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

Gauthier S[1], Proaño JV[2], Jia J[3], Froelich L[4], Vester JC[5], Doppler E[6]

[1]McGill Centre for Studies in Aging, Montreal, Canada; [2]National Disease Medical Research Unit, Instituto Mexicano del Seguro Social México, México; [3]Department of Neurology, Xuan Wu Hospital, Beijing, China; [4]Department of Geriatric Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; [5]idv Data Analysis & Study Planning, Department of Biometry & Clinical Research, Krailling, Germany; [6]EVER Neuro Pharma GMBH, Unterach, Austria

Contact: serge.gauthier@mcgill.ca

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Introduction

A previous meta-analysis of Cerebrolysin (Cere) in mild to moderate Alzheimer's disease (AD)[1], based on aggregate data, showed serious shortcomings: ADAS-cog effect sizes of two included studies were incorrect (0.92 instead of -0.84, -4.10 instead of -3.63), short and long term results were mixed in the same meta-analysis, handling of missing data and responder definitions were inconsistent across studies. Thus, there was rationale for a fresh, updated meta-analysis avoiding previous drawbacks. Cere is a parenterally administered neuropeptide preparation with pharmacodynamic properties similar to those of endogenous neurotrophic factors. Efficacy outcomes and safety data from randomized, placebo-controlled clinical trials in mild to moderate stages of AD have been reviewed by Plosker and Gauthier. The current review is based on a systematic meta-analysis of RCTs 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 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 PubMed using the search terms Cere and Alzheimer, from a large Cere review by the Center for Collaborative Neurosciences, as well as from the sponsor's own list of Cere studies. It is interesting to note that the Cochrane Dementia and Cognitive Improvement Group announced a review of "Cerebrolysin for Alzheimer's Disease" in 2002, with amendment in 2008[4], however, no results were published up to now.

For all randomized, double-blind, and placebocontrolled studies published data were available, thus, no study had to be excluded from metaanalysis. In addition to aggregate data from publications, for three studies, raw data were available for individual patient data analyses.

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 broadest possible summary of clinical efficacy results could be reached. Compared to pure "aggregate data" meta-analyses the mixed approach assures a higher level of validity and is recommended by leading researchers wherever feasible.

The included studies[2-7] assessed outcome using a variety of measures, including the such as: Alzheimer´s Disease Assessment Scale – cognitive subscale (ADAS-cog), ADAS-cog+ (extension of ADAS-cog with three additional items), MMSE (Mini Mental State Examination), and Trail-Making Test (Zahlen Verbindungs-Test, gerontopsychological version; ZVT-G), Clinician´s Interview Based Impression of Change with Caregiver Input (CIBIC+) or Clinical Global Impression (CGI).

Results

There were 6 eligible RTCs comparing 30 ml/d Cere vs. placebo. For all studies either individual patient data and/or published data (aggregate data) were available. With respect to the primary cognitive assessments this resulted in available data for month 1 on 763 (97.3%) of a total of 784 ITT patients and for month 6 on 519 (90.4%) of a total of 574 ITT patients (studies with 6 months observational period). Regarding global clinical change this resulted in available data for month 1 on 780 (99.5%) of a total of 784 ITT patients and for month 6 on 525 (91.5%) of a total of 574 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 studies. While all studies had 20 infusions during the first 4 weeks with 30 ml of Cere per day, in one study an additional treatment cycle of 20 infusions after a treatment-free interval of 8 weeks was introduced and in one study treatment was continued after 4 weeks with 2 infusions per week for another treatment period of 8 weeks. Study findings are summarized in figures 1-4.

Discussion

This meta-analysis comprised results of six individual double-blind, placebo-controlled studies of Cere in patients with mild to moderate AD. Cere treatment resulted in a statistically significant benefit in the two main efficacy domains suggested by the FDA as of primary interest: the cognitive and global endpoint[8]. The six studies in this meta-analysis had a similar design, and all were placebocontrolled, double-blind, and parallel-group trials, with a double-blind treatment period of at least 4 weeks. Patients in the studies were randomly assigned to either placebo or active treatment and treatment arms were equally balanced with regard to age, gender, etc. The standardized effect size of Cere on the 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 global domain (OR 3.1), as assessed by the CIBIC+ instrument (by itself a measure of clinical relevance) or CGI, supported the clinical importance of this cognitive benefit. The LOCF analysis resulted in similar overall effect sizes.

Conclusion

This meta-analysis provides evidence that Cere has an overall beneficial effect and a favorable benefitrisk 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.

