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Longitudinal plasma amyloid beta in Alzheimer's disease clinical trials

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Abstract

Introduction: Little is known about the utility of plasma amyloid beta (Aβ) in clinical trials of Alzheimer's disease (AD).

Methods: We analyzed longitudinal plasma samples from two large multicenter clinical trials: (1) donezepil and vitamin E in mild cognitive impairment (n = 405, 24 months) and (2) simvastatin in mild to moderate AD (n = 225, 18 months).

Results: Baseline plasma Aβ was not related to cognitive or clinical progression. We observed a decrease in plasma Aβ40 and 42 among apolipoprotein E epsilon 4 (*APOE* ε4) carriers relative to noncarriers in the mild cognitive impairment trial. Patients treated with simvastatin showed a significant increase in Aβ compared with placebo. We found significant storage time effects and considerable plate-to-plate variation.

Discussion: We found no support for the utility of plasma Aβ as a prognostic factor or correlate of cognitive change. Analysis of stored specimens requires careful standardization and experimental design, but plasma Aβ may prove useful in pharmacodynamic studies of antiamyloid drugs.

Keywords: Alzheimer's disease; Mild cognitive impairment; Plasma amyloid; Biomarkers; Apolipoprotein E; Bioassay; Luminex; Innogenetics; Donepezil; Simvastatin

1. Introduction

Biomarkers of Alzheimer's disease (AD) have profoundly affected the course of AD research, drug development, and clinical practice. Cerebrospinal fluid (CSF) and neuroimaging measures of amyloid, presumably reflecting principal pathology of AD, are among the leading biomarkers. Given the somewhat invasive nature of CSF sampling and the expense of neuroimaging, plasma amyloid beta (Aβ) would be an attractive alternative biomarker. Although it is known that there is communication between the peripheral and central Aβ pools (via receptor mediated and passive mechanisms), the utility of plasma Aβ measurements has remained limited. Some studies have shown correlations between plasma Aβ and dementia risk and/or progression, although many of such findings have been inconsistent. Biological and methodological issues likely contribute to these limitations, thereby underlining the need for a better understanding of the biology and dynamics of plasma Aβ and the need for studies with longer follow-up to determine the clinical utility of measuring plasma Aβ.

As with CSF, changes in plasma Aβ may reflect changes within the brain [1–3], but may also be more affected by peripheral factors. In subjects with familial AD or Down syndrome, plasma Aβ begins to increase before dementia onset, perhaps reflecting increased Aβ production [4–9].

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Investigations of plasma Aβ as a predictor of dementia in sporadic or late-onset forms of AD have had inconsistent results (reviewed in [10]). Relationships have been found with plasma Aβ40 or 42 and dementia, but the direction of these associations varies among studies [11–16]. Some studies have found an association between lower Aβ42:40 ratios and higher risk of AD [17,18]. The sources of variability in findings from existing studies are potentially due to variability in subject age and with disease severity [12,19,20], but may also relate to study size; very few large-scale studies have been attempted. A recently published study in a cohort of N = 997 nondemented elderly patients found that cognitive reserve and plasma Aβ42:40 are associated, and the relationship is accentuated in those with low cognitive [21]. However, the predictive value of the plasma Aβ42:40 ratio was low.

Rodent studies demonstrate that a high cholesterol diet can increase levels of Aβ, which can be reversed by 3-hydroxy-3-methyl-glutaryl-(HMG) CoA reductase inhibitors (statins) drug treatment [22,23]. Simvastatin, an HMG CoA reductase inhibitor penetrates the central nervous system and has been shown to reduce the risk of cardiovascular disease and death. It was selected for use in an Alzheimer's Disease Cooperative Study (ADCS) randomized clinical trial to test the hypothesis that lipid lowering could reduce the clinical progression in subjects with AD who have cholesterol levels not otherwise requiring treatment. The study concluded that cholesterol levels decreased significantly in the statin group, but there was no effect on cognitive decline [24]. The effect of statin treatment on plasma Aβ was not assessed in the primary analysis, although it has been the subject of several investigations [25–28]. No studies of Aβ in plasma or CSF have found an effect of statin treatment [28–31], although several reported changes in amyloid precursor protein and improvements in cognition.

We assessed the relationships among plasma Aβ and clinical progression, treatment, and apolipoprotein E (*APOE*) using banked plasma from two large ADCS clinical trials: (1) donezepil and vitamin E in mild cognitive impairment (MCI; n = 405, 24 months) [32,33] and (2) simvastatin in mild to moderate Alzheimer's (n = 225, 18 months) [24]. Our primary goal was to determine covariates that may be associated with plasma Aβ40, 42, or ratio in the setting of AD clinical trials of 18–24 months duration. We also investigated the value of plasma Aβ as a predictive biomarker of clinical change, or an outcome measure in pharmacodynamic studies.

2. Methods

2.1. ADCS MCI trial

The 36-month, three-arm, placebo-controlled ADCS MCI trial examined the effect of vitamin E or donepezil in MCI patients (clinicaltrials.gov identifier: NCT00000173) [33]. A total of 769 patients with amnestic MCI were randomized to vitamin E, donepezil, or placebo. Complete information on inclusion, exclusion criteria, and the treatment regimen has been reported [32,33]. Serial blood samples were taken and plasma was aliquoted and banked (Appendix A, available in the online Supplementary Materials).

2.2. ADCS simvastatin trial

The potential benefit of 18 months of statin treatment on cognitive decline in AD was examined by the ADCS (clinicaltrials.gov identifier: NCT00053599). Individuals aged 50 years or older with probable AD and Mini-Mental State Examination (MMSE) within the range 12 to 26 were included. Individuals were excluded if they had other neurological or psychiatric diagnoses that could interfere with cognitive function, were taking lipid lowering drugs, or had conditions requiring cholesterol lowering treatment as defined by the Adult Treatment Panel (ATP III) guidelines. They were also excluded if they had low-density lipoprotein cholesterol below 80 mg/dl or triglycerides >500 mg/dl. Complete information on inclusion, exclusion and treatment regimen has been reported [24]. As with the MCI study, blood samples were taken and plasma was banked (Appendix A, available online).

2.3. Plasma analysis and internal standard

Plasma was assayed, quantified, and quality controlled as described in Appendices B and C, available online. Each assay plate also included a plasma sample derived from blood drawn by venipuncture of a 56-year-old cognitively normal volunteer in a single afternoon. This internal standard provided a means for adjusting plate-to-plate variation and assessing freezer storage effects.

2.4. Statistical methods

Storage effects on the internal standard were estimated by ordinary least squares regression of Aβ concentration on the number of years because the sample was obtained from the volunteer. We examined the associations between covariates of interest and plasma Aβ at baseline using linear mixed-effects models adjusting for the internal standard [34]. The covariates of interest include age, education, gender, *APOE* ε4, Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog), Activities of Daily Living (ADL), MMSE, urea nitrogen, creatinine, total protein, albumin, total cholesterol, hemoglobin, and platelets. See Appendix D, available online, for details.

To estimate the correlation between *change* in Aβ and *change* specific covariates, we used a multivariate outcome linear mixed-effects model approach [35]. Typically one would estimate the correlation of change by a two-step process: (1) calculate or estimate each individual's change from baseline for each outcome, (2) calculate the usual correlation coefficients for change in each pair of outcomes. Instead we used multivariate outcome mixed-effect models to estimate in a single step the correlation of change in each pair of outcomes. The model directly estimates the correlation