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Targeting prodromal Alzheimer’s disease: too late for prevention?

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Prodromal Alzheimer’s disease is a novel area of research, with clinical research definitions still under development. The LipiDiDiet trial,¹ published in *The Lancet Neurology*, was one of the first completed trials based on the International Working Group (IWG-1) criteria for prodromal Alzheimer’s disease.² The study was a non-pharmacological intervention (medical food Souvenaid) in prodromal Alzheimer’s disease.

Fortasyn Connect, the active component of Souvenaid, was developed based on the premise that a specific combination of nutrients enhances synaptic functions.³ Fortasyn Connect consists predominantly of omega 3 (1500 mg per day of docosahexaenoic acid and eicosapentaenoic acid), phospholipids, choline, high doses of vitamin B (B12, B6, and folic acid), vitamin E, vitamin C, selenium, and uridine monophosphate. Souvenaid is a marketed product of Nutricia and is taken as a once-a-day drink with breakfast.

Three Fortasyn Connect trials have been done in patients with mild-to-moderate Alzheimer’s disease. In Souvenir I,⁴ 225 drug-naïve patients with mild Alzheimer’s disease participated in a randomised, double-blind, controlled trial of Fortasyn Connect versus placebo for 12 weeks. There was a significant improvement in one of the coprimary outcomes (delayed verbal recall task), but not in the 13-item modified Alzheimer’s Disease Assessment Scale cognitive subscale or other cognitive outcomes.⁴ The Souvenir II study⁵ was a 24-week, randomised, double-blind, controlled trial in 259 drug-naïve patients with mild Alzheimer’s disease. The primary outcome, neuropsychological test battery (NTB) memory domain Z score, was significantly improved in the active compared with the control group, but the composite NTB total composite Z score was not significantly different.⁵ In the S-connect study,⁶ add-on intake of Fortasyn Connect for 24 weeks did not slow cognitive decline in 527 people with mild-to-moderate Alzheimer’s disease.

In LipiDiDiet,¹ 311 people with prodromal Alzheimer’s disease were randomly assigned to Fortasyn Connect or a control isocaloric drink for 24 months. The primary outcome was the change in the NTB composite score. Secondary outcomes included NTB Z scores, progression to Alzheimer’s disease dementia, clinical dementia rating sum of boxes (CDR-SB), and atrophy rates on MRI. No statistically significant differences were observed between the active and control groups for the primary outcome or four of the secondary outcomes. Two of the secondary outcomes suggested that Fortasyn Connect had a beneficial response: there was less worsening in CDR-SB in the active group (mean change of 0.56 [SD 1.32]) than in the control group (1.12 [1.72]) with an effect size of 0.33 (p=0.005), and supplementation with Fortasyn Connect slowed hippocampal atrophy rate with an effect size

of 0.22 ($p=0.005$). However, 59 (37%) participants in the control group and 62 (41%) in the active group were diagnosed with dementia during the trial.

Several important lessons can be learned from the LipiDiDiet trial. First, LipiDiDiet, together with past trials, does not provide sufficient evidence for the use of Fortasyn Connect in mild or prodromal Alzheimer's disease. The suggestion of benefit in two of the secondary outcomes is encouraging, but needs to be confirmed in further research.

Second, most of the participants who were screened were included in the trial, which was attributed to participants primarily coming from memory clinic populations with recent detailed assessments. Although this approach enhanced the selection of this group of individuals, it limits the external validity of this study outside of specialised memory clinics.

Third, baseline memory scores were very similar to mild Alzheimer's disease, with a higher-than-expected conversion rate to Alzheimer's disease during the trial. Despite this extent of impairment, changes in the primary outcome were not significant. This result indicates the limitations and challenges of constructing composite outcomes in the absence of validated data relevant to the population studied.

Fourth, the intervention appears to be targeting the disease at a late stage. A preplanned analysis in LipiDiDiet suggested that better baseline cognitive function (Mini-Mental State Examination score ≥ 26) was associated with a better drug placebo response in CDR-SB, hippocampal volume, and the primary endpoint in the per-protocol analysis.

Prodromal Alzheimer's disease defined by the IWG-1 criteria² requires evidence of neurodegeneration, such as medial temporal lobe atrophy, for inclusion into the study. As neurodegeneration progresses, the ability of preventive therapies to reverse progression to Alzheimer's disease is attenuated.⁷ Identification of people at risk of Alzheimer's disease, but who have no evidence of significant neurodegeneration, is crucial to the success of preventive strategies. Sensitive and less invasive biomarkers are needed to correctly identify Alzheimer's disease at its earliest stages for long-term prevention interventions.

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