Dementia: Alzheimer’s disease, clinical data

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

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Background

Basilicostricular and cholinergic neurons degenerate in AD

There is a deficit of trophic factors in early AD brains

Introduction

Cerebrolysin is effective as a monotherapy for mild to moderate AD (Axelera et al. 2006, 2009; Pellicer & Santiago, 2008) and seems to constitute a good option for the combined therapy in AD

Rationale

The clinical 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 cholinergic support, which is present in early AD stages, might account for the degeneration of cholinergic neurons (Muldoon et al., 2007, 2008). The use of compounds with neurotrophic activity might therefore increase and/or prolong the efficacy of cholinergic treatments by protecting cholinergic neurons from degeneration.

Methods

Primary endpoints:

• Global outcome (CBIC+ score distribution) at week 28
• Change from baseline in concomitant medications, vital signs, and/or prolong the efficacy of ChEIs by protecting cholinergic neurons from degeneration.
• Combined ADAS-cog+ and CIBIC+ responder rate
• Changes in behaviour (NPI) at weeks 16 and 28
• Changes in functioning (ADCS-ADL) at weeks 16 and 28
• Global outcome (CIBIC+ score distribution) at week 28

Secondary endpoints:

• Changes from baseline in concomitant medications, vital signs, and/or prolong the efficacy of ChEIs by protecting cholinergic neurons from degeneration.

Safety:

• Changes from baseline in concomitant medications, vital signs, and/or prolong the efficacy of ChEIs by protecting cholinergic neurons from degeneration.

Statistical methods:

• Descriptive Statistics, ANOVA, ANCOVA, Logistic Regression, t-test, Wilcoxon-Mann Whitney u-test, Fisher’s exact test, Chi-square, Monte Carlo simulation

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 24, 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 (Figure 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 diarrhoea were more frequent in patients treated with donepezil, whereas diarrhoea and agitation appeared more frequently in Cerebrolysin treated patients (Table 2).

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

2. POSTER: A. Alvarez et al. 2011. Neurotrophic and combined treatment in mild to moderate AD: Results of a randomized clinical trial. Poster presented during ICAD 2010 in Honolulu, Hawaii

Fig. 1. Treatment and Visit Schedule

Table 1. Patient disposition and analysis populations

Table 2. Most frequent adverse events

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

Fig. 3. CBIC+ 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