Effective pharmacological treatment for STROKE patients

Cerebrolysin And Recovery after Stroke (CARS), Muresanu D.F. et al., Stroke 2016; 47:151-159

Published in Stroke
Enrollment and disposition of all patients participating in the clinical study

All patients screened and enrolled (N=208)

All patients randomized and treated (Safety Analysis Set) (N=208) [104 vs. 104]

Premature discontinuation (N=12) [4 vs. 8]

Adverse event: 2 vs. 5
Consent withdrawn: 2 vs. 2
Administrative reason: 0 vs. 1
Of these: No post-baseline data (N=3) [0 vs. 3]

Full Analysis Set (mITT) (N=205) [104 vs. 101]

Major protocol violations (N=0)

Per-Protocol Analysis Set (PP) (N=205) [104 vs. 101]

OBJECTIVE

The aim of this trial was to investigate whether stroke patients who receive Cerebrolysin (added to early rehabilitation) show improved motor function in the upper extremities at day 90 compared with patients who receive placebo (rehabilitation only).

DESIGN

• Prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group study
• 208 stroke patients (18-80 years of age) with confirmed ischemic supratentorial stroke with a volume >4cm³ were included
• Patients included had no significant pre-stroke disability, no other stroke within the previous three months, an Action Research Arm Test (ARAT) score of <50 and a Goodglass and Kaplan Communication Scale score of >2
• Study compared the effects of 30ml Cerebrolysin versus placebo during early rehabilitation after stroke
• Cerebrolysin, n=104; Placebo, n=104
• Treatment started 24-72 hours post stroke and continued for 21 days
• All patients participated in an accompanying standardized rehabilitation program for 21 days (5 days/week, 2 hours/day)
• The primary study endpoint was ARAT score at day 90
• Study visits were conducted on day 7, 14 and 21 after baseline assessment and on day 42 and 90 post-stroke
Primary Efficacy Criterion

The primary efficacy criterion was the change from baseline in the Action Research Arm Test (ARAT) score on day 90, assessing the recovery of the upper limb motor function.

Secondary Efficacy Criteria

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 (National Institutes of Health Stroke Scale [NIHSS])
- The level of disability or dependence in activities of daily living (Barthel index, modified Rankin Scale [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], Mental Component Summary [MCS])
- The extent of depression (Geriatric Depression Scale)

Safety Analyses

A complete medical history and physical examination including vital signs were performed at screening. All adverse events have been documented and evaluated in terms of severity and causality.

Baseline characteristics

<table>
<thead>
<tr>
<th>Comparison of Baseline Characteristics (Safety Analysis Set)</th>
<th>Total N=208</th>
<th>Cerebrolysin N=104</th>
<th>Placebo N=104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Parameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex: N (%)</td>
<td>133 (63.9)</td>
<td>70 (67.3)</td>
<td>63 (60.6)</td>
</tr>
<tr>
<td>Right-handed: N (%)</td>
<td>199 (95.7)</td>
<td>99 (95.2)</td>
<td>100 (96.2)</td>
</tr>
<tr>
<td>Mean age: years (SD)</td>
<td>64.0 (10.2)</td>
<td>64.9 (9.8)</td>
<td>63.0 (10.6)</td>
</tr>
<tr>
<td>Mean BMI: kg/m² (SD)</td>
<td>27.4 (4.2)</td>
<td>27.2 (4.1)</td>
<td>27.6 (4.3)</td>
</tr>
<tr>
<td>Mean time until treatment initiation: hours SD</td>
<td>53.2 (12.3)</td>
<td>51.9 (12.7)</td>
<td>54.6 (11.7)</td>
</tr>
<tr>
<td>Thrombolytic treatment: N (%)</td>
<td>4 (1.9)</td>
<td>2 (1.9)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Prevalence of risk factors: N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>173 (83.2)</td>
<td>86 (82.7)</td>
<td>87 (83.7)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>105 (50.5)</td>
<td>55 (52.9)</td>
<td>50 (48.1)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>39 (18.8)</td>
<td>19 (18.3)</td>
<td>20 (19.2)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>54 (26.0)</td>
<td>26 (25.0)</td>
<td>28 (26.9)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>83 (39.9)</td>
<td>38 (36.5)</td>
<td>45 (43.3)</td>
</tr>
<tr>
<td>Past/current smoker</td>
<td>67 (32.2)</td>
<td>33 (31.8)</td>
<td>34 (32.7)</td>
</tr>
<tr>
<td>Baseline efficacy criteria (mITT): mean±SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrolysin N=104</td>
<td>Placebo N=101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARAT (paretic side)</td>
<td>10±15.9</td>
<td>10±16.5</td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>9±3.2</td>
<td>9±3.2</td>
<td></td>
</tr>
<tr>
<td>Barthel index</td>
<td>35±24.9</td>
<td>35±24.6</td>
<td></td>
</tr>
<tr>
<td>Modified Rankin scale</td>
<td>3.9±0.8</td>
<td>3.9±0.8</td>
<td></td>
</tr>
</tbody>
</table>

