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REVIEW

Cerebrolysin: a multi-target drug for recovery after stroke

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ABSTRACT

Introduction: Cerebrolysin is a neuropeptide preparation with neurotrophic effects and promotes recovery after brain injury. Its preclinical profile promises wide applications due to its multi-target effects. Currently, Cerebrolysin is used for treatment of cerebral ischemia and neurodegeneration.

Areas covered: In stroke, earlier clinical trials with Cerebrolysin were performed mostly in mildly affected stroke populations, which usually have a favorable prognosis. Due to this selection, a floor or ceiling effect of recovery measures in the mild cases may have prevented to show a clear benefit between treatment groups. In contrast, subgroup analyses of more severely affected patients reveal a strikingly positive effect for enhanced recovery. Based on the findings from several studies, it became evident that the effect size of Cerebrolysin was increasing with stroke severity. Other controlled studies showed that Cerebrolysin can be safely used in combination with thrombolysis. More recently, Cerebrolysin has been tested not only for neuroprotection but also for its neurorecovery potential and also showed efficacy in patients with moderate to severe strokes.

Expert commentary: Cerebrolysin shows a benefit mostly in moderate to severe ischemic stroke patients and an overall significant effect for functional recovery when combined with neurorehabilitation versus neurorehabilitation alone. This gives lead to the planning of a more rigorous study design in the future.

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Cerebrolysin; ischemic stroke; neuroprotection; neurorecovery; neurotrophic factors

1. Introduction

Stroke is a time critical and life-threatening medical condition. First priorities are accurate diagnosis and stabilization of the patient. The goal in the acute management of stroke patients is the restoration of blood flow in order to limit brain damage and post-stroke complications. Recanalization therapies such as thrombolysis or mechanical thrombectomy are used. Additional treatment with neuroprotective drugs has been tested in animals with the focus on the limitation of brain damage but has not been shown to work in a consistent fashion in humans. Today, it is held that drugs that are considered to bear a neuroprotective potential have been used either too late or in situations where revascularization was not reached or not demonstrated. In a recent overview, Neuhaus et al. [1] argue that with contrast CTA or MR angiography the recanalizing effects of thrombolysis and rapid thrombectomy can be readily demonstrated and that the application of neuroprotectants can be tested in a much more appropriate manner with additional use of advanced penumbra imaging. Thus, they see a new era of testing and applying neuroprotectants in a more sensitive biological setting.

2. Efficacy of Cerebrolysin early post-stroke

Neuroprotective effects were the focus of early studies with Cerebrolysin. Cerebrolysin is a neuropeptide preparation that mimics the action of neurotrophic factors. These regulate normal physiological functioning as well as survival and regeneration of nervous tissue after injury. One of these early stroke studies was a randomized, double-blind, placebo-controlled trial (RCT) with 146 patients, published by Ladurner et al. [2]. This trial showed beneficial effects of Cerebrolysin (50 ml/day for 21 days) on motor function recovery and in cognitive performance, especially within the first 14 days, but missed significant treatment effects at Day 90 (Figure 1). This was explained by the rather mild baseline impairment, particularly spontaneous recovery, which was reflected by a Barthel Index (BI) of ≥85 at Day 90 in 66.2% of placebo patients.

Such early treatment effects were shown also in the study by Lang et al. [3]. This RCT assessed efficacy and safety of Cerebrolysin (30 ml/day for 10 days) in combination with alteplase (rt-PA) in 119 patients. Distribution of modified Rankin Scale (mRS) scores at Day 90, the primary study end point, resulted in equally good outcome (mRS 0 or 1) in 53% of patients in both groups. Additional responder analysis has shown a positive trend toward accelerated recovery in the Cerebrolysin group at early time points of assessment, in particular at Days 5 and 10 when assessed by the mRS, National Institutes of Health Stroke Scale (NIHSS), and the BI. In terms of safety, there were no concerns reported for the combined treatment regimen. Of note, the observed beneficial effects of Cerebrolysin were shown on top of the effects seen with rt-PA alone; thus, powering the study to detect an effect size of 20% has been too optimistic.

