Cerebrolysin in mild to moderate Alzheimer’s disease: A meta-analysis of randomized controlled clinical trials

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Dementia: Alzheimer’s disease, clinical data

Introduction

A previous meta-analysis of Cerebrolysin (Cere) in mild to moderate Alzheimer’s disease (AD), based on aggregate data, showed serious short-coming: ADAS-cog effect sizes of two included studies were correct (892 instead of -0.8, 4.10 instead of -0.16), short and long term results were mixed in the same meta-analysis, Bellvue et al., for example, reported a trial that was identified as a randomized clinical trial, in mild to moderate stages of AD of 24 weeks. This current review is based on a systematic meta-analysis of RTCs using Cere compound. The need for such a review is to have a fresh look at an alternative to amyloid-targeting compounds who have failed so far to significantly impact on patients care.

Methods

Trials were included in this review if only if they were randomized, double-blind, and placebo-controlled. Trials were identified from the Cochrane Dementia Group database of trials by searching the term “Cere” from 1999 to 2004, using the search terms and Alzheimer and from a large Cere review by the Center for Collaborative Neurosciences, as well as from the sponsors own list of Cere studies. It is important to note that the Cochrane Dementia and Cognitive Improvement Group announced a review of “Cerebrolysin for Alzheimer’s Disease” in 2000, with amendments in 2004 but, however, no results were published yet.

For all randomized, double-blind, and placebo-controlled studies published data were available to us, no study had to be excluded from meta-analysis.

In addition to aggregate data from publications, for these trials, raw data were available for individual patient data analysis.

This way a combination of all studies by means of a mixed meta-analysis approach was possible integrating results from individual patient data (IPD) re-analyses as well as from aggregate data from publications. Thus, the broader possible summary of clinical efficiency results could be reached. Compared to pure aggregate data meta-analyses the mixed approach ensures a higher level of validity and is recommended by leading researchers whenever feasible.

The included studies investigated efficacy and safety of Cere and a common outcome was used. The primary outcome was the change from baseline to end of treatment in the primary cognitive domain in the present analysis (SMD -0.29, OC, month 6) was comparable to the range seen for other anti-dementia treatments. The effect size of Cere on the primary outcome was 0.1 (95% CI -0.29 to 0.58).

Results

There were 6 eligible RTCs comparing 30 ml/d Cere vs. placebo. For all studies either individual patient data (IPD) or published data (aggregate data) were available. With respect to the primary cognitive assessments this resulted in available data for month 1 on 780 (99.5%) of a total of 783 ITT patients (studies with 6 months observational period). Thus, at clinical change this resulted in available data for month 1 on 763 (97.3%) of a total of 777 ITT patients (studies with 6 months observational period). Thus, at all points in time, the number of missing observations was below 10%, i.e., within the range recommended for class I evidence based quality standards.

Conclusion

This meta-analysis provides evidence that Cere has an overall beneficial effect and a favorable benefit-risk ratio in patients with mild to moderate AD. Cere as a therapeutic agent should be considered by clinicians seeking treatment options for mild to moderate AD.

Related references

2. POSTER: A. Meyer et al., 2005. 24week, double-blind, placebo-controlled study of Cerebrolysin in patients with mild to moderate Alzheimer’s disease (AD).
4. POSTER: Marks et al., 2007. A 28 week double-blind placebo-controlled study with Cerebrolysin in patients with mild to moderate AD.

Fig. 1. Comparison of Cere (30 ml/d) vs Placebo at Month 6, Primary Cognitive Outcome Measures, Changes from Baseline: Effect Size: Standardized Mean Difference (SMD), DC

Fig. 2. Comparison of Cere (30 ml/d) vs Placebo at Month 6, Global Clinical Change, Effect Size: Odds Ratio, DC

Fig. 3. Comparison of Cere (30 ml/d) vs Placebo at Month 6, Global Benefit: Combined Global Clinical Change + Primary Cognitive Outcome Measures (Multivariate), Effect Size: Mann-Whitney (MW), DC

Fig. 4. Comparison of Cere(30 ml/d) vs Placebo, Various Safety Criteria, Crude Pooling, Effect Size: Odds Ratio, DC

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