LB11 ADCOMS: A post-hoc analysis using data from the LipiDiDiet trial in prodromal Alzheimer's disease

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Backgrounds

The LipiDiDiet study was designed to investigate the effects of the multinutrient combination Fortasyn Connect over 24 months in prodromal Alzheimer's disease (AD). Main results were published in Soininen et al., Lancet Neurology 2017.[1]

The LipiDiDiet study was initiated shortly after the first definition for prodromal AD was finalized by Dubois et al (2007),[2] and as such is one of the first randomized clinical trials (RCTs) in this population using these criteria. Evaluating efficacy of therapeutic interventions for mildly affected populations with only limited cognitive and functional decline and subtle impairment depends on sufficiently sensitive and informative composite outcome measures. Clinical Dementia Rating - Sum of Boxes (CDR-SB) has been proposed as such a measure.[3] More recently, the AD Composite Score (ADCOMS) was developed as a broader composite clinical outcome measure for trials in prodromal and mild AD dementia.[4] It consists of cognitive and functional items from three commonly used scales in AD dementia trials: the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog), Mini-Mental State Examination (MMSE), and CDR-SB. The combination of selected items from these scales was shown to have the highest sensitivity for measuring changes and treatment effects over time in early AD subjects as compared to the individual scales.[4] In 2018, for the first time, results were presented from an RCT using ADCOMS as the primary outcome.[5] Results were interpreted as supporting the applicability of this composite score. However, more studies are needed to establish general applicability across different trial settings and the contribution of the different subdomains to the composite.

Objectives

The main aim of the present post-hoc analysis was to explore the effects of a multinutrient intervention on cognition and global function, as captured by ADCOMS and its subdomains, using data from the LipiDiDiet trial. Additionally, evaluating ADCOMS in a second, independent, early AD population provides broader knowledge of the utility of ADCOMS as a single clinical outcome measure in early AD trials.

Methods

The LipiDiDiet study (NTR1705) was a 24-month, double-blind, parallel-group, multi-center RCT (11 sites in Finland, Germany, the Netherlands, and Sweden), with optional 12-month double-blind extensions. A total of 311 participants with prodromal AD, defined according to the International Working Group (IWG)-1 criteria,[2] were enrolled. Participants were randomly assigned (1:1) to active product (125 mL drink containing the multinutrient combination Fortasyn Connect) or iso-caloric control product once daily. Primary outcome was the change in a cognitive function composite z-score based on five items of a neuropsychological test battery (NTB). Secondary outcomes included CDR-SB, whereas the ADAS-cog-13 and MMSE were included as exploratory parameters.

ADCOMS was calculated using the selected items and corresponding partial least squares coefficients.[4] Score ranges from 0.0 to a maximum of 1.97, with increased values indicating worse performance. Contribution of the separate (ADAS-cog, MMSE, and CDR-SB) subdomains to the total score was explored by calculating the separate domains based on the same items and coefficients. Statistical analyses were performed using a linear mixed model for repeated measures in a modified intention-to-treat population.[1]

Results

Scores on ADCOMS in this prodromal AD population at baseline were 0.258 (standard deviation [SD] 0.143, n=138) in the active group and 0.247 (SD 0.140, n=140) in the control group. During the 24 months intervention, worsening on ADCOMS was 36% less in the active group than in the control group. Estimated mean change from baseline (standard error) was 0.085 (0.018) in the active group and 0.133 (0.018) in the control group; estimated mean treatment difference was -0.048 (95% CI -0.090 to -0.007; p=0.023). Changes were mainly driven by the contribution of the 6-item CDR-SB subdomain (estimated mean change from baseline [standard error]: 0.065 [0.016] in the active group and 0.099 [0.016] in the control group, p=0.033), and to a lesser extent by the 2-item MMSE subdomain (0.007 [0.005] in the active group and 0.019 [0.005] in the control group, p=0.065). No differences between groups were observed for the 4-item ADAS-cog subdomain.

Conclusions

In this post-hoc analysis of the LipiDiDiet study data, the active group showed significantly less clinical decline over 24 months as measured by ADCOMS, suggesting that the specific multinutrient intervention has beneficial effects on cognition and global function in a prodromal AD population. These analyses further contribute to the validation of ADCOMS in early AD and suggest applicability and sensitivity across different intervention strategies in the earliest stages of AD.

References

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