Neurotrophic and cholinergic treatment in Alzheimer's disease: Results of a randomized clinical trial

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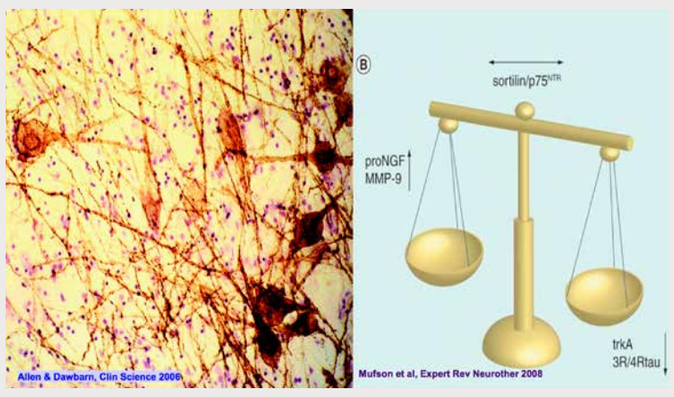
Background

Basal forebrain cholinergic neurons degenerate in AD



There is a deficit of trophic factors in early AD brains

Rationale

The clinical efficacy of cholinesterase inhibitors (ChEIs) in AD patients decreases over time [Cortes et al, 2007]. This loss of efficacy of cholinergic drugs might be due, at least in part, to the fact that cholinergic neurons of the basal forebrain degenerate progressively in AD. A deficit of cholinotrophic support, which is present in early AD stages, might account for the degeneration of cholinergic neurons [Mufson et al, 2007, 2008]. The use of compounds with neurotrophic activity might, therefore, increase and/or prolong the efficacy of ChEIs by protecting cholinergic neurons from degeneration.

Methods

Primary endpoints:

- Global outcome (CIBIC+ score distribution) at week 28
- Cognition (change from baseline in ADAS-cog+) at week 28

Secondary endpoints:

- Changes in functioning (ADCS-ADL) at weeks 16 and 28
- Changes in behaviour (NPI) at weeks 16 and 28
- ADAS-cog+ responder rate (improvement of ≥4 points)
- CIBIC+ responder rate (improvement: score ≤3)
- Combined ADAS-cog+ and CIBIC+ responder rate

Safety:

- Adverse events
- Changes from baseline in concomitant medications, vital signs, EKG, Lab parameters, physical and neurological examinations

Statistical methods:

- Descriptive Statistics, ANOVA, ANCOVA, Logistic Regression, t-test, Wilcoxon-Mann-Whitney-U-test, Fischer's exact test, Chi^2-test, Cochrane-Mantel-Haenszel Test

Introduction

Cerebrolysin is a brain-derived neurpeptide preparation, which consists of low molecular weight peptides able to cross the blood-brain barrier and to mimic the effects of endogenous neurotrophic factors.

Cerebrolysin acts as a multimodal drug:

- Has NGF and BDNF-like trophic actions [Akai et al, 1992; Masliah et al, 1999]
- Modulates neuro-inflammation [Alvarez et al, 1999, 2009]
- Reduces brain amyloid- and tau-related pathology by inhibiting GSK3β and CDK5 activity [Rockenstein et al, 2002, 2006]
- Prevents synaptic loss [Masliah et al, 1999] and neuronal degenerationapoptosis [Alvarez et al, 1999]
- Promotes neurogenesis [Chen et al, 2007; Rockenstein et al, 2007]

Cerebrolysin is effective as a monotherapy for mild to moderate AD [Alvarez et al, 2006, 2009; Plosker & Gauthier, 2009] and seems to constitute a good option for the combined therapy in AD.

