analysis, the NNT for achieving an mRS score of 0 to 1 was 4.5 for OTT of <90 minutes, 9 for OTT 91 to 180 minutes, and 14 for OTT 181 to 270 minutes (8). Median baseline NIHSS scores were 15, 13, and 10, respectively. For rt-PA, the sooner the treatment is given, the better. The most recent meta-analysis showed that despite early increases in fatal intracranial haemorrhage, alteplase significantly improves the overall likelihood of good outcome (mRS <1), with the proportional benefits increasing with earlier treatment (15).

On the other hand, our study showed that in the CHIMES cohort, patients with OTT ≥48 hours paradoxically have better treatment effects than in the overall cohort with NNT comparable to that of rt-PA. This may not be as surprising since the therapeutic effects of rt-PA (ie, revascularization) is most relevant during the hyperacute phase of stroke, while the putative mechanism of action of MLC601 (ie, neurorestoration) is more important at a later stage after brain injury. In addition, patients who arrive for treatment much later after a stroke have generally poorer prognosis (18), which is another important factor in demonstrating treatment effects.

Stroke is a heterogeneous condition and the deficits are variable. Prognosis for natural recovery can be different depending on severity, with mild strokes expected to recover remarkably and more severe ones recovering only to a certain extent (19). In trials wherein clinical measures are used to detect therapeutic effects, treatment benefit may not be demonstrated as obviously in those who would spontaneously recover fully regardless of intervention and in those who are too severe to realistically expect significant improvement.

The three subgroups we analyzed in this study showed placebo response rates that appear to be inversely related to the OR, implying higher treatment effects with MLC601 among patients with worse prognosis. A high response rate in the placebo arm can affect the potential of detecting treatment effects in clinical trials (20–22). In the CHIMES study, almost half in the placebo group achieved functional independence (mRS 0 to 1) at the end of 3 months. By selecting patients with relatively more severe NIHSS in the current analysis, the lower placebo response rate allowed for better detection of differences despite a smaller sample size. The even larger effects seen by the combination of more severe NIHSS and longer OTT further suggests that inclusion of stroke patients at a time when their deficits are more established and unlikely to fluctuate can help identify a population with more homogenous prognosis among whom treatment effects can be better seen. It further supports the theory that in recovery trials, the sample size required to detect improvement may be reduced as severity and time since stroke increases (19).

In terms of safety, we have previously shown comparable rates of non-serious and serious adverse events, including intracerebral and gastrointestinal hemorrhage, between MLC601 and placebo groups (3).

There are some limitations in this study. This is a post hoc analysis. In addition, the source study population was restricted only to patients with NIHSS of 6 to 14 and stroke

onset within 72 hours of randomization and findings may not be applicable to patients outside these criteria. However, the data used were collected prior to unblinding and were obtained from a randomized double-blind large clinical trial with a high quality of follow-up.

Numerous stroke trials, including the use of neuroprotective drugs, have met many difficulties in translating significant findings in preclinical models to clinical benefits as measured in clinical trials (23). The reasons for this failure have been extensively discussed (24–26). Clinically, patient selection may be among the most important factors that should be considered when designing trials in stroke. While every effort must be made to have adequate demographic representation (eg, age, sex, race–ethnicity, etc) in clinical trials, there are treatment- and disease-specific eligibility factors that may be important in achieving a more homogeneous study population.

Conclusions

Our study shows that selection of patients who have moderately severe strokes and delay in OTT demonstrates better treatment effects with MLC601, which can become valuable particularly for those who are ineligible to receive intravenous thrombolysis or do not significantly respond to treatment in the acute phase. Together with the understanding of time window when the intervention is most likely to be effective, these variables are valid targets to guide patient selection in future ischemic stroke trials in order to reduce sample sizes.

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