Cerebrolysin in patients with acute ischemic stroke in Asia results of a double-blind, placebo-controlled randomized trial

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Introduction

Cerebrolysin showed neuroprotective and neurotrophic properties in various preclinical models of ischemia and small clinical trials. The aim of this large double-blind, placebo-controlled randomized clinical trial was to test its efficacy and safety in patients with acute ischemic stroke.

Methods

CASTA was a Phase IV clinical trial designed as a multicenter, randomized, double-blind placebo-controlled parallel-group study. The study included patients with acute hemispheric ischemic strokes based on a clinical diagnosis from 51 centers from China (1024 patients), Hong Kong (4 patients), South Korea (16 patients), and Myanmar (26 patients). The severity of the neurological deficit at baseline was assessed using the National Institutes of Health Stroke Scale (NIHSS). The study compared 2 groups of patients treated either with 30 mL Cerebrolysin diluted in saline (total of 100 mL) at an intravenous infusion or with matched placebo (100 mL saline). Both groups received 100 mg aspirin orally as standard treatment. Treatment was administered as single daily dose for 10 days starting within 12 hours of stroke onset. A total of 90.2% of the patients in the Cerebrolysin group and 85.2% of the patients in the placebo group were still exposed to treatment at Day 10. The median number of doses administered per patient was 10 in both groups. The primary efficacy criterion was defined as the combined result of Barthel Index (BI), modified Rankin Scale (mRS), and the NIHSS evaluated in 1 global test. Primary end point for assessing efficacy was 90 days after the stroke event. The secondary study end points included responder analysis based on responder definitions for mRS, BI, and NIHSS. Again, the criteria were evaluated combined into 1 global test. Additional secondary study end points included the global test as described for the confirmatory analysis, but this time evaluated for Day 30 instead of Day 90, quality-of-life assessment using the SF-12 at Day 90, overall death rate, and time to death. There were 4 stratified analyses of the BI preplanned in the blind review with subgroups as follows: (1) stratification for thrombolysis therapy; (2) for age (≤65 years/age>65 years); (3) for severity of disease at baseline (NIHSS≤7, NIHSS 8–12, NIHSS>12); and (4) side of infarction. Additionally, post hoc stratified analyses were performed, for example, for NIHSS and mRS (with strata as defined previously for BI). Furthermore, there were post hoc subgroup analyses for baseline NIHSS>17 points (study centers in Hong Kong and South Korea only) primary efficacy criterion in subgroup NIHSS>12, mortality in subgroup NIHSS>12, and responder in subgroup NIHSS>12. Inclusion and exclusion criteria as well as other details of study protocol are available under International Journal of Stroke Vol 4, October 2009, 406–412.

Results

A total of 1070 patients were enrolled in this study. Five hundred twenty-nine patients were assigned to Cerebrolysin and 541 to placebo. The confirmatory end point showed no significant difference between the treatment groups.

When the predefined stratification by severity was repeated with the criterion NIHSS, however, a small superiority for Cerebrolysin in the subgroup with baseline NIHSS>12 (OR, 1.27; CI-LB, 0.97; P=0.04) could be shown (Table 1, Fig. 1). Also, when applying the mRS, a small superiority in the subgroup with baseline NIHSS>12 (OR, 1.27; CI-LB, 0.90; P=0.09) was found. The following analysis also focused on the subgroup baseline NIHSS>12 points only and provided a global test result for all 3 criteria combined. This global test results in MW=0.53 (CI-LB, 0.47; P=0.16), which showed a beneficial trend for Cerebrolysin in the study patients. The findings for the individual criteria all showed a positive trend for superiority of the Cerebrolysin group. In this subgroup, the cumulative mortality by 90 days was 20.2% in the placebo and 10.5% in the Cerebrolysin group (hazard ratio, 1.9661; CI lower bound, 1.0013; Fig. 2). Very similar results could also be shown for patients with even more severe strokes (NIHSS baseline score>17). In this subgroup, the global test resulted in MW=0.54 (CI-LB, 0.42; P=0.28).

Conclusions

The results from the present study show that Cerebrolysin can be applied safely and according to the post hoc subgroup analyses may provide beneficial effects in acute ischemic stroke. Another confirmatory study is needed to determine whether Cerebrolysin has a clearly significant benefit in patients with moderate to severe stroke.

