

The relationship between cognitive and functional treatment effects in Alzheimer's patients

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Today, Eli Lilly announced results from new analyses of two Phase 3 trials evaluating the relationship between cognitive and functional treatment effects in patients with mild Alzheimer's disease. Based on post-hoc analyses of the Phase 3 trials, the findings suggested that cognitive deficits were more apparent than functional deficits in mild Alzheimer's disease when measured with the Alzheimer's disease Assessment Scale-Cognitive (ADAS-Cog) and the Alzheimer's disease Cooperative Study-Activities of Daily Living (ADCS-ADL) subscales. The apparent treatment effect on cognition based on these analyses led to the apparent treatment effect on function. These data were published in the December 2 issue of the *Journal of Alzheimer's Disease*.

"These data are important as they suggest that functional outcomes should be considered key secondary endpoints in a clinical trial of patients with mild Alzheimer's [disease](#) dementia, and they are consistent with the idea that Alzheimer's disease is primarily a disease of cognition and the [functional deficits](#) are mostly a consequence of these [cognitive](#) deficits," said Hong Liu-Seifert, Ph.D., study research advisor at Eli Lilly and Company. "We believe cognition and function are important to patients and caregivers and these data suggest that cognitive treatment effect drives functional treatment effect and can be considered a leading indicator for functional effect in patients with mild Alzheimer's disease."

Using pooled data from the solanezumab Phase 3 EXPEDITION and

EXPEDITION2 trials, these post-hoc path analyses investigated the origins of the effects of solanezumab on cognition and function. This analysis showed that the effect on function was largely driven by effects of treatment on cognition (87 percent), with a relatively small portion (13 percent) due to a direct effect of solanezumab or through aspects of cognition not measured by the ADAS-Cog14. When the analysis was reversed, the effect on cognition was primarily due to a direct effect of solanezumab or through indirect effects not measured by the instrumental ADL (ADCS-iADL) (67 percent) with a smaller portion (33 percent) driven by an effect on function.

Further, normalized ADAS-Cog and ADCS-ADL subscales showed cognitive impairment was more evident than functional impairment in mild Alzheimer's disease.¹ The correlation between cognition and function increased over time. Results also showed that the iADL subscale showed greater impairment compared to the basic ADL (bADL) subscale, consistent with previous findings that iADL impairment precedes bADL impairment in the course of Alzheimer's disease progression. The results also suggest that iADL measures can be more sensitive than bADL measures in mild Alzheimer's disease patients.¹ Similar patterns were observed regarding the apparent treatment difference of solanezumab versus placebo, with effect on ADAS-Cog being the greatest, followed by effect on iADL and bADL with the lowest impairment score. The outcomes of these analyses are consistent with findings from previous studies, which showed that cognitive deficits predict subsequent functional deficits and suggest that slowing cognitive decline may lead to slowing decline in function.

Analysis Methods

Data from patients with mild Alzheimer's disease were pooled from two multicenter, double-blind, Phase 3 studies (EXPEDITION and EXPEDITION2), which were identical in design. Patients were

randomized to infusions of 400-mg solanezumab (n = 654), or placebo (n = 660) every four weeks for 18 months. Cognitive and functional outcome measures were assessed using the ADAS-Cog and the ADCS-ADL, respectively. Post-hoc analyses included comparisons among normalized scales, correlations between outcome measures, and path analyses to model the relationship of treatment effect on cognition and function.

More information: Liu-Seifert H., et al. "Cognitive and Functional Decline and Their Relationship in Patients with Mild Alzheimer's Dementia." *Journal of Alzheimer's Disease*. 2014. [DOI: 10.3233/JAD-140792](https://doi.org/10.3233/JAD-140792).

Zadhone ,L., et al. "Cognitive Declines Precede and Predict Functional Declines in Aging and Alzheimer's Disease." *PLOS One*. September 2013. [DOI: 10.1371/journal.pone.0073645](https://doi.org/10.1371/journal.pone.0073645).

Liu-Seifert H., et al. "Cognitive Impairment Precedes and Predicts Functional Impairment in Mild Alzheimer's Disease." Presented at AAIC 2014. July 2014.

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