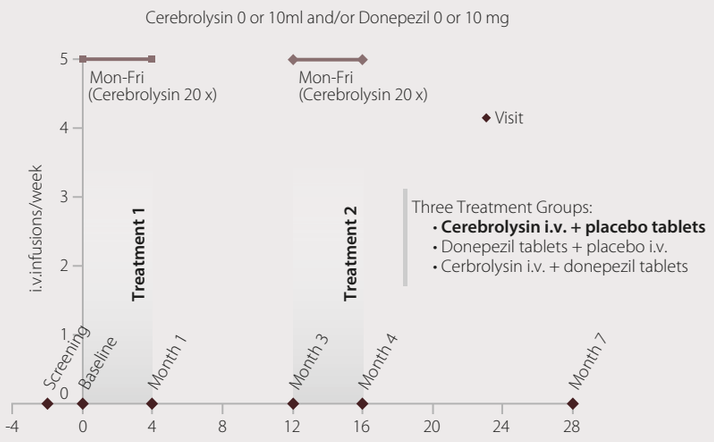
Methods

We compared the safety and efficacy of Cerebrolysin (10 ml; n=70), donepezil (10 mg; n=75) and a combination of both treatments (n=72) in mild-to-moderate (MMSE score 14-25) probable AD patients enrolled in a prospective, randomized, double-blind, active-drug controlled, parallel group, 28-week, multicenter trial.

Patients received i.v. infusions of Cerebrolysin or placebo (5 days/week) on weeks 1 to 4 and 12 to 16, and Donepezil or placebo tablets once daily during 28 weeks (5mg for 4 weeks and 10mg thereafter) (Figure 1).

Of the 217 patients with probable AD (according to DSMIV and NINCDS-ADRDA criteria) randomized, 200 started treatment (safety data set) and 197 were valid for the intention to treat (ITT) analysis (Table 1).

Fig. 1. Treatment and Visit Schedule



Results

The highest percentage of patients showing a combined improvement in cognition and global functioning at week 28 was observed with the combination therapy, followed by Cerebrolysin and donepezil (Figure 4).

- In addition, patients treated with both drugs showed the same rate of combined responders at weeks 16 and 28, while this rate decreased in both monotherapy groups

No significant treatment group differences were found at week 28 for either functioning in activities of daily living or neuropsychiatric symptoms (figures 5, 6).

- The performance in ADL improved significantly ($p<0.05$) in the combination group as compared with the donepezil group at week 16, but not at week 28.

Safety data showed no significant group differences.

- Nausea and diarrhea were more frequent in patients treated with Donepezil, whereas dizziness and agitation appeared more frequently in Cerebrolysin-treated patients (table 2).

Results

Treatment effects were similar in all study groups with improvements in global outcome and cognition being descriptively higher with the combination therapy and Cerebrolysin

Cognitive performance improved in all treatment groups, without significant group differences (Figure 2).

- The improvement of cognition was higher with the combined therapy than with any monotherapy at all study visits.

A significant superiority of Cerebrolysin to Donepezil (p=0.032) and a marginal significant superiority (p=0.068) of the Combination to Donepezil was found for the global clinical outcome (CIBIC+) at week 28 (figure 3).

- The odds ratio for the proportion of patients achieving a CIBIC+ response was significantly higher in Cerebrolysin (p=0.003) and combination (p=0.004) groups than in the donepezil group

Table 1. Patient disposition and analysis populations

	Cerebrolysin + Placebo N (%)	Donepezil + Placebo N (%)	Cerebrolysin + Donepezil N (%)	Total N (%)
Total randomized	70 (100)	75 (100)	72 (100)	217 (100)
Total treated[1]	65 (92.9)	68 (90.7)	67 (93.1)	200 (92.2)
ITT analysis set	64 (91.4)	66 (88.0)	67 (93.0)	197 (90.8)
PP analysis set	52 (74.3)	52 (69.3)	54 (75.0)	158 (72.8)
Safety analysis set	65 (92.8)	68 (90.7)	67 (93.0)	200 (92.2)
Total completed	57 (74.3)	52 (69.3)	55 (76.4)	159 (73.3)
Total discontinued	18 (25.7)	23 (30.7)	17 (23.6)	58 (26.7)
Reasons:				
• Consent withdrawn	10 (14.3)	7 (9.3)	8 (11.1)	8 (11.1)
• Noncompliance/ protocol violation	**4 (5.7)**	**9 (12.0)**	**6 (8.3)**	**6 (8.3)**
• Adverse event	**1 (1.4)**	**5 (6.7)**	**2 (2.8)**	**2 (2.8)**
• Death	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)
• Safety Risk	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
• Other Reasons	3 (4.3)	1 (1.3)	1 (1.4)	1 (1.4)