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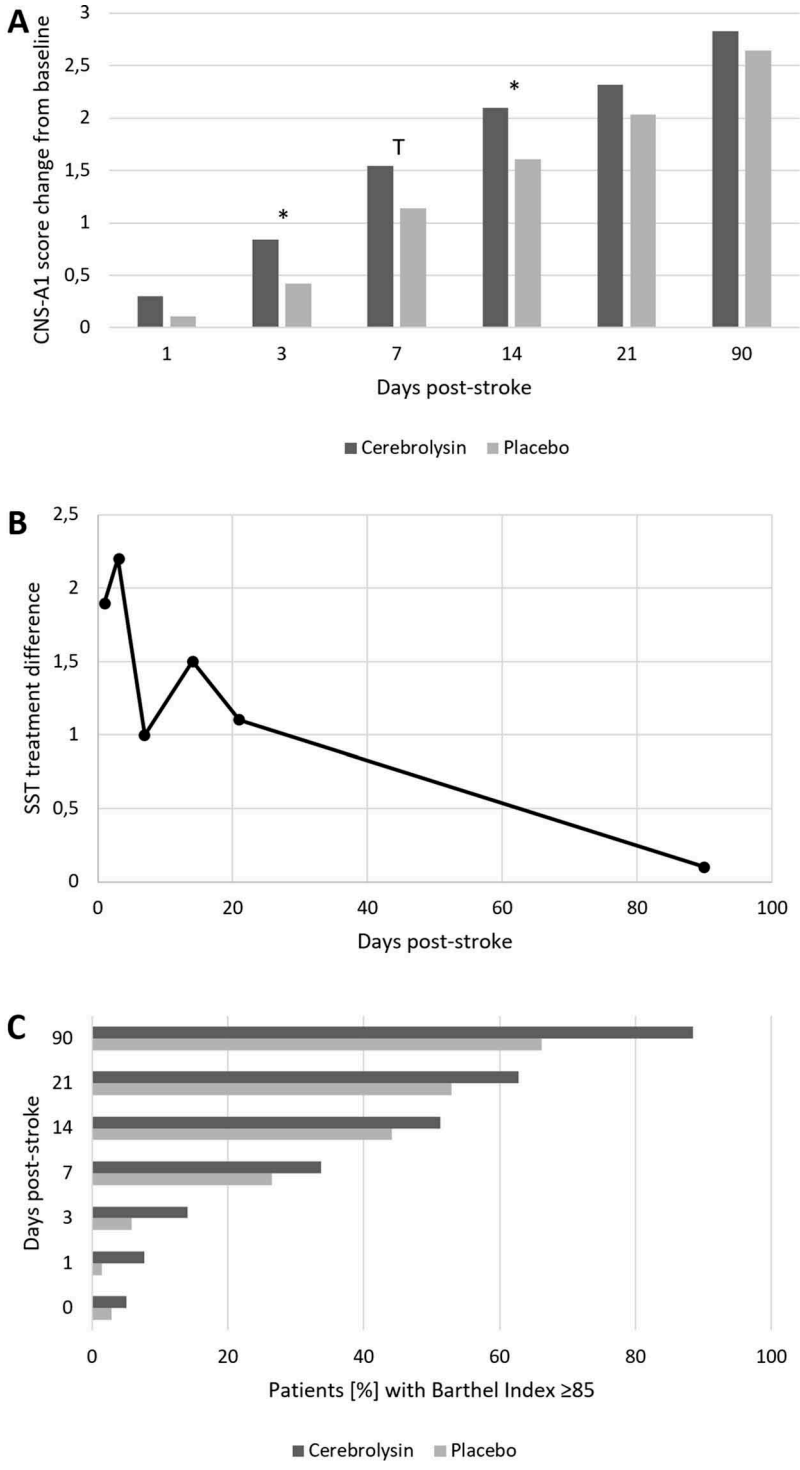

