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CARS trial – rehabilitation after stroke with Cerebrolysin®

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In stroke management, great hopes are being pinned on neuroregenerative treatments. The results of the CARS trial that were recently published in the journal 'Stroke' suggest that the neuroregenerative features of Cerebrolysin® intensify the effects of rehabilitation efforts after stroke. *Text: Maria Uhl*

Over the last few years, a lot of progress has been made in the acute treatment of ischaemic stroke through thrombolysis and mechanical thrombectomy. However, only a minor proportion of patients can benefit from reperfusion treatment. Therefore, much hope is being placed on treatment options that target the pathophysiological cascade from ischaemia to irreversible tissue damage, and that have multimodal effects with regard to both neuroprotection and neurorecovery.

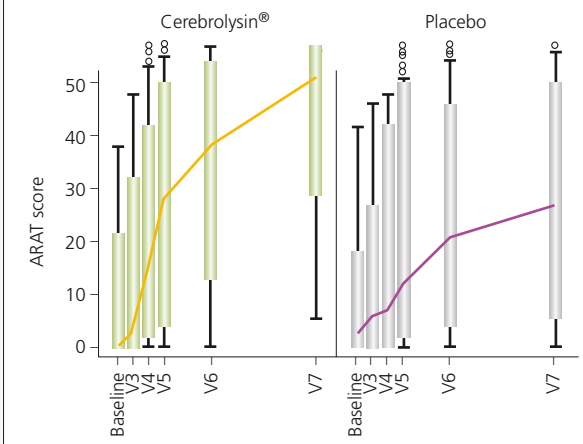
For Cerebrolysin®, various experimental studies have established neuroprotective properties, such as activity against excitotoxicity, and inhibition of microglial activation/ neuroinflammation and apoptosis. Moreover, it has been shown that Cerebrolysin® has neurotrophic effects and stimulates neuronal plasticity as well as neurogenesis. In experimental ischaemia models, these features have given rise to reductions in infarction volume and improvements in functional recovery[1].

Although promising experimental results that were achieved with other neurotrophic agents have not been confirmed in the clinical setting, favourable results have been obtained for Cerebrolysin® in clinical trials in acute stroke[2]. The double-blind, placebo-controlled CASTA study showed that Cerebrolysin® induced a trend for improved outcomes and reductions in mortality in patients with severe stroke (National Institutes of Health Stroke Scale [NIHSS] >12)[3]. In the earlier trials, Cerebrolysin® treatment was started in the acute setting after the onset of stroke, and was continued for 10 days. The focus has thus been primarily on the neuroprotective effects of Cerebrolysin®, while its neurorecovery-promoting properties have been neglected in the context of rehabilitation. To close this gap, the CARS (Cerebrolysin And Recovery after Stroke) study evaluated the efficacy and safety of prolonged treatment with Cerebrolysin® in patients undergoing rehabilitation after stroke. The results of CARS were recently published in the highly regarded journal 'Stroke'[4].

The CARS trial

The placebo-controlled, double-blind, multi-centre CARS trial[4] enrolled a total of 208 patients who had suffered ischaemic supratentorial stroke with a volume of >4 cm^3, as confirmed by computed tomography or magnetic resonance imaging. None of these patients had significant pre-stroke disability (modified Rankin Scale [mRS] score, 0-1). They were randomised to either Cerebrolysin® or

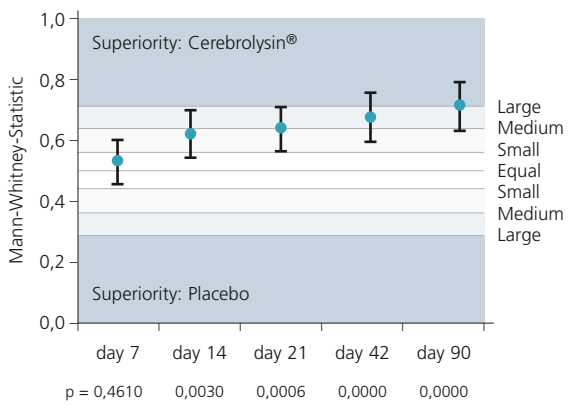
Fig. 1: ARAT score: significant improvement with Cerebrolysin® treatment compared to placebo



V7 = day 90

Source: Muresanu DF et al., Stroke 2016; 47(1):151–9

Fig. 2: Effect sizes (Mann-Whitney) for the ARAT score over time



Source: Muresanu DF et al., Stroke 2016; 47(1):151–9

placebo. Cerebrolysin® was administered at 30 mL daily i.v. for 21 days, with the treatment started within 24-72 hours of the onset of stroke. From the second or third day, all of the patients also received a standardised rehabilitation programme that included passive and active physiotherapy for 21 days (2 hours/day for 5 days/week).