[1]Treated=received at least one dose of study drug. Values are N (%)

Fig. 2. Change from baseline in ADAS-cog+ score

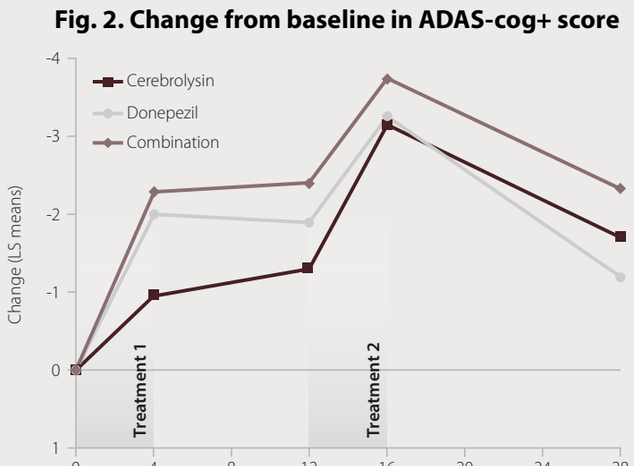


Fig. 3. CIBIC+ score distribution at week 28

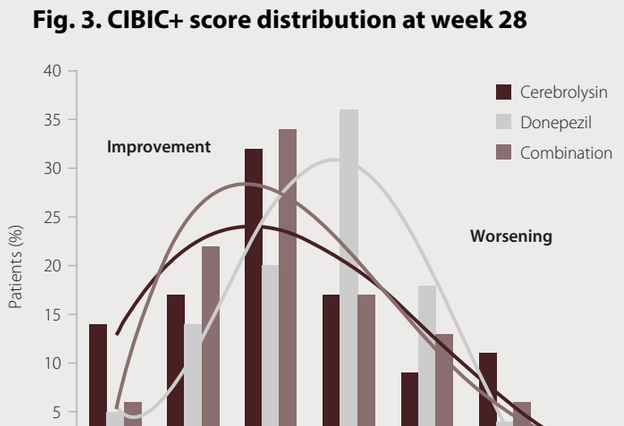


Fig. 4. Combined ADAS-cog+ and CIBIC+ responders

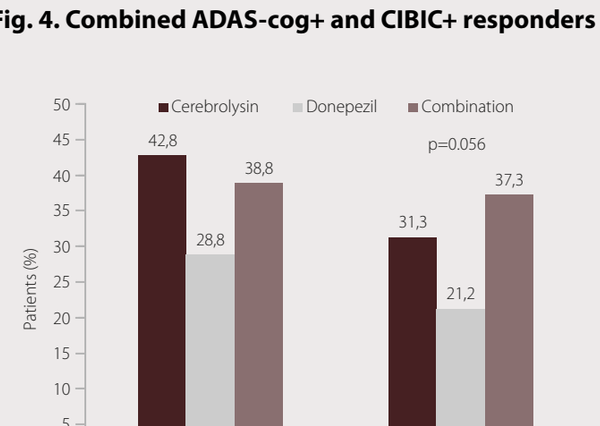


Fig. 5. Change from baseline in ADCS-ADL scores

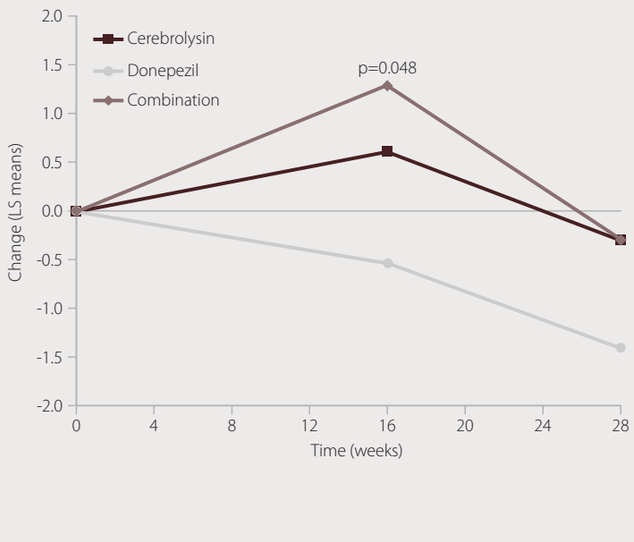


Fig. 6. Change from baseline in NPI scores

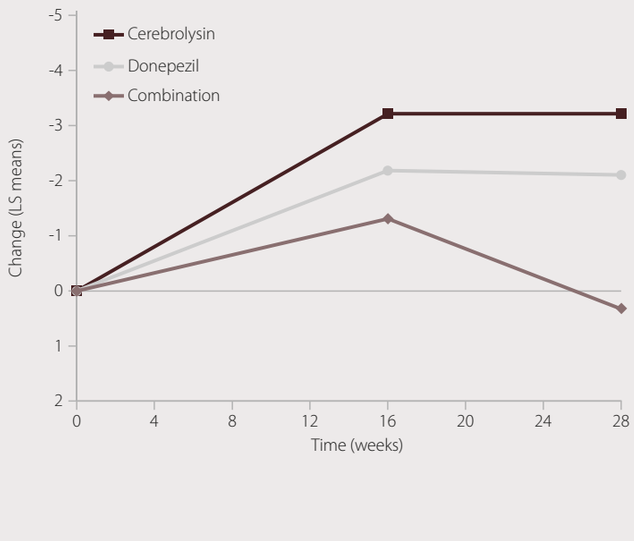


Table 2. Most frequent adverse events

Adverse Event	Cerebrolysin + Placebo	Donepezil + Placebo	Cerebrolysin + Donepezil	Total
Dyspepsia	7,7%	10,3%	7,5%	8,5%
Agitation	13,8%	4,4%	6,0%	8,0%
Dizziness	9,2%	2,9%	10,4%	7,5%
Nasopharyngitis	7,7%	8,8%	6,0%	7,5%
Dysthymia	4,6%	5,9%	10,4%	7,0%
Diarrhoea	3,1%	8,8%	7,5%	6,5%
Nausea	1,5%	8,8%	7,5%	6,0%
Anorexia	7,7%	4,4%	6,0%	6,0%
Confusion	7,7%	5,9%	4,5%	6,0%
Anxiety	4,6%	8,8%	4,5%	6,0%

Conclusions

- **Cerebrolysin shows similar, and descriptively even better efficacy than donepezil in mild to moderate AD**
- **The combined treatment with Cerebrolysin and donepezil was safe and showed a tendency for superiority versus donepezil monotherapy, suggesting a long-term synergistic effect**
- **The combination of neurotrophic (Cerebrolysin) and cholinergic (donepezil) treatment might provide long-term clinical benefits in AD.**

Related references

1. Original publication: Current Alzheimer Research, 2011, 8, 583-591
2. POSTER: A. Alvarez et al., 2011. Neurotrophic and combined treatment in Alzheimer's disease: Modulatory effects on free IGF-I and TNF-alpha
3. POSTER: A. Alvarez et al., 2014. Cerebrolysin and combination therapy enhance serum BDNF levels in Alzheimer's disease patients

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