Figure 1. Cerebrolysin versus placebo effects on motor recovery and cognition. (**a**) Mean score change from baseline in the improvement of motor functions according to the Canadian Neurological Scale (CNS) Section A1 (no comprehension deficit). Baseline-adjusted group comparisons are significant ($p < 0.05$) at Days 3 and 14; Day 7 shows a tendency ($p < 0.10$). Analysis refers to the intention-to-treat population using the observed cases approach. (**b**) Mean score differences in the Syndrome Short Test (SST) between Cerebrolysin and placebo groups in favor of Cerebrolysin ($p < 0.05$; Mantel-Haenszel test; ITT-OC). (**c**)Percentage of patients with a BI score of at least 85 points at Day 90 indicating that no help is needed or in certain issues only (ITT-LOCF; $N = 146$). From Ladurner et al. [2], published in *Journal of Neural Transmission.*

A recent meta-analysis [4] of nine randomized, double-blind, placebo-controlled studies with 1879 patients confirmed that Cerebrolysin has a beneficial effect on early global neurological deficits. In the NIHSS on Day 30 (or 21), Cerebrolysin was superior to placebo (Mann-Whitney 0.60, $p < 0.0001$, Figure 2); the number needed to treat (NNT) for clinically relevant changes in early NIHSS (at least 4 points or resolution of symptoms [NINDS definition]) was 7.7 (95% confidence interval [CI] 5.2–15.0).

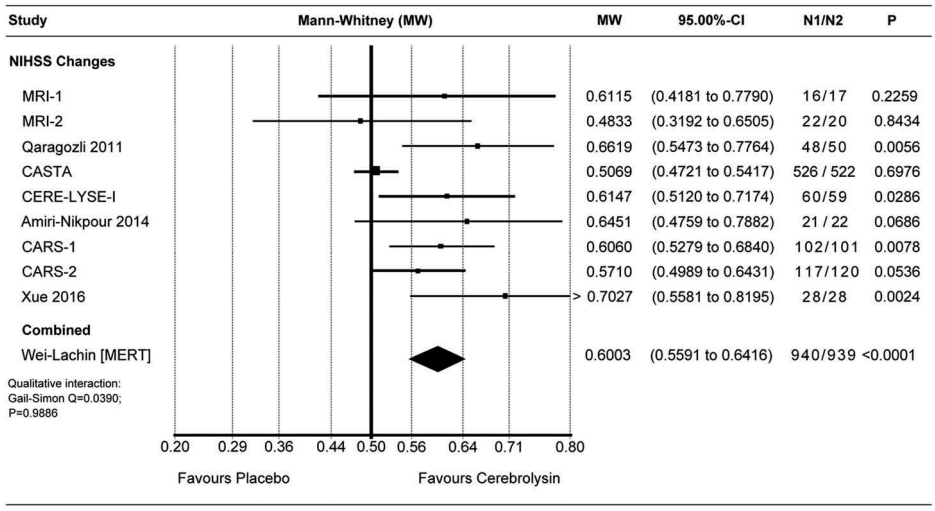

Figure 2. Meta-analysis of NIHSS changes from baseline. Comparison of Cerebroylsin versus placebo at Day 30 (or 21) in the ITT population; LOCF. Wei-Lachin pooling procedure (MERT), effect size: Mann-Whitney (MW). Republished under Creative Commons (http://creativecommons.org/licenses/by/4.0/) from Bornstein et al. [4].

3. Stroke severity matters

Whereas an early benefit of Cerebrolysin was observed on Days 10 to 14 independently of stroke severity, this benefit could only be demonstrated at Day 90 with increased stroke severity (due to the high rate of good outcome in less severely affected patients).

