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EFFICACY OF A MEDICAL FOOD ON COGNITION IN ALZHEIMER'S DISEASE: RESULTS FROM SECONDARY ANALYSES OF A RANDOMIZED, CONTROLLED TRIAL

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Abstract: *Objective:* To investigate the extent that baseline cognitive impairment and intake adherence affected the 13-item Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) intervention response of a medical food in Alzheimer's Disease (AD) patients. *Design/setting/participants /intervention/measurements:* This analysis was performed on data from a proof-of-concept study, consisting of a 12-week, double-blind, randomized, controlled, multicenter trial, followed by a similarly designed 12-week extension study. Patients with mild AD (Mini-Mental State Examination [MMSE] score of 20–26) were randomized to receive active or control product as a 125 ml daily drink. One of the co-primary outcome measures was the 13-item ADAS-cog. In this analysis, the study population was divided into two subgroups: patients with 'low' baseline ADAS-cog scores (<25.0) and patients with 'high' baseline ADAS-cog scores (≥25.0). Repeated Measures Models (RMM) were used to determine the relationship between ADAS-cog score and intervention. *Results:* A significant treatment effect ($F[1,319]=4.0$, $p=0.046$) was shown in patients with 'high' baseline ADAS-cog, but not in patients with 'low' baseline ADAS-cog ($F[1,250]=1.25$, $p=0.265$). Overall, intake adherence was significantly correlated with ADAS-cog improvement in the active product group (correlation coefficient=-0.260; $p=0.019$), but not the control group. *Conclusion:* These data indicate that baseline ADAS-cog significantly influenced the effect of Souvenaid intervention on ADAS-cog outcome. A higher intake of active study product was also associated with greater cognitive benefit. These findings highlight the potential benefits of Souvenaid in AD patients and warrant confirmation in larger, controlled studies.

Key words: Alzheimer's disease, cognition, treatment outcome, nutrition.

Introduction

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder characterized by memory loss, cognitive deterioration, executive and visuospatial dysfunction and impaired ability to perform activities of daily living (1). Synaptic loss is thought to be a primary cause of the symptoms of AD (2, 3), particularly hippocampal and cortical synapse loss, as indicated by the nature of the cognitive dysfunction typical of the disorder (3).

Preclinical studies have indicated that the administration of nutrients involved in the synthesis of synaptic membranes increases synapse and synaptic membrane formation in the brain. These include precursors for membrane phosphatidylation such as uridine, choline and omega-3 polyunsaturated fatty acids (4-6). Reports have also indicated that combining these nutrients may improve cognition and increase hippocampal dendritic spines (7), again suggesting a positive effect on the formation of new synapses (8-10). It was therefore hypothesized that such agents may play a role in the management of AD.

This hypothesis led to the development of the medical food Souvenaid® (Nutricia N.V., Zoetermeer, The Netherlands) (11), a multinutrient drink designed to provide the precursor and supporting nutrients that may enhance synaptic membrane formation and function in patients with AD. A recent proof-of-concept study demonstrated that dietary supplementation with Souvenaid was well tolerated, and resulted in a significant improvement of memory, as measured by 12-week delayed verbal recall testing (12). The co-primary outcome measure for the study, the modified 13-item Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) (13) showed no overall intervention effect for Souvenaid, with neither the control nor active group showing any decline over 24 weeks on this outcome measure, which was attributed to a potential lack of sensitivity with the ADAS-cog measure in mild AD patients over this study period (12). ADAS-cog is widely regarded by regulatory authorities as the 'gold standard' outcome measure for assessing cognitive change in clinical trials, and as such it is important to further investigate factors that might influence the effect on ADAS-cog. This formed the rationale for investigating the extent that baseline cognitive impairment affected the ADAS-cog intervention response. In addition, we studied the influence of intake adherence on

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ADAS-cog response.