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

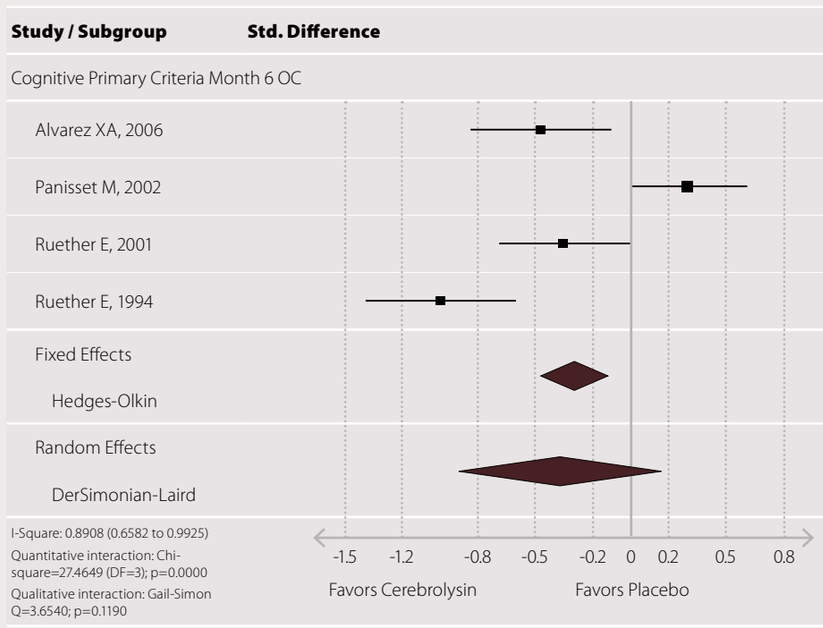


Fig. 2. Comparison of Cere (30 ml/day) vs Placebo at Month 6, Global Clinical Change, Effect Size: Odds Ratio, OC

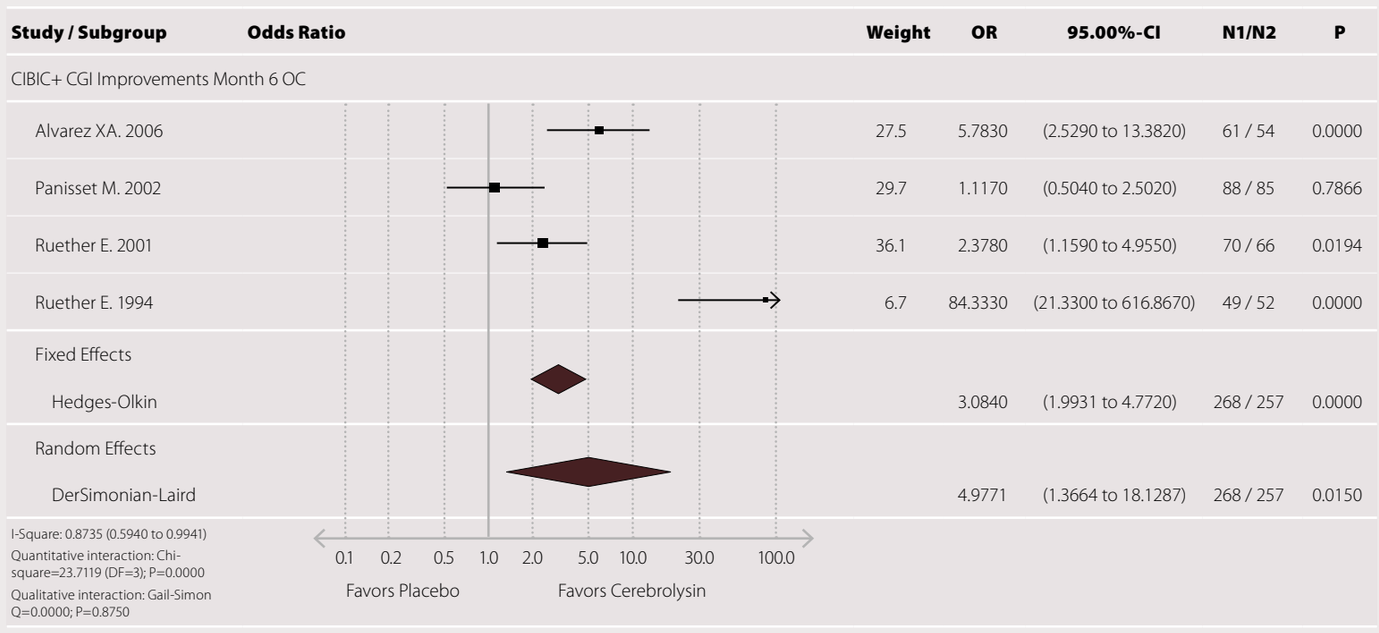


Fig. 3. Comparison of Cere (30 ml/day) vs Placebo at Month 6, Global Benefit: Combined Global Clinical Change + Primary Cognitive Outcome Measures (Multivariate), Effect Size: Mann-Whitney (MW), OC