One of the largest studies performed with Cerebrolysin was the CASTA trial [5,6] with 1070 randomized patients. This trial compared a 10-day therapy of 30 ml of intravenous Cerebrolysin daily with matched placebo but had mostly included mild cases. It showed overall neutral results of a combined outcome measure of NIHSS, mRS, and BI at Day 90. It became quite obvious that due to the case mix, which included many mild strokes, a ceiling effect had likely prevented to show any benefit of Cerebrolysin in the full study sample; however, subgroup analysis in patients with moderate to severe stroke (NIHSS >12; N = 252) showed superiority of Cerebrolysin versus placebo in the NIHSS, mRS, and BI. Also in the meta-analysis of Bornstein et al. [4] the effect size in the mRS at Day 90 was in favor of Cerebrolysin when moderate to severe patients were separately analyzed.

4. Neuroplastic intervention to enhance stroke recovery

While early studies with Cerebrolysin focused on its neuroprotective effects, its impact on neurorecovery was demonstrated recently. There is preclinical evidence that Cerebrolysin has a modulatory effect on brain plasticity such as synaptic remodeling [7] and transmission (long-term potentiation) [8], neurite outgrowth [9–12], oligodendrogenesis [13], and neurogenesis [14–16], and has a beneficial effect on endogenous brain recovery processes [17–19]. Also, neuroimaging studies indicate that cortical reorganization and compensatory mechanisms contribute to the structural and functional changes that occur after stroke [20]. Furthermore, also rehabilitation therapies are thought to reduce impairment by activity-dependent plastic changes [21], which was already shown by constraint-induced therapy [22], treadmill training [23], and prism adaptation [24]. The combination of rehabilitation and a pharmacological agent is considered to be a new and pragmatic therapeutic approach in the treatment of stroke, giving way to a concept of 'recovery enhancers'.

The success of such a combination has been shown for the first time in the CARS-1 trial [25], which compared the combination of Cerebrolysin treatment (30 ml/day for 21 days) and early rehabilitation to rehabilitation alone in 208 patients. This RCT assessed efficacy and safety of Cerebrolysin in patients with moderate stroke in the acute and recovery phases. Primary efficacy parameter was the Action Research Arm Test (ARAT) on Day 90. This trial has shown that Cerebrolysin had a significant positive influence on motor function recovery of the upper extremities (ARAT) and also the global outcome was significantly higher at Day 90 in patients treated with Cerebrolysin as compared to patients who received rehabilitation only. At Day 90, it became quite evident that patients in the placebo group either could not complete the ARAT test or only with difficulty, whereas most patients treated with Cerebrolysin regained their fine motor skills after 90 days.

The CARS-2 study (N = 240) [26] had an identical design as CARS-1 and did not confirm the significant improvements in the primary and secondary outcomes. In both studies, the CARS-1 and CARS-2, the ARAT scores on Day 90 were similar for Cerebrolysin but differed substantially for placebo (Last Observation Carried Forward, Intention To Treat, median score: CARS-1: 27.0, CARS-2: 53.0). While the CARS-1 study showed only moderate final improvement in the placebo group, the placebo levels in the CARS-2 study reached the ceiling of the ARAT scale and were almost comparable to the Cerebrolysin levels. This was explained by the less severe ARAT baseline levels in CARS-2 (mean 25.1 versus 10.4 in CARS-1), allowing a good outcome after 90 days also in the placebo group. Observations in the NIHSS point in the same direction with 70% of the patients having an NIHSS baseline level of ≤7

as compared to 30% of patients in CARS-1. A score of 0 or 1 in the motor assessment of the NIHSS was found in 16.8% of patients in the CARS-1 study but in 60.0% of patients in the CARS-2 study (Figure 3).