Materials and Methods

Study design

The 24-week proof-of-concept study (12) consisted of a 12-week, double-blind, randomized, controlled, multicenter trial, followed by a similarly designed, optional 12-week extension study, to evaluate the effect of Souvenaid® on cognitive function in patients with mild AD. The methodology has been described in detail previously (12). In summary, patients ≥50 years of age with a diagnosis of probable AD and a Mini-Mental State Examination (MMSE) score of 20–26 were recruited. Patients were randomized to receive either active or control product as a 125 ml daily drink. Primary outcome measures were a delayed verbal recall task (WMS-r) (14) and ADAS-cog (13-item version, range 0–85, higher scores indicating greater cognitive deficit) (13) measures of delayed verbal memory and cognition. These parameters were measured at baseline and at Weeks 6, 12 and 24. Adherence to study product intake was measured via patient documentation of the amount of study product taken each day and verified by measuring blood plasma parameters. The study was conducted in accordance with the Declaration of Helsinki and The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use / WHO Good Clinical Practice (ICH-GCP) guidelines, as appropriate to nutritional products and legislation of the country in which the research was conducted. The clinical trial registration number is ISRCTN72254645.

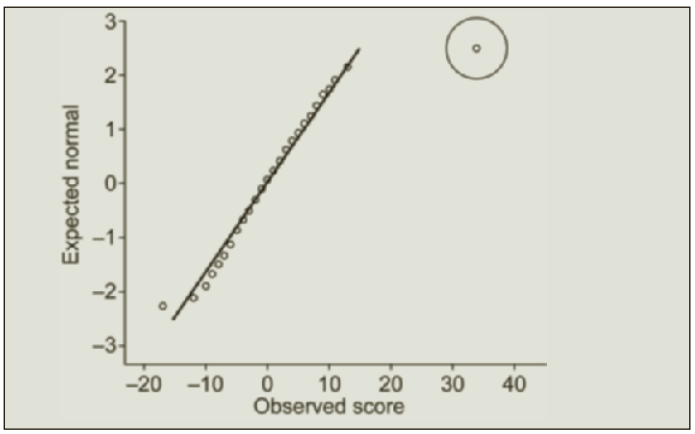
Modeling analysis

The primary analysis population was the intention-to-treat (ITT) efficacy population from the proof-of-concept study, defined as all randomized patients who received at least one dose of study product and one post-baseline assessment. For the modeling analyses presented here, one patient (from the active study group) was excluded from the ITT efficacy population as he showed an extreme outlying response on the 24-week ADAS-cog outcome (Figure 1). This may be explained by a leg amputation 8 days prior to the 24-week ADAS-cog assessment, which took place in the hospital and was recorded as a serious adverse event. Based on the median as a cut-off value, the study population was divided into two subgroups: patients with 'low' baseline ADAS-cog scores (<25.0; lower scores indicating reduced cognitive deficit) and patients with 'high' baseline ADAS-cog scores (≥25.0; indicating greater cognitive deficit).

Repeated Measures Models (RMM) for each subject were used to determine the relationship between ADAS-cog score and intervention up to 24 weeks. The SAS procedure PROC MIXED (15) was used to model the covariance among the repeated measures obtained on the same individuals (16). Different structures for the means and different variance–covariance structures were tested. The structure with the best fit was selected based on the likelihood ratio test for nested models and the Akaike Information Criterion (AIC) for non-nested models.

Figure 1

A quantile-quantile (Q-Q)-plot to show individual patient data variations (ADAS-cog) from the normal distribution. One extreme case (circled) with various co-morbidities was shown to deviate considerably and was excluded from the modeling analyses



Results

Overall, 225 patients were randomized: 112 to active product and 113 to the control product. Of these, 161 completed the 24-week study (12). Baseline characteristics for the control and active patient populations in the current analysis are reported for all subjects, together with those for the 'high' and 'low' baseline ADAS-cog subgroups (Table 1). There were no statistically significant differences in baseline characteristics between active/control groups (Table 1).

