Cerebrolysin and Recovery after Stroke (CARS): A randomized, placebo-controlled, double-blind, multicenter trial

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Introduction

Cerebrolysin is a multimodal neuropeptide preparation of porcine origin produced by a standardized manufacturing process and consisting of low-molecular-weight neuropeptides (<10 kDa) and free amino acids. Cerebrolysin has been shown to have neuroprotective properties and to exhibit neurotrophic activity, promote neuronal sprouting, improve cellular survival and stimulate neurogenesis.The aim of the study was to investigate whether stroke patients who receive both Cerebrolysin and early rehabilitation show improved motor function in the upper extremities over 90 days compared with patients who receive only early rehabilitation (and placebo).

Methods

This was a prospective, randomized, double-blind, placebo-controlled, multicenter, parallel-group study. Patients were treated with Cerebrolysin (30 ml/day) or a placebo (saline) once daily for 21 days, beginning at 24-72 hours after stroke onset. The primary endpoint was the Action Research Arm Test score on day 90. Each patient included in the study participated in an accompanying standardized rehabilitation program for 21 days, beginning within 48-72 h after stroke onset (5 days/week for 2 h/day). This program included massages and passive and active movements of the upper and lower limbs. The patients continued with 2 x 15 min of active movement for three days per week after discharge. Study visits were conducted at 7, 14, and 21 days after baseline and on days 42 and 90 post-stroke. The study duration for each patient was 90 days. The study was performed in Romania, Ukraine and Poland, and it is registered with EudraCT (2007-000870-21). All study procedures were conducted in accordance with the applicable laws and guidelines, GCP and ethical standards. Analyses were performed according to a pre-defined statistical analysis plan.

EFFICACY CRITERIA

The primary efficacy criterion was a change in the ARAT score, and it was used to assess upper limb motor function from baseline to day 90. The secondary efficacy criteria were changes from baseline to day 21 (the last day on which the study medication was administered) and to day 90 in gait velocity (Gait Velocity Test), fine motor function (9-Hole Peg Test), the global neurological state (NIHSS), the level of disability or dependence in activities of daily living (Barthel Index, mRS), the extent of aphasia (Goodglass and Kaplan Communication Scale), the extent of neglect (Line Cancellation Test, Gap Detection Test), quality of life (SF-36 Health Survey, Physical Component Summary [PCS], and Mental Component Summary [MCS]) and the extent of depression (Geriatric Depression Scale).

Results

The baseline characteristics of study population are listed in Table 1. A total of 208 patients were enrolled in this study between April 2008 and September 2010. There were no relevant group differences observed at baseline (Table 1). The mean age of the patients was 64 years, 63.9% of the patients were male, and the mean NIHSS score was 9.2 (median of 8.0). Study characteristics are presented in table 2.

The upper limb motor function was evaluated as the primary efficacy measure. Time course ARAT with Cerebrolysin (30 ml/day) and placebo is shown at Fig. 1 as boxplot diagrams (P10, P90) for days 7 (V3), 14 (V4), and 21 (V5) post baseline and days 42 (V6) and 90 (V7) post stroke. The ITT-LOCF population on day 90 included a total of 205 patients (Cerebrolysin, n=104; placebo n=101) as shown on panel A. Effect sizes (Mann-Whitney) of ARAT score changes from baseline in the ITT-LOCF population are presented on panel B. The ARAT score was statistically significantly different in the preplanned first-line analysis and in the subgroup analysis of patients with ARAT baseline scores >0. This finding was confirmed in the LOCF and OC sensitivity analyses. The significant superiority of Cerebrolysin on day 90 may be interpreted to have occurred as a result of the neurorestorative action of Cerebrolysin, which intensifies initial improvement and beneficial effects of rehabilitation.

In the global status on day 90 analysis (Fig. 2), Mann-Whitney effect sizes (MW) for the single and combined (Wei-Lachin procedure) efficacy parameters reflected changes from baseline in the ITT-LOCF population (n=205). The global outcome was statistically significantly different in the first-line analysis and in the pre-planned subgroup analysis of patients with ARAT baseline scores >0. This finding was confirmed in the LOCF and OC sensitivity analyses. A medium superiority (MW≥0.64) of Cerebrolysin was observed in six of the 12 efficacy criteria, including ARAT, NIHSS, Barthel Index, mRS, SF-36 PCS and depression (Geriatric Depression Scale) scores. A small superiority (MW≥0.56) of Cerebrolysin was demonstrated using the Gait Velocity Test, 9-Hole Peg Test, Goodglass and Kaplan Communication Scale and the SF-36 MCS. Cerebrolysin did not affect neglect (Line Cancellation Test, Gap Detection Test); the proportion of patients with neglect at baseline was very low in both groups. The combined result (Wei-Lachin) revealed a small superiority of Cerebrolysin compared to the placebo, with an MW effect size of 0.62 (95% CI, 0.58-0.65).