A pre-planned meta-analysis of both CARS studies ($N = 442$) [26] showed a significant superiority (MW 0.62, $p < 0.0001$) of Cerebrolysin over placebo in the ARAT at Day 90 despite the heterogeneity in baseline severity. This meta-analysis also showed treatment effects of Cerebrolysin at an earlier point in time, i.e. before ceiling effects were reached. This was done using data of the NIHSS at Day 21, as the NIHSS is most sensitive for such earlier points in time [27]. The odds ratio for a clinically relevant change in the NIHSS (NINDS definition) at Day 21 was 1.805 (95% CI: 1.19–2.73; $p = 0.0053$) in favor of Cerebrolysin. The combined NNT for clinically relevant changes in early NIHSS was 7.1 (95% CI: 4–22).

Treatment effect of Cerebrolysin depending on stroke severity was also seen in the ECOMPASS trial [28]. This RCT ($N = 70$) assessed additional benefit of Cerebrolysin (30 ml/day for 21 days) on motor recovery (changes in hand and arm function) on top of a standardized rehabilitation therapy in subacute stroke patients with moderate to severe motor impairment. Whereas both groups improved significantly over time in the Fugl-Meyer assessment, significant group differences were reported only in patients with more severe motor involvement, both at Days 60 and 90 post-stroke. Imaging analyses of motor network plasticity by diffusion tensor imaging (DTI) and resting state functional magnetic resonance imaging (rsfMRI) supported the beneficial effect of Cerebrolysin on motor network plasticity (Figure 4).

5. Safety profile of Cerebrolysin

In these reported studies, Cerebrolysin has been shown to be safe and well tolerated, also when administered with rt-PA [3]. Adverse events did not differ substantially across the individual studies or treatment groups (see also the meta-analyses by Bornstein et al. [4]) and no study showed an unusual adverse event pattern. Generally, most adverse events reported from clinical trials were mild to moderate in severity,