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

The median ARAT scores increased from 0.0 at baseline to 51.0 on day 90 in the Cerebrolysin group (30ml/day) and from 2.0 to 27.0 in the placebo group (Figure 1).

CONCLUSIONS

• A beneficial effect of Cerebrolysin was shown in the primary efficacy criterion, the ARAT score
• Treatment with Cerebrolysin leads to a significant improvement of upper limb motor functions by +88%
• Early therapeutic success on day 14 in the Cerebrolysin group
• The large superiority of Cerebrolysin on day 90 may be interpreted to have occurred as a result of neurorecovery, the neurorestorative action of Cerebrolysin, which intensifies initial improvement and beneficial effects of rehabilitation
Cerebrolysin significantly improves quality of life

Similar to the results of the primary outcome - ARAT score - substantial differences were also found in the secondary efficacy criteria between the Cerebrolysin and placebo group.

**CONCLUSIONS**

- The results in stroke patients undergoing early rehabilitation demonstrate a beneficial effect of Cerebrolysin compared to placebo for the global outcome after 90 days.

- **NIHSS**: The improvement of this scale by 3 points demonstrates an excellent outcome of Cerebrolysin after 90 days considering that the overall median initial score was 8.

- **Barthel index**: Very strong improvement in activities of daily living – this correlates perfectly with the SF36-PCS.

- The self-assessment of SF36-PCS shows that patients treated with Cerebrolysin feel a significant better improvement in their daily life vs. group treated with early rehabilitation only.

- Early onset of therapy success correlates strongly with improved patient motivation. As a consequence post-stroke depression is far less prevalent in the combination therapy group.

- A superiority (MW > 0.56) of Cerebrolysin was also 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.

### Figure 3: Global status on day 90. The effect sizes (Mann-Whitney MW) for the single and combined (Wei-Lachin procedure) efficacy parameters reflect changes from baseline in the mITT-LOCF (n=205).

<table>
<thead>
<tr>
<th>Study / Subgroup</th>
<th>MW Statistic</th>
<th>MW</th>
<th>95% CI</th>
<th>N1/N2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARAT</td>
<td>0.7118</td>
<td>(0.6307 to 0.7928)</td>
<td>104/101</td>
<td>0.0000</td>
<td></td>
</tr>
<tr>
<td>GAIT VELOCITY</td>
<td>0.5933</td>
<td>(0.4585 to 0.7289)</td>
<td>34/25</td>
<td>0.1743</td>
<td></td>
</tr>
<tr>
<td>N9 HOLE PEG</td>
<td>0.5612</td>
<td>(0.4777 to 0.6448)</td>
<td>90/93</td>
<td>0.1509</td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.6754</td>
<td>(0.5977 to 0.7530)</td>
<td>104/101</td>
<td>0.0000</td>
<td></td>
</tr>
<tr>
<td>BARTHEL</td>
<td>0.6720</td>
<td>(0.5922 to 0.7518)</td>
<td>104/101</td>
<td>0.0000</td>
<td></td>
</tr>
<tr>
<td>MRS</td>
<td>0.7339</td>
<td>(0.6612 to 0.8065)</td>
<td>104/101</td>
<td>0.0000</td>
<td></td>
</tr>
<tr>
<td>GOODCLASS</td>
<td>0.7614</td>
<td>(0.6938 to 0.8290)</td>
<td>104/101</td>
<td>0.0000</td>
<td></td>
</tr>
<tr>
<td>LINE CANC.</td>
<td>0.4696</td>
<td>(0.4041 to 0.5351)</td>
<td>98/100</td>
<td>0.3627</td>
<td></td>
</tr>
<tr>
<td>LAV</td>
<td>0.4981</td>
<td>(0.4281 to 0.5681)</td>
<td>97/100</td>
<td>0.9534</td>
<td></td>
</tr>
<tr>
<td>SF36 PCS</td>
<td>0.6727</td>
<td>(0.5900 to 0.7553)</td>
<td>102/95</td>
<td>0.0000</td>
<td></td>
</tr>
<tr>
<td>SF36 MCS</td>
<td>0.5602</td>
<td>(0.4795 to 0.6409)</td>
<td>102/95</td>
<td>0.1438</td>
<td></td>
</tr>
<tr>
<td>DEPRESSION</td>
<td>0.6893</td>
<td>(0.6007 to 0.7603)</td>
<td>102/96</td>
<td>0.0000</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>0.6159</td>
<td>(0.5799 to 0.6518)</td>
<td>104/101</td>
<td>0.0000</td>
<td></td>
</tr>
</tbody>
</table>
Regain full independence with Cerebrolysin