The primary endpoint was improvement in motor function in the upper limbs at day 90 in patients treated with Cerebrolysin® plus early rehabilitation, as compared to patients who received placebo plus early rehabilitation. This was assessed using the Action Research Arm Test (ARAT), which estimates the restoration of motor skills according to the ability of the patient to handle objects of different shapes, sizes and weights.

Secondary endpoints included gait velocity, fine motor function, global neurological state (NIHSS), impairment of activities of daily living (Barthel Index, mRS), extent of aphasia and neglect, quality of life (SF-36 Health Survey, physical and mental component), and depression (Geriatric Depression Scale).

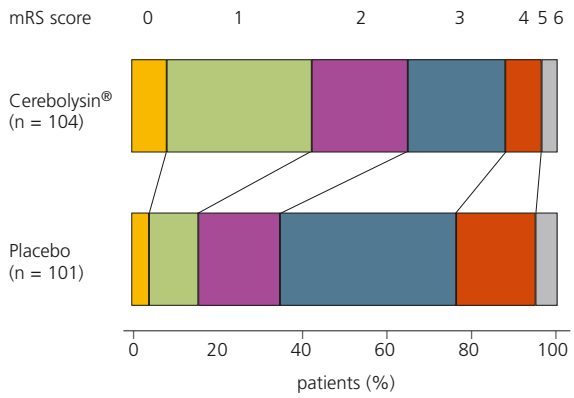
Improvement in outcomes

According to the analysis, motor skills improved considerably in the Cerebrolysin®-treated group to a significantly larger extent than in the placebo group, with a Cerebrolysin® versus placebo difference in the ARAT score of 24. In the Cerebrolysin®-treated group, the ARAT score increased to a median of 51 to day 90 (study visit 7), which is equivalent to near-complete restoration of fine motor function (i.e., 57 points). In contrast, the placebo group only showed increases to a median of 27 (**Fig. 1**). The distinct superiority of Cerebrolysin® treatment in combination with early rehabilitation over placebo was confirmed by non-parametric analysis of the ARAT effect size. Here, the difference was already significant at day 14 ($p = 0.0030$), and it continued to increase to day 90 (Mann-Whitney estimator [MW], 0.71; 95% CI, 0.63-0.79; $p < 0.0001$; **Fig. 2**).

Moreover, a substantial benefit was observed with respect to the mRS score: at day 90, 42.3% of the Cerebrolysin®-treated patients had no symptoms or no significant disability (mRS 0-1), while with placebo treatment, this was only the case in 14.9% of patients (**Fig. 3**).

Likewise, improvements were seen for the most pertinent secondary efficacy endpoints. Apart from the ARAT and mRS scores, treatment effects of MW ≥ 0.64 occurred with regard to NIHSS, Barthel Index, quality of life (SF-36 Health Survey, physical component) and depression. For gait velocity (Gait Velocity Test), fine motor function (9-Hole Peg Test), and aphasia (Goodglass and Kaplan Communication Scale), the treatment effects promoted MW ≥ 0.56. Cerebrolysin® showed good overall tolerability, with adverse effects remaining at the placebo level.

Fig. 3: Distribution of modified Rankin Scale scores with Cerebrolysin® treatment and placebo at 90 days



Source: Muresanu DF et al., Stroke 2016; 47(1):151–9

Conclusion

The CARS trial shows that early treatment with Cerebrolysin® in combination with a rehabilitation programme has favourable effects on motor function, neurological impairment, activities of daily living, quality of life, and depression. Cerebrolysin® therapy gave rise to rapid improvements in motor function according to ARAT, which continued to increase over the follow-up period of 90 days, and to an improved mRS score at day 90. As the researchers noted, the positive results of the CARS study need to be confirmed in a larger trial. ■

[1] Zhang et al., Int J Stroke 2016 Jan 12 (e-pub ahead of print)
[2] Lang W et al., Int J Stroke 2013; 8:95–104
[3] Heiss WD et al., Stroke 2012; 43(3):630–6
[4] Muresanu DF et al., Stroke 2016; 47(1):151–9, DOI: 10:1161/STROKEAHA.115.0009416

ABBREVIATED PRESCRIBING INFORMATION. Consult Summary of Product Characteristics before prescribing. 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. Therapeutic indications: Organic, metabolic and neurodegenerative disorders of the brain, especially senile dementia of Alzheimer's type. Post-apoplectic complications, Craniocerebral trauma. Post-operative trauma, cerebral contusion or concussion. Contraindications: Hypersensitivity to one of the components of the drug. Epilepsy. Severe renal impairment. Product-licence holder and Manufacturer: EVER Neuro Pharma GmbH, A-4866 Unterach. List of excipients: Sodium hydroxide and water for injection. Date of last revision: October 2009. For further information please contact: EVER Neuro Pharma GmbH, A-4866 Unterach, Austria.

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Muresanu, et al., 2016

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