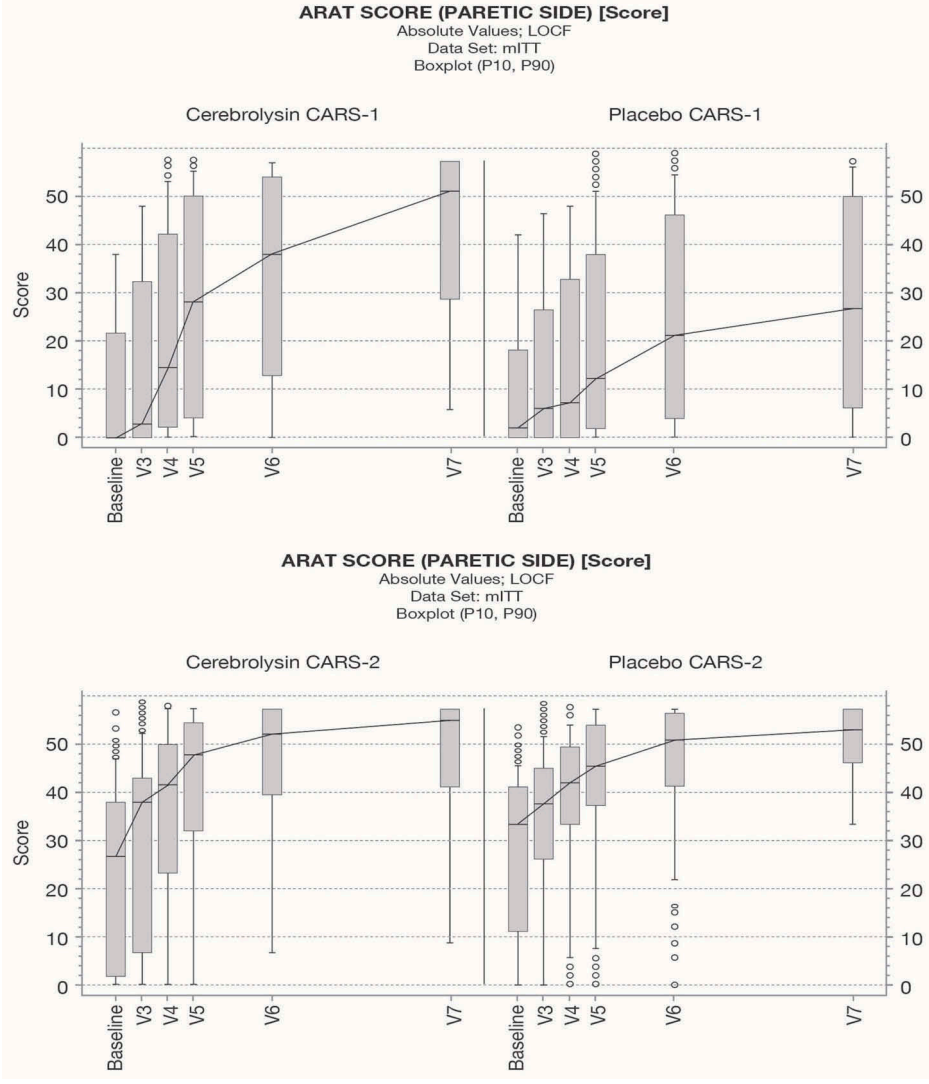

Figure 3. Main results from CARS trials testing Cerebrolysin coupled with neurorehabilitation versus neurorehabilitation alone. Time course of the Action Research Arm Test (ARAT) scores in the Cerebrolysin and placebo groups of CARS-1 (upper panel; $N = 208$) and CARS-2 (lower panel; $N = 240$). Boxplot (P10, P90), absolute values, mITT-LOCF. Republished under Creative Commons (http://creativecommons.org/licenses/by/4.0/) from Guekht et al. [26].