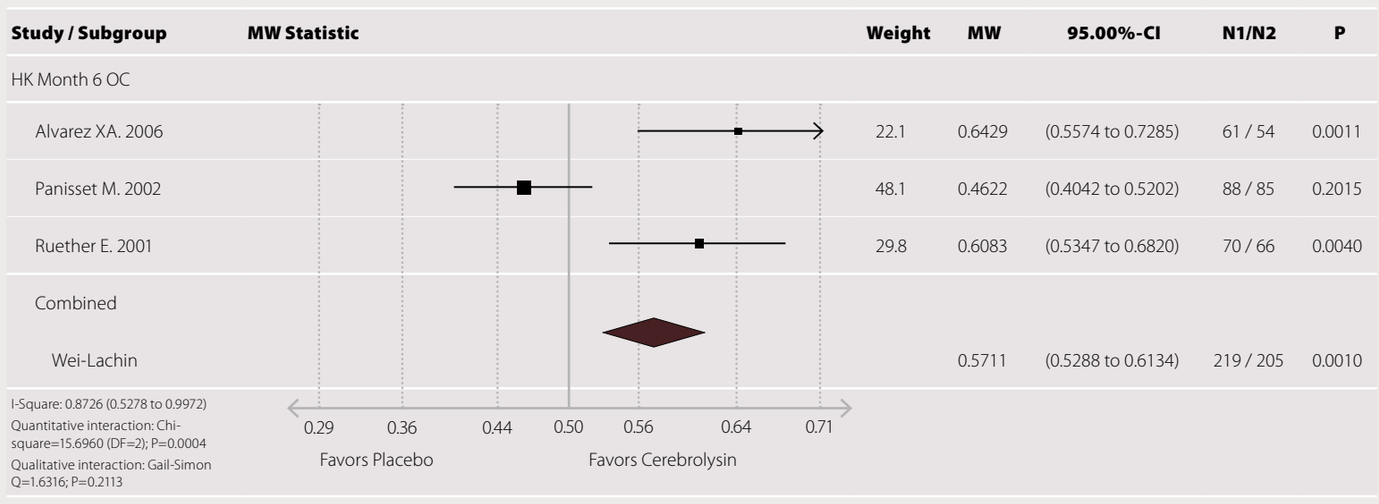
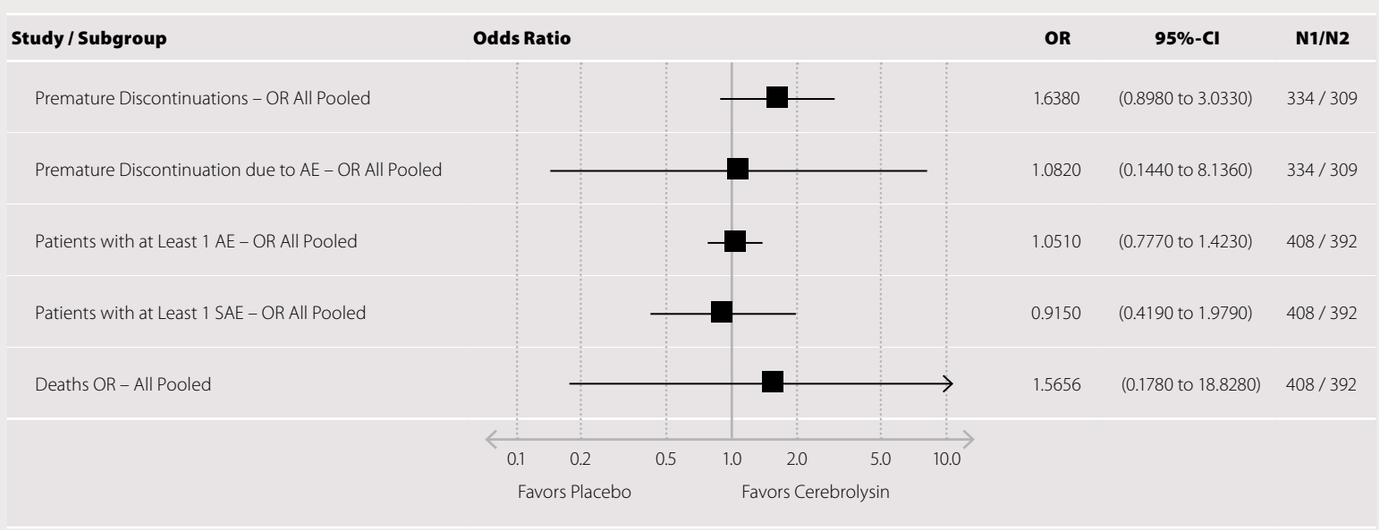


Fig. 4. Comparison of Cere(30 ml/day) vs Placebo, Various Safety Criteria, Crude Pooling, Effect Size: Odds Ratio, OC



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