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Analysis of the Relationship of Cognitive Impairment and Functional Impairment in Mild Alzheimer's Disease in EXPEDITION 3

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Abstract

BACKGROUND: Clinical progression of Alzheimer's disease is characterized by impairment in cognition and function.

OBJECTIVE: To assess the relationship between cognitive and functional impairment in mild Alzheimer's disease.

DESIGN: Spearman's rank correlations between cognitive and functional measures were calculated. Autoregressive cross-lagged panel analyses were used to determine the temporal relationship between cognitive and functional decline.

SETTING: Post-hoc analysis of clinical trial data.

PARTICIPANTS: Placebo-treated patients with mild Alzheimer's disease from the Phase 3 solanezumab study EXPEDITION 3.

INTERVENTION: Placebo

MEASUREMENTS: Cognitive and functional measures were assessed at baseline and at six post-baseline time points through Week 80.

RESULTS: Correlation between cognitive and functional measures was 0.41 at baseline and 0.65 at Week 80. Autoregressive cross-lagged panel analysis demonstrated that cognitive impairment preceded and predicted subsequent functional decline, but functional scores did not predict cognitive outcomes.

CONCLUSIONS: This study supports the hypothesis that functional impairment predictably follows cognitive decline in mild Alzheimer's disease dementia.

Key words: Cognition, function, Alzheimer's disease, correlation

Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by a progressive decline in cognitive function and in the ability to perform activities of daily living that ultimately leads to death due to complications of the disease or age-related mortality.

Pathologic hallmarks of AD identified at autopsy include the presence of neuritic amyloid beta peptide (Aβ) plaques, neurofibrillary tangles, and neuronal loss in brain regions important for cognition, such as the hippocampus and temporal cortex (1). Clinically, AD is characterized by memory impairment and executive dysfunction progressively interfering with daily life activities. Diagnosis has relied on an extensive medical history from the patient and his or her caregiver, neuropsychological testing, and assessment of symptoms over time. With the advent of magnetic resonance imaging, the discovery of cerebrospinal fluid biomarkers, and the advent of amyloid positron emission tomography, the diagnostic criteria for AD have been refined and new criteria have been established (2-4). These new criteria incorporate biomarker evidence in addition to clinical manifestations and enable assessment of the disease in earlier stages. For example, mild cognitive impairment (MCI) due to AD is clinically defined by the level of cognitive impairment (2). Functional decline is not apparent until later in the disease process and is not included in the MCI clinical criteria. Proposed research diagnostic criteria for different stages in the continuum of AD assume that cognitive decline precedes functional decline (2, 4). We and others have interrogated the temporal relationship of cognitive deficit and functional impairment in AD.

To better understand the relationship between cognition and functional decline, Spearman's rank correlations, path analysis, and autoregressive cross-lagged (ARCL) panel analyses have been used (5-8). The ARCL panel analysis is a classical structural equation model used to simultaneously analyze multiple outcomes that are measured repeatedly over time. It is designed to assess the strength of potential reciprocal causal relationships between the outcomes and infer the influence of one variable over the other. Using ARCL panel analyses, Zahodne et al (8) investigated the temporal ordering of cognition and functional declines in older adults without dementia and patients with AD. They concluded that cognitive decline appears to precede functional decline prior to and following dementia diagnosis (8). We (5) have investigated the relationship between cognitive and functional impairment in mild AD dementia using ARCL panel analysis in several clinical studies, including EXPEDITION, EXPEDITION 2, IDENTITY, IDENTITY2, and the Alzheimer's Disease

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Neuroimaging initiative (ADNI). Analyses from these databases indicated that cognitive decline precedes and predicts subsequent functional decline in mild AD. Additional studies investigating the correlations between cognition and function across the spectrum of AD corroborated these findings, leading to the suggestion that cognitive impairment may be used as a predictor of future functional impairment in mild AD (6, 7). Further studies to support or deny this hypothesis are warranted.

EXPEDITION 3 was a Phase 3 study comparing solanezumab with placebo in patients with mild AD (NCT01900665; 9). The EXPEDITION 3 database provides an additional resource to further confirm the temporal relationship that cognitive decline precedes functional decline in mild AD. This post-hoc analysis uses ARCL panel analysis to assess the relationship between cognitive impairment and functional impairment in placebo patients with mild AD and positive amyloid imaging and compares the relative strength of the two directions.

Methods

Study Design

EXPEDITION 3 was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study of the effects of solanezumab (9). Solanezumab is a humanized monoclonal antibody designed to clear soluble amyloid-β (Aβ) from the brain and has been studied as a potential disease-modifying agent for the treatment of AD (10). The study enrolled mild AD dementia patients (Mini-Mental State Examination [MMSE] score 20 to 26) with evidence of amyloid pathology confirmed by florbetapir positron emission tomography scan or documentation of low Aß levels in CSF. Placebo-treated patients (n=1068) from EXPEDITION3 were included in this post-hoc analysis. All patients provided informed consent before participation in EXPEDITION 3, and the study protocol was approved by ethical review boards at each participating site.