Table 1

Patient characteristics at baseline

Characteristic	Randomized study group	
	Control product	Active product
Total patient population	(n = 106)	(n = 105)
Men, n (%)	52 (49)	53 (50)
Age ± SD, yr	73.3 ± 7.8	74.1 ± 7.3
13-item ADAS-cog, mean ± SD	25.5 ± 8.8	25.9 ± 7.6
MMSE, mean ± SD	24.0 ± 2.5	23.9 ± 2.7
'Low' baseline ADAS-cog group	(n = 43)	(n = 52)
Men, n (%)	25 (58)	35 (67)
Age ± SD, yr	71.4 ± 8.4	73.6 ± 6.9
13-item ADAS-cog, mean ± SD	17.6 ± 5.4	19.8 ± 3.2
MMSE, mean ± SD	25.3 ± 2.1	25.0 ± 2.1
'High' baseline ADAS-cog group	(n = 63)	(n = 53)
Men, n (%)	27 (43)	18 (34)
Age ± SD, yr	74.6 ± 7.0	74.5 ± 7.7
13-item ADAS-cog, mean ± SD	30.9 ± 6.3	31.9 ± 5.7
MMSE, mean ± SD	23.1 ± 2.4	22.7 ± 2.7

All patients included in the modeling analysis: intention-to-treat efficacy population (12) minus one outlier; ADAS-cog = Alzheimer's Disease Assessment Scale – cognitive subscale (0–85; higher scores indicate greater cognitive dysfunction); MMSE = Mini-Mental State Examination (0–30; lower scores indicate greater cognitive dysfunction).

Subgroup of patients with 'high' baseline ADAS-cog

Raw mean ADAS-cog scores for patients with 'high' baseline ADAS-cog are summarized in Table 2 (at baseline and Weeks 6, 12 and 24). Within this subgroup the ADAS-cog data were substantially skewed and a transformation was performed to adjust for this.

Table 2

Raw mean (± SD) ADAS-cog scores for the patient subgroups

	'Low' baseline ADAS-cog group				'High baseline ADAS-cog group			
	n	Control	n	Active	n	Control	n	Active
Baseline	43	17.6 ± 5.4	52	19.8 ± 3.2	63	30.9 ± 6.3	53	31.9 ± 5.7
Week 6	41	18.2 ± 5.9	51	20.6 ± 4.8	61	29.5 ± 6.9	48	30.5 ± 8.1
Week 12	39	19.3 ± 6.0	51	21.6 ± 5.6	60	30.1 ± 5.7	50	30.3 ± 7.1
Week 24	34	17.4 ± 5.8	44	20.7 ± 6.1	45	30.1 ± 5.9	38	29.8 ± 8.4

All patients included in the modeling analysis: intention-to-treat efficacy population (12) minus one outlier; ADAS-cog = Alzheimer's Disease Assessment Scale – cognitive subscale (0–85; higher scores indicate greater cognitive dysfunction).

RMM slope analysis of the transformed ADAS-cog, using ADAS-cog at baseline, 6, 12 and 24 weeks as the dependent variable, showed a significant treatment effect ($F[1,319] = 4.0$, $p = 0.046$). Sensitivity analyses showed a strong indication (all p-values ranging from 0.029–0.067) that this effect is independent of: (a) the type of structure for the means used (modeling each visit separately using dummy variables instead of modeling the means as a straight-line and evaluating slopes); (b) the type of variance–covariance model used (compound symmetry instead of heterogeneous compound symmetry); and (c) the type of ADAS-cog transformation used (logarithm instead of square-root). Figure 2 shows the results from the RMM analyses (estimated means) for ADAS-cog over 24 weeks for patients with 'high' baseline ADAS-cog scores. The clear upward slope (representing a decrease in ADAS-cog score and indicating cognitive improvement) for the active group contrasts with the almost unchanged level of the control group. These data indicate that Souvenaid significantly improved cognitive performance *versus* the control product in patients with 'high' baseline ADAS-cog.