Conclusions

The results of this trial support the view that a comprehensive treatment strategy combining pharmacological treatment and structured rehabilitation create synergisms and therefore improve the outcome of stroke patients. Cerebrolysin had a beneficial effect on function and global outcome in early rehabilitation patients after stroke. Its safety was comparable to that of the placebo (Table 3), suggesting a favorable benefit-risk ratio. Because this study was exploratory and had a relatively small sample size, the results should be confirmed in a large-scale, randomized clinical trial.

Related references

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Table 1. Comparison of baseline characteristics (safety analysis set)

Demographic Parameter	Total N=208	Cerebrolysin N=104	Placebo N=104
Male sex: N (%)	133 (63.9)	70 (67.3)	63 (60.6)
Right-handed: N (%)	199 (95.7)	99 (95.2)	100 (96.2)
Mean age: years (SD)	64.0 (10.2)	64.9 (9.8)	63.0 (10.6)
Mean BMI: kg/m^2 (SD)	27.4 (4.2)	27.2 (4.1)	27.6 (4.3)
Mean time until treatment initiation*: hours SD)	53.2 (12.3)	51.9 (12.7)	54.6 (11.7)
Thrombolytic treatment: N (%)	4 (1.9)	2 (1.9)	2 (1.9)
Prevalence of risk factors: N (%)			
Hypertension	173 (83.2)	86 (82.7)	87 (83.7)
Hyperlipidemia	105 (50.5)	55 (52.9)	50 (48.1)
Diabetes mellitus	39 (18.8)	19 (18.3)	20 (19.2)
Arrhythmia	54 (26.0)	26 (25.0)	28 (26.9)
Coronary artery disease	83 (39.9)	38 (36.5)	45 (43.3)
Past/current smoker	67 (32.2)	33 (31.8)	34 (32.7)
Baseline efficacy criteria (ITT): mean+SD		**Cerebrolysin N=104**	**Placebo N=101**
ARAT (paretic side)		10.1±15.9	10.7±16.5
NIHSS		9.1±3.2	9.2±3.2
Barthel index		35.5±24.9	35.4±24.6
Modified Rankin scale		3.9±0.8	3.9±0.8

ARAT, Action Research Arm Test; BMI, body mass index; ITT, intention-to-treat; mean, arithmetic mean; N, Number; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation. * Calculated from stroke onset.

Table 2. Study characteristics

Trials	Trial duration	Number of infusions	Total N randomized	Total N ITT[a]	Valid N (LOCF/OC) for ARAT day 90	Valid N (OC) for Global Outcome[b] day 90	Age[c] (years; mean)	Male[c] (%)	Baseline NIHSS[d] (mean)
EBE-RO-061215 (CARS1)	3 months	21	208	205	205/200	200	64.0	63.9	9.2

[a] ITT definition: baseline assessment of the primary efficacy criterion (ARAT), at least one dose of the study medication and at least one ARAT assessment after the first dose of the study medication [b] Composite outcome of 12 scales [c] Randomized patients [d] ITT patients
N – patient number ITT – intention-to-treat LOCF – last observation carried forward OC – observed cases