Cognitive and Functional Outcome Measures

Cognitive and functional outcome measures were assessed at baseline and at six post-baseline time points up to Week 80. Cognition was assessed using the 14-item Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog14). ADAS-Cog14 assesses areas of cognitive function most typically impaired in AD: orientation, verbal memory, language, praxis, delayed free recall, digit cancellation, and maze-completion measures (11). The score for ADAS-Cog14 can range from 0 to 90, with higher scores indicating greater disability. Function was assessed using a subset of the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL) (12). The subset of items (7 through 23) for instrumental activities of daily living (ADCS-iADL) is designed to measure higher level function activities such as food preparation and shopping rather than basic activities of daily living (e.g., eating, toileting). The ADCS-iADL score can range from 0 to 56, with lower scores denoting greater loss in function.

Statistical Analyses

Spearman's rank correlations between scores for cognition and function were calculated at baseline and at each post-baseline visit. To examine the longitudinal relationships between cognitive and functional impairment over the course of the study, an ARCL model was used. The core of the ARCL model is that the value at the time of (t) is explained by the value at the time of the previous point, (t-1). As previously described (5), the interrelationship between cognitive performance and functional abilities were evaluated based on the estimates of the cross-lagged regression coefficients from time (t-1) to time (t). Previous visit was included in the model to account for the impact of the previous visit (t-1) on the following visit (t). Full Information Maximum Likelihood estimation was used to make use of all available data from all patients. The overall model fit was determined using three standard measures, including the comparative fit index (CFI), root mean square error of approximation (RMSEA), and a standardized root mean square residual (SRMR). A model was considered acceptable with values of RMSEA <0.08, SRMR <0.05, CFI >0.95 (5).

Results

Baseline patient characteristics have been published previously (9). Briefly, the placebo patient cohort (n=1072) had a mean age of 73.26 years, a mean (standard deviation [SD]) MMSE was 22.96 (2.004), and a mean (SD) education of 13.67 (3.777) years.

There were 1068 patients included in this analysis. Mean (SD) scores for cognitive and functional measures for placebo patients (n=1068) with mild AD at each visit are reported in Figure 1A. Mean (SD) ADAS-Cog14 scores ranged from 29.71 (8.50) at baseline to 36.11 (14.27) at Week 80. Mean (SD) ADCS-iADL scores ranged from 45.37 (8.13) at baseline to 38.99 (11.86) at Week 80. Spearman's rank correlation between ADAS-Cog14 and ADCS-iADL was 0.41 at baseline and increased to 0.65 at Week 80 (Figure 1B).

The ARCL panel analysis model fit statistics for EXPEDITION3 was the following: RMSEA = 0.0357 (90% confidence interval: 0.02768, 0.0435), SRMR = 0.0591, and CFI = 0.9955, which indicates the model fit is appropriate. Results demonstrated cognitive impairment significantly predicts functional impairment in 5 of 6 time points

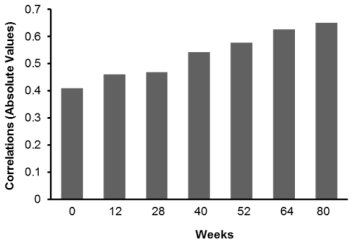
(Table 1). When the same analysis was performed to test the reverse hypothesis, functional scores predicted cognitive outcome in only one time point, Week 64 predicting Week 80 (Table 1). As expected, the cognition at a given visit significantly predicted cognition at the following visit, and the same is true for function. The magnitude of cross-lagged coefficients was greater for cognition predicting subsequent function than function predicting cognition (Table 1).

Figure 1. Cognitive and functional scores (1A) and the correlation between cognitive and functional measures (1B) in EXPEDITION3

A.

Weeks	Cognition[a] Mean (SD)	Function[b] Mean (SD)
Baseline	29.71 (8.50)	45.37 (8.13)
12	30.07 (9.51)	44.21 (9.0)
28	31.36 (10.66)	43.20 (9.80)
40	31.58 (11.84)	42.36 (10.30)
52	34.15 (12.02)	41.40 (11.05)
64	34.82 (13.07)	40.20 (11.58)
80	36.11 (14.27)	38.99 (11.86)

B.



a. Cognitive measures included: 14-item Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog14); b. Functional measures included: Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living (ADCS-iADL). Comparison of ADAS-Cog14 versus ADCS-iADL. All correlations include absolute values for comparisons across different scales.