Subgroup of patients with 'low' baseline ADAS-cog

Raw mean ADAS-cog scores for patients with 'low' baseline ADAS-cog are summarized in Table 2 (at baseline and Weeks 6, 12 and 24). Within this subgroup there was no suggestion of an intervention effect, indicated by a non-significant intervention*time parameter ($F[1,250] = 1.25$, $p = 0.265$).

Baseline ADAS-cog value as a predictor of ADAS-cog change from baseline

In order to determine whether the two ADAS-cog subgroups significantly differed from each other, they were combined into a single model. A patients' membership to either subgroup was found to be a significant predictor of ADAS-cog intervention response (RMM: $F[1,657] = 3.94$, $p = 0.048$ for the subgroup*slope coefficient, using untransformed ADAS-cog and allowing for different heterogeneous compound symmetry variance–covariance matrices for subgroups).

Figure 2

Estimated marginal mean ADAS-cog scores over 24 weeks for patients receiving active or control product who recorded a 'high' (≥median) ADAS-cog score at baseline (back-transformed data; transformed [square-root] data were squared)

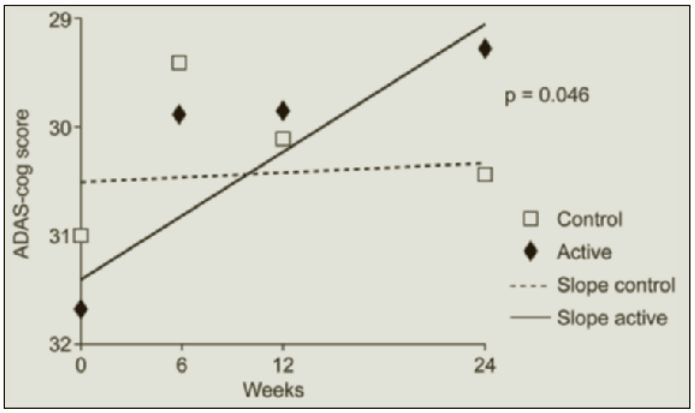
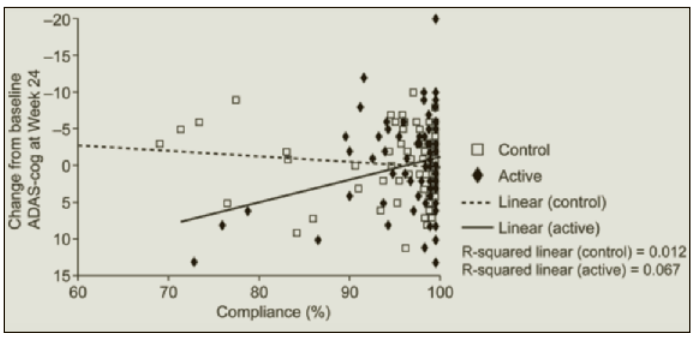


Figure 3

Scatter-plot of individual patient ADAS-cog change from baseline (24-week, non-transformed) by intake adherence (percentage of prescribed product taken), for both active and control groups. Regression lines are included for each intervention group



Impact of intake adherence on intervention response

The relationship between intake adherence (represented as a percentage of the total study product consumed by the patient) and 24-week ADAS-cog change is shown in Figure 3. The active group showed a significant correlation between intake adherence and ADAS-cog improvement (correlation coefficient = -0.260; $p = 0.019$), but this correlation was not observed in the control group (correlation coefficient = 0.108, $p = 0.343$). This difference in correlation coefficients between the active and control group was statistically significant (Fisher's Z transformation, $Z = 2.32$, $p = 0.020$). Effect modifier analyses to determine the relationship between intake adherence and ADAS-cog response showed a significant interaction ($F[1,546] = 5.88$, $p = 0.016$; RMM model using untransformed

ADAS-cog and including variable "intake adherence").