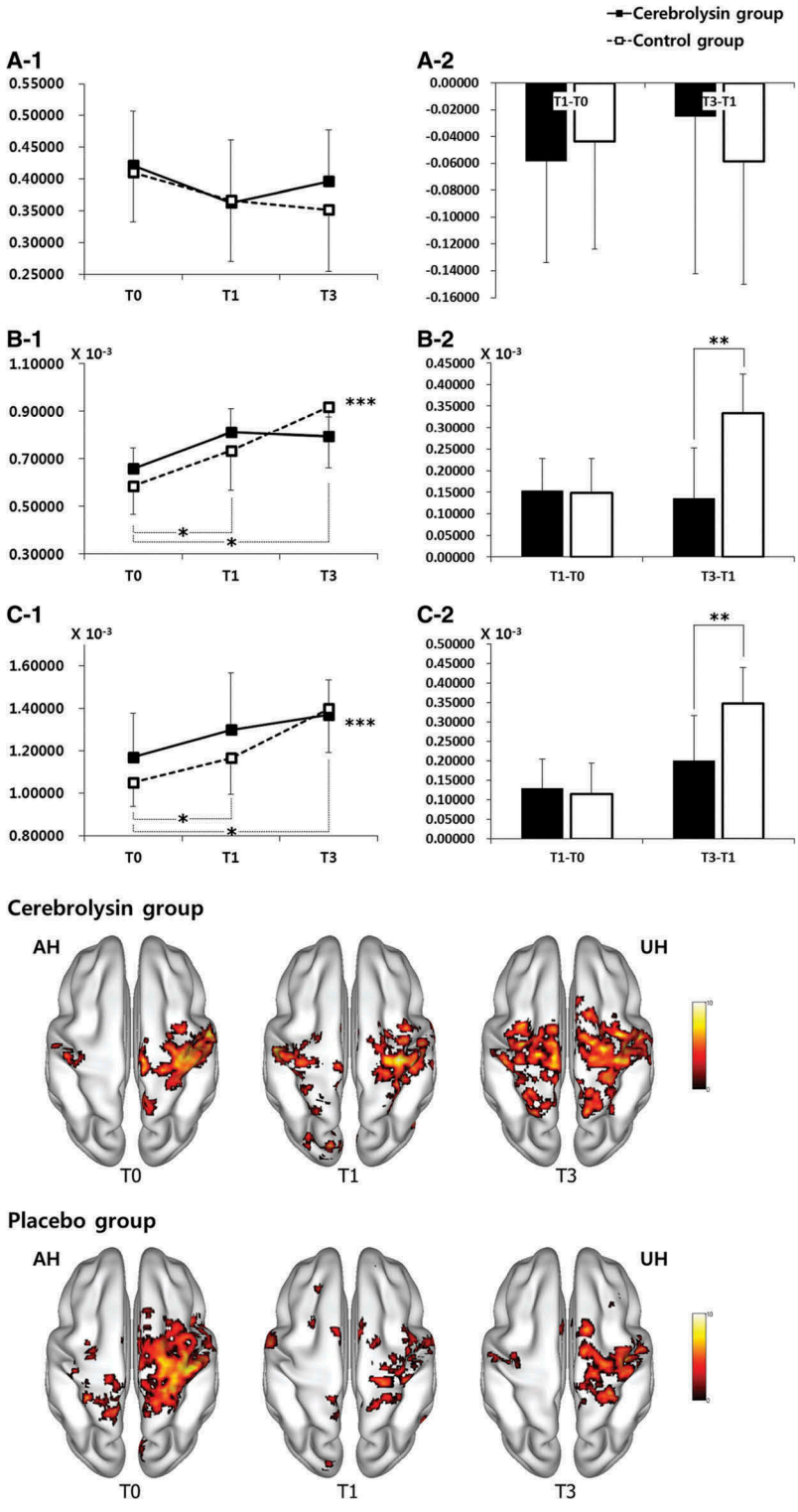

Figure 4. Cerebrolysin versus placebo in revovery from stroke in the ECOMPASS trial: Clear clinical benefit in moderate to severe cases coroborated by neuroimaging. Upper panel. Changes in the diffusion tensor imaging (DTI) in the Cerebrolysin and placebo groups at baseline (Day 8, T0), immediately after treatment (Day 29, T1) and three (Day 90, T3) months after stroke onset (per protocol analysis; $N = 66$). Time courses (1) and changes from baseline (2) are given for the fractional anisotropy (FA; A), the axial diffusivity (AD; B), and the radial diffusivity (RD; C). *$p < 0.05$ between time points in each group; **$p < 0.05$ between both groups; ***$p < 0.05$ between groups over time (ANOVA). **Lower panel**. Resting state of the sensorimotor network as shown by the resting state functional MRI (rsfMRI) for Cerebrolysin and placebo in the affected (AH) and unaffected (UH) hemispheres at baseline (Day 8, T0), immediately after treatment (Day 29, T1), and three (Day 90, T3) months after stroke onset (per protocol analysis; $N = 66$). Republished under Creative Commons (http://creativecommons.org/licenses/by/4.0/) from *Chang et al. 2016* [28].

transient and classified as not related to the study drug by the investigator. In terms of serious adverse events, no differences were observed between study groups neither in the rates nor in unexpected patterns. No marked hematologic and other laboratory abnormalities other than those reported as serious adverse events have been found in clinical studies.

6. Conclusion

Cerebrolysin has a potential to enrich the current pharmacologic armamentarium of stroke therapy. It can be widely used without relevant restrictions. Cerebrolysin does not have a strictly limited time window and has shown to be safe and well tolerated. Furthermore, there is considerable experimental evidence that Cerebrolysin protects the brain against the detrimental impact of the ischemic cascade and supports the brain in the neuronal reorganization process. Clinical studies have shown a fast onset of action with an early separation from placebo controls mainly from Day 5 to Day 21, thus potentially allowing a more efficient early rehabilitation. As appears from individual study results, the clinical benefit of Cerebrolysin tends to be higher in patients with severe strokes compared to mild cases. This is most likely due to the better recovery rate of patients with less severe strokes. For example, deGraba et al. [29] reported that 45% of patients with an initial NIHSS of 7 and below were functionally normal already after 48 h. Notably, also in the milder affected patients, Cerebrolysin treatment resulted in accelerated recovery rates before reaching a ceiling effect. However, possibly due to a variety of unsystematic and systematic influences, e.g. patients received at least standard care, participated in a neurorehabilitation program, etc., patients continued to improve over time so that treatment differences were usually less pronounced at Day 90.