Related references

1. Original article: Stroke. 2012;43:630-636
2. POSTER: G. Ladurner et al., 2005. Neuroprotective treatment with Cerebrolysin in patients with acute stroke: a randomised controlled trial
3. POSTER: W. Lang et al., 2013. A prospective, randomized, placebo-controlled, double-blind trial about safety and efficacy of combined treatment with alteplase (rt-PA) and Cerebrolysin in acute ischaemic hemispheric stroke

Fig. 1.
The results at NIHSS>12 indicate a trend for a beneficial effect of Cerebrolysin in the more severely affected subgroup. (OR=1.2724; 95 % CI 0.9719 to 1.6657, 125 patients Cerebrolysin, 121 patients placebo)

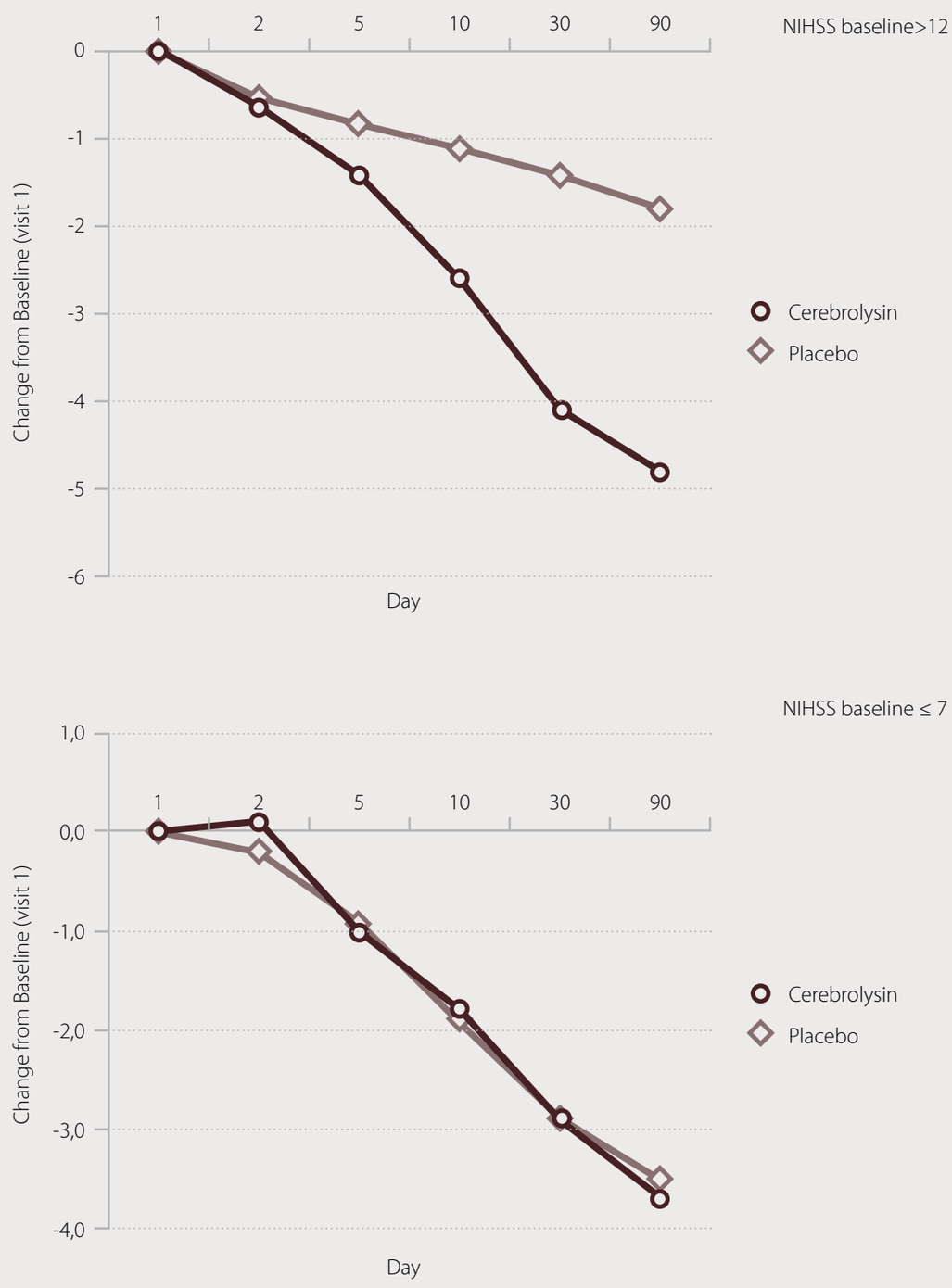

Table 1.
NIHSS (Change From Baseline, LOCF), Descriptive Statistics for Subgroup Baseline NIHSS>12, ITT Population

NIHSS	Baseline	Visit 2	Visit 3*	Visit 4	Visit 5	Visit 6
Cerebrolysin	16.6	-0.6	-1.4	-2.6	-4.1	-4.8
Mean/SD	3.40	2.97	6.52	8.02	9.36	10.76
Placebo	16.2	-0.5	-0.8	-1.1	-1.4	-1.8
Mean/SD	3.02	4.74	7.77	9.73	11.92	13.87

NIHSS indicates National Institutes of Health Stroke Scale; LOCF – last observation carried forward; ITT – intention-to-treat
*Start of LOCF substitution.

Fig. 2.
Kaplan-Meier survival curve (cumulative percentage) for subgroup baseline NIHSS>12 points (N=252, 126 patients per group); ITT population. HR, 1.9661 (CI-LB, 1.00; P=0.0497 in a 2-sided test with alfa=0.05). NIHSS indicates National Institutes of Health Stroke Scale; ITT, intention-to-treat; HR, hazard ratio; LB, lower bound