In summary, together with the incidence of adverse events (12), baseline ADAS-cog and intake adherence appear to be important effect modifiers that can influence the 24-week ADAS-cog intervention effect.

Discussion

This post-hoc analysis indicates that baseline ADAS-cog score significantly influenced the effect of Souvenaid intervention on this outcome measure. Within the group of patients with higher ADAS-cog scores at baseline, Souvenaid significantly improved ADAS-cog scores compared with the control group. These observations are in line with recent publications that bring into question the sensitivity of ADAS-cog in mild cognitive impairment and mild AD (17-19). This may be due to the poor psychometric properties of the ADAS-cog measure, such as inadequate assessment of cognitive domains such as attention, working memory and executive function (19, 20) and the presence of floor effects (17). Furthermore, several recent studies have reported slower rates of placebo decline in AD patients than traditionally assumed by older models and clinical trials (12, 21-23); they have also shown that baseline ADAS-cog significantly affects the rate of AD progression (23, 24).

Most AD intervention studies report on a mild–moderate dementia population. Only a few prospective intervention studies have been performed in an exclusively mild AD population using ADAS-cog as an outcome measure (25-28). Of these, only the study reported by Seltzer et al. (25) reported a significant benefit on ADAS-cog.

In the study reported here, an absolute difference in ADAS-cog score between study groups of 2 points was demonstrated in favor of the active intervention group, for patients with higher ADAS-cog at baseline. This subgroup represents patients at a more advanced stage within the mild AD study population. This effect was observed despite the small sample size of this subgroup. However, it should also be noted that the statistical phenomenon of linear regression to the mean may have contributed to the apparent treatment effect.

The clinical importance of ADAS-cog change has been reviewed in several recent publications (22, 29). Vellas et al. reported that a 2-point effect on ADAS-cog outcome at 18 months may be considered clinically relevant, but greater differences (3–4 points) for clinical relevance have also been proposed (30). Taking these suggestions into account, the 2-point ADAS-cog intervention difference (13-item scale, range 0–85) may be considered a relevant finding that warrants further investigation in patients at a more advanced stage of AD.

Within the active study group a significant correlation between intake adherence and ADAS-cog improvement was observed. This indicates that a higher intake of Souvenaid (up to and including the prescribed dosage) provides greater cognitive benefit in AD patients up to 24 weeks. As expected, this relationship was not observed in the control group. In the study, excellent intake adherence was also demonstrated: the average 24-week compliance was 94% (percentage product intake versus prescribed dosage). These results, combined with the finding that intake adherence appears positively correlated to ADAS-cog improvement, highlight the potential of Souvenaid in AD.

Thus, although ADAS-cog is still considered the 'gold standard' measure of cognitive function in clinical trials for AD and other dementias, in modern studies it may be unable to detect subtle changes in patients with milder stages of the disease (18). To account for this issue, an ongoing study to investigate the efficacy of Souvenaid in AD with ADAS-cog as the primary outcome measure (S-CONNECT; NTR1683) includes patients with more moderate cognitive dysfunction (MMSE 14–24) than the original study (MMSE 20–26). Certainly, in the current analysis when the subgroup of AD patients with 'high' ADAS-cog scores at baseline was analyzed using RMM, the data showed that Souvenaid provided beneficial effects compared with control for up to 24 weeks. In addition, the results of this analysis indicate that adverse events, baseline cognitive severity and intake adherence should be taken into account when designing, and interpreting the results of, future studies.

In conclusion, the results of a controlled, 24-week, proof-of-concept study demonstrated that dietary supplementation with Souvenaid yields improvements in the memory of patients with mild and very mild AD (12). The analysis presented here also suggests that Souvenaid may provide cognitive benefits to patients with more moderate stages of the disease. These hypothesis-generating results warrant confirmation in larger scale, controlled studies.

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