Fig. 1. Time course of ARAT score

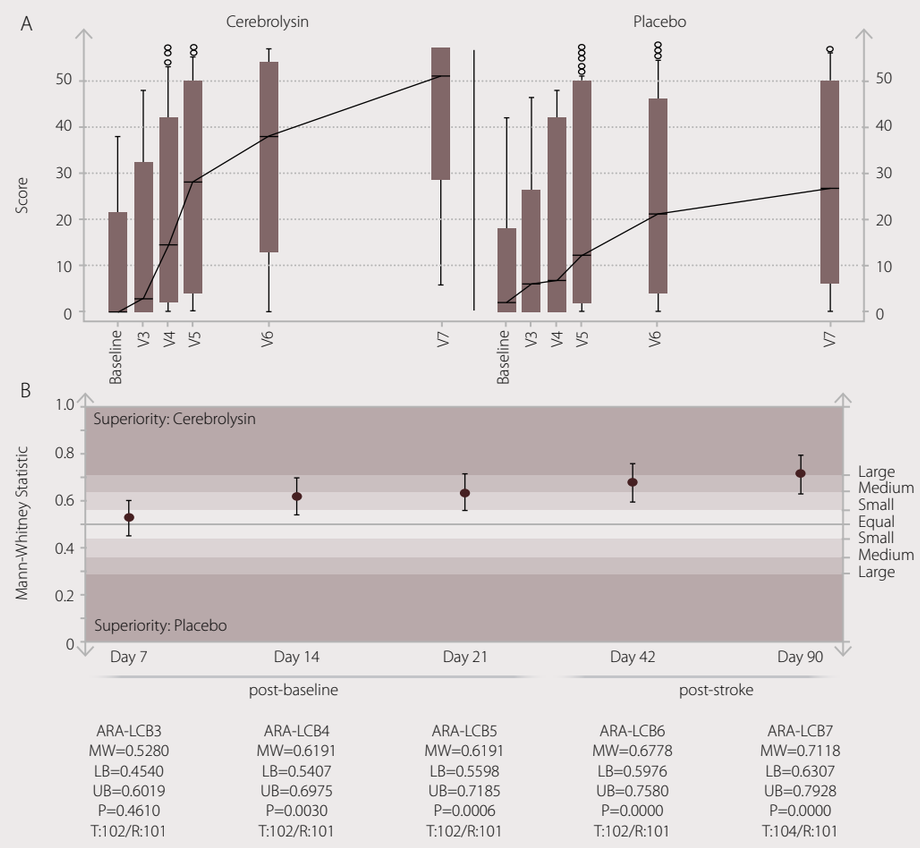
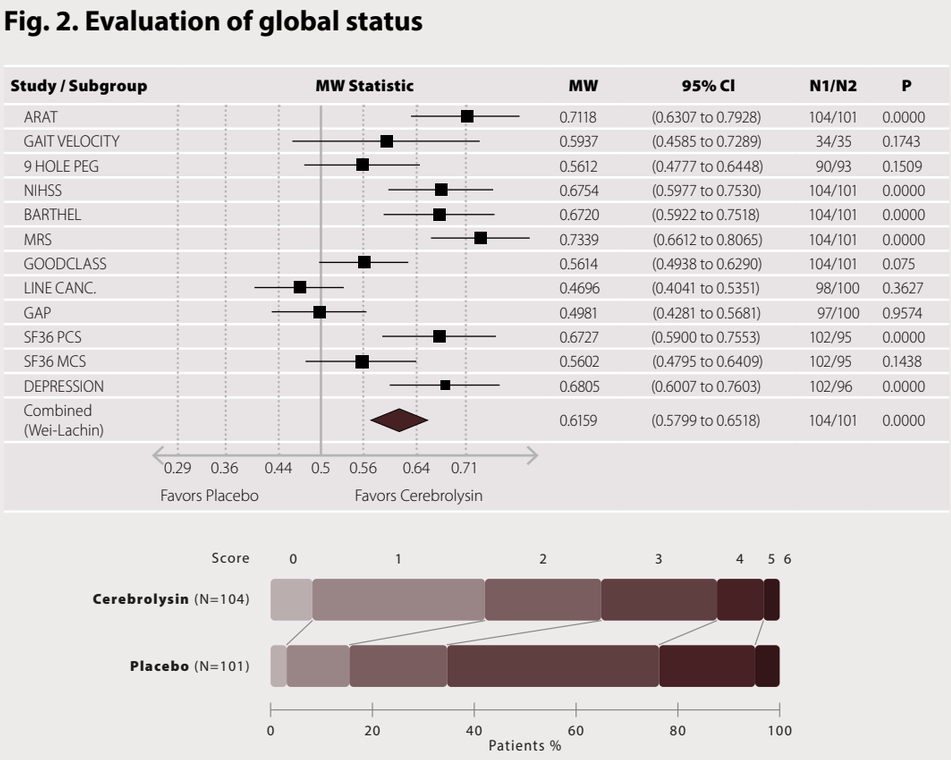


Fig. 2. Evaluation of global status



Distribution of modified Rankin Scale scores. Cumulative percentage (Cerebrolysin vs placebo): 8.65 vs 2.97 (0), 42.31 vs 14.85 (1), 65.38 vs 33.66 (2), 88.46 vs 75.25 (3), 98.08 vs 96.04 (4), and 100.0 vs 100.0 (5). Definitions of scores: 0=no symptoms at all; 1=no significant disability despite symptoms: able to carry out all usual duties and activities; 2=slight disability: unable to carry out all previous activities but able to look after own affairs without assistance; 3=moderate disability: requiring some help, but able to walk without assistance; 4=moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance; 5=severe disability: bedridden, incontinent, and requiring constant nursing care and attention; and 6=dead

Table 3. Safety analysis (safety analysis set)

Preferred Term	Cerebrolysin, n=104 n (%) freq	Placebo, n=104 n (%) freq
Urinary tract infection	13 (12.5) 15	17 (16.3) 18
Depression	11 (10.6) 11	10 (9.6) 10
Insomnia	6 (5.8) 6	4 (3.8) 4
Carotid arteriosclerosis	5 (4.8) 5	5 (4.8) 5
Headache	6 (5.8) 8	3 (2.9) 3
Carotid artery stenosis	6 (5.8) 6	2 (1.9) 3
Hypertension	9 (8.7) 15	12 (11.5) 18
Cytolytic hepatitis	10 (9.6) 10	8 (7.7) 8
Upper abdominal pain	6 (5.8) 6	4 (3.8) 5

Patients were counted only once for a particular AE. The TEAEs were coded according to MedDRA 13.1. Freq indicates the frequency with which each event was reported; and TEAEs, treatment-emergent adverse events (newly occurred or worsened under study treatment).