Discussion

In this post-hoc investigation ARCL panel analysis was used to evaluate the temporal relationship between cognitive and functional impairment in patients with mild AD and positive amyloid pathology from EXPEDITION3. Over time, the correlation between cognition and function increased continuously. ARCL panel analyses demonstrated that cognitive impairment, as measured by the ADAS-Cog14, preceded and predicted subsequent functional decline, as measured by ADCS-iADL, in mild AD. Functional impairment did not predict future cognitive decline. These results further support the current hypothesis and existing evidence that cognitive decline precedes functional decline in mild AD.

The correlation observed between cognition and function, in this dataset of patients with mild AD, started as modest at baseline and steadily increased. A similar correlation pattern was observed in three other independent datasets (EXPEDITION/2, IDENTITY/2, ADNI) of patients with mild AD (6, 7). Similar to our previous studies (6, 7), the correlation between cognition and function in patients with mild AD of EXPEDITION3 ranged from approximately 0.41 at baseline to 0.65 at the end of study. Thus, the correlation observed in the EXPEDITION3 dataset supports the hypothesis that as disease progresses cognition becomes more clearly related to function and the two measures become more strongly associated. EXPEDITION3 required patients to have demonstrated amyloid pathology as demonstrated by florbetapir positron emission tomography scans or by CSF Aβ1-42 analysis. Although this represents a more accurately defined patient population, the correlations between cognition and function and the cross-lagged analyses were similar to earlier studies (EXPEDITION/2 and IDENTITY/2) that did not have a requirement for known amyloid pathology. The current analyses confirm the earlier observations in this more rigorously defined participant group.

ARCL analysis demonstrated cognitive impairment predicts functional impairment in mild AD. Results of this post-hoc analysis further supports those of other ARCL analyses, which included non-demented older adults (8), patients with emergent dementia (8), and patients with mild AD dementia (5, 8). As we have previously noted (5), it is not the aim of ARCL modelling to quantitate the trajectory of disease progression in AD but rather the aim is to evaluate the temporal ordering of cognitive impairment and functional impairment. Different models and techniques are required to estimate the disease progression curves along the continuum, which are beyond the scope of this study.

Current thoughts are that AD should be considered as a biological and clinical continuum and should not be viewed only as a disease with distinct clinical stages (13). An important realization over the past decade is that pathophysiological changes, indicated by increasing biomarker evidence of disease, begin 10 to 20 years prior to the onset of clinical impairment (13). Within the symptomatic phase, studies such as ours suggest that cognitive decline precedes functional decline; if this is true then treatments that slow cognitive decline would be

Table 1. ARCL panel analysis results for the EXPEDITION3 placebo patient cohort with mild AD

Regression Effect	Cognition on Function Estimate (SE)	t Value	Function on Cognition Estimate (SE)	t Value
Baseline predicting week 12	-0.057 (0.027)*	-2.120	-0.000 (0.031)	-0.002
12 week predicting 28 week	-0.027 (0.023)	-1.157	0.039 (0.028)	1.394
28 week predicting 40 week	-0.105 (0.020)***	-5.368	-0.001 (0.025)	-0.058
40 week predicting 52 week	-0.053 (0.019)**	-2.828	-0.010 (0.024)	-0.406
52 week predicting 64 week	-0.084 (0.019)***	-4.462	-0.007 (0.024)	-0.278
64 week predicting 80 week	-0.077 (0.018)***	-4.282	0.051 (0.024)*	2.076

*p<0.05, **p<0.01, ***p<0.001; Cognitive measures included: 14-item Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog14); Functional measures included: Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living (ADCS-iADL); SE=standard error.

expected to slow functional decline.

There are limitations to this post-hoc analysis. The findings of this study are based on the ADAS-Cog14 and ADCS-iADL scores for cognition and function, respectively. Although these assessment tools are commonly used in clinical studies they may not be the most sensitive scales to measure changes in a mild AD population. Because this was a multinational study, a functional test with culturally neutral elements and one that will identify very mild functional changes may detect greater magnitudes of impact of cognitive impairment on functional ability. Lastly, baseline correlations may not represent a true correlation as subjects were required to have a specific cognitive score (based on MMSE) to be eligible for EXPEDITION3.

In conclusion, this analysis provides further support to the hypothesis that cognitive impairment precedes functional impairment in mild AD. This is the first confirmation of this finding in patients with biomarker support of their clinical diagnosis. If in the natural course of AD cognitive impairment precedes and predicts functional impairment, then cognition could be used as an indicator of future functional decline. The regulatory implication of this relationship is that early cognitive measures could be used as an indicator of future functional outcomes in trials testing new treatments for AD.

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Ethical standards: Ethical review board approval and informed consent of subjects were reported in the primary publication of the study noted in this article.

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