A favorable mRS score of 0 and 1 was found in 42.3% of the patients in the Cerebrolysin group compared to 14.9% of those in the placebo group. Similar results were found for mRS scores of 0 to 2.

Cerebrolysin is safe and well tolerated

The safety of Cerebrolysin was comparable with that of the placebo, suggesting that Cerebrolysin possesses a favorable benefit/risk ratio.

Summary

The results of this trial indicate that a comprehensive treatment strategy combining pharmacological treatment with Cerebrolysin and structured rehabilitation create synergisms and therefore improve the outcome of stroke patients.

Such a strategy should include the following:

- Interventions to re-establish, or at least improve, perfusion of the ischemic brain
- Early administration of drugs that interfere with the pathophysiological cascade and improves the neurorestorative capacity of the neuronal network such as Cerebrolysin (30ml/day)
- Rehabilitative activities to stimulate recovery of motor functions
Cerebrolysin's mode of action

Cerebrolysin is a multi-modal neuropeptide drug which improves the brain’s ability for self-repair by stimulating neurorecovery.

**Cerebrolysin**

### Administration:

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Daily dosage</th>
<th>Initiation of treatment</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute stroke</td>
<td>10-50 ml</td>
<td>Immediately after rt-PA or as soon as possible</td>
<td>Up to 20 days</td>
</tr>
<tr>
<td>Post acute stroke</td>
<td>10-50 ml</td>
<td>After acute treatment</td>
<td>Up to 20 days</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>10-50 ml</td>
<td>As soon as possible</td>
<td>Up to 30 days</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>5-30 ml</td>
<td>As soon as possible</td>
<td>2-4 cycles per year 1 cycle: 5 days weekly/4 weeks</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>5-30 ml</td>
<td>As soon as possible</td>
<td>2-4 cycles per year 1 cycle: 5 days weekly/4 weeks</td>
</tr>
</tbody>
</table>

### Product information

**Calpain system**

- Oxidative stress

**Excitotoxicity**

- Inflammation

**Pathological apoptosis**

- Amyloidogenesis tau hyperphosphorylation

**Sprouting**

- Synaptogenesis

**Cerebrolysin’s mode of action**

- NEUROPROTECION
- Pleiotropic effect

- NEURORECOVERY
- Pleiotropic effect

- NEUROTROFICITY

- NEUROPLASTICITY

- NEUROGENESIS
LITERATURE

1. Muresanu D.F. et al., Cerebrolysin and Recovery After Stroke (CARS) – A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial, Stroke 2016; 47:151-159
7. Sugita et al – Protective effects of Cerebrolysin against free radicals: radicals measured before and after ischaemia.

ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin - Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of porcine brain-derived peptide preparation (Cerebrolysin concentrate) in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: Organic, metabolic and neurodegenerative disorders of the brain, especially senile dementia of Alzheimer’s type - Post-apoplectic complications - Cranio-cerebral trauma; post-operative trauma, cerebral contusion or concussion. Contraindications: Hypersensitivity to one of the components of the drug, epilepsy, severe renal impairment. Marketing Authorisation Holder: EVER Neuro Pharma GmbH, A-4866 Unterach. Only available on prescription and in pharmacies. More information about pharmaceutical form, posology and method of administration, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, overdose, pharmacodynamics properties, pharmacokinetic properties, preclinical safety data, incompatibilities, shelf life, special precautions for storage, nature and contents of the container and special precautions for disposal is available in the summary of product characteristics.

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