7. Expert commentary

In experimental research, Cerebrolysin shows neurotrophic factor-like effects and promotes neuroplasticity and endogenous neurogenesis in the ischemic brain. While Cerebrolysin has been on the market for several decades in many countries around the world, these modulatory effects have only been shown recently and the experimental studies performed have been aligned with the STAIRS criteria that represent a new era of stringent criteria developed for such research. Today, there are better means of looking at the effects of recovery in stroke patients. Functional and molecular imaging allows looking more precisely at blood flow, biomarkers, and predictors of recovery and should supplement the clinical measurements [28].

Current findings suggest that Cerebrolysin has more effect on neuroplasticity, neurorestoration, and recovery than on neuroprotection. It is not so effective to protect the neurons from dying but rather to restore or develop new networks of activity. Therefore, Cerebrolysin probably has most impact in the rehabilitation phase; nevertheless, the treatment should be started as early as possible. This is in line with increasing evidence for an enhanced functional and neurological outcome if stroke rehabilitation therapy is already initiated in the stroke unit or acute-care hospital once the patient's overall condition has been stabilized, often between 24 and 48 h [30–32].

Controlled clinical trials with Cerebrolysin used 30–50 ml daily doses applied over 21 days. With one notable positive exception [25], all these trials had a neutral overall outcome. Some showed an early benefit at Day 10 or 30, which did not last to the primary end point at 90 days. Further exploratory analyses of these trials showed that severely affected cases responded best. What does this say? Either the end points or combined end points used might not be sensitive enough to pick up group differences of samples with milder impairments. They might not be sensitive enough at all to show what we expect to see. Clinical trialists pioneering in this field have now come to the conclusion that any such trial must be based on a case load of mostly severely affected stroke cases in order to neutralize a ceiling or floor effect in comparison to a matched control group. Continuously improved acute therapy and specialized care in stroke units are both influencing outcomes and thus decrease the chance to see a drug treatment effect between treatment groups.

It is a fact that Cerebrolysin is safe and does not harm recovery. Most impressively, the homogeneity of the positive trends is encouraging and was consistently found in more severely affected patients.

8. Five-year view

This points at the possibility of designing a new trial with inclusions and outcome measures better suited to reflect treatment differences among groups. For this, it takes careful planning of the intervention and outcome measures that are most sensitive to reflect group differences. A minimum of 3–4% absolute difference in a recovery parameter would significantly influence the NNT and result into a clinically meaningful effect, in terms of improved outcomes such as disabilities avoided or reduced, or an overall cost-effectiveness. When considering effects of recovery, one must also consider cognition, emotion, and well-being. Up to 80% of survivors complain about loss of cognitive abilities, changes of mood, fatigue, or apathy. Cognitive outcome is a major determinant of recovery and strongly influences overall outcome and long-term effects including participation in the community. Thus, such eminent domains should be included in any future trial, especially since previous stroke studies indicated beneficial effects of Cerebrolysin on cognitive performance and depression [2,25].

Key issues

- Detailed analyses of experimental and clinical data provide quite compelling evidence for the neurorestorative effects of Cerebrolysin in patients after stroke.
- Probably, a combination of therapies seems best to prove a clinically meaningful outcome, as was the case in the CARS-1 trial [25].
- Furthermore, Cerebrolysin is a safe and valuable enrichment to current stroke therapy, especially in combination with neurorehabilitation.

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