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Featured Article

Longitudinal decline in mild-to-moderate Alzheimer's disease: Analyses of placebo data from clinical trials

Ronald G. Thomas[a], Marilyn Albert[b], Ronald C. Petersen[c], Paul S. Aisen[a,*]

[a]*Department of Neurosciences, University of California San Diego, San Diego, CA, USA*
[b]*Department of Neurology, The Johns Hopkins Hospital, Baltimore, MD, USA*
[c]*Department of Neurology, Mayo Clinic, Rochester, MN, USA*

Abstract

Background: Accurate estimates of cognitive and clinical decline rates are essential to the design of clinical trials in Alzheimer's disease (AD) dementia.

Methods: To investigate the trajectories of individuals enrolled in therapeutic trials in mild-to-moderate AD, we analyzed the placebo arm data from 20 clinical trials including over 4500 subjects. We analyzed decline as measured by two cognitive instruments, the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAScog) and the Mini-Mental State Examination, and one clinical rating scale, the Clinical Dementia Rating Sum of Boxes.

Results: Trajectories were generally similar across trials and nearly linear. Greater cognitive impairment at baseline, younger age, and greater education were associated with increased rate of cognitive decline. Effect sizes for the ADAScog were generated as a function of population characteristics.

Conclusions: These data will inform the design of future studies of potential disease-modifying therapies for mild-to-moderate AD dementia.

Keywords: Alzheimer's dementia; Therapeutic trials; Cognitive assessment

1. Introduction

Therapeutic trials in mild-to-moderate stage Alzheimer's disease (AD) dementia rely on assessment tools that measure cognition, function, and clinical state. These measures are variable and influenced by a number of trial characteristics including enrollment criteria and rater performance. Optimal drug testing requires efficient utilization of assessment data, typically including longitudinal modeling and/or imputation of missing data. Analysis plans therefore should be informed by prior observations of longitudinal data in the target population. We undertook an analysis of pooled data sets from pharmaceutical industry and academic trials in mild-to-moderate AD to characterize trajectories of decline.

The primary cognitive outcome measure in most trials in mild-to-moderate AD is the cognitive subscale of the Alzheimer's Disease Assessment Scale or ADAScog [1]. This is an 11 item test of orientation, memory, executive function, visuospatial ability, language, and praxis, with a range of scores from 0 to 70 (a higher score indicates greater impairment). Trials also frequently use the Mini-Mental State Examination [2] (MMSE) score, both as an entry criterion and as a secondary outcome measure. The MMSE yields scores from 30 to 0 (a lower score indicates greater impairment).

The Food and Drug Administration and other regulatory bodies generally require co-primary outcome measures in trials in AD dementia, including both a measure of cognitive performance and an assessment of function (i.e., an interview of a study partner regarding performance on activities of daily living) or global clinical status (an interview based assessment of clinical stage or clinical change). One such measure that has been increasingly included as a co-primary outcome in relatively lengthy trials is the Clinical Dementia Rating Scale sum-of-boxes [3]. Box scores reflect

*Corresponding author. Tel.: +1-858-246-1365; Fax: +1-858-246-0138.

E-mail address: paisen@ucsd.edu or http://www.adcs.org (P.S.A.)

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assessment in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care, with scores ranging from 0 to 3 for each box and 0 to 18 for the total (a higher score indicates greater impairment).

We analyzed the longitudinal trajectories of the ADAS-cog, MMSE, and CDR-SB in the placebo arms of 20 clinical trials, to assess sensitivity to change, variability, shape of curves, and influence of predictive factors.

2. Methods

Data sets from 20 studies were collected and analyzed. The total number of placebo subjects analyzed was 4500. The essential features of the 20 trials are shown in Table 1. To combine data sets, we developed common metrics among the studies to facilitate comparisons. Using the Alzheimer's Disease Assessment Scale-Cognitive Subset (ADAS-Cog) as an example, the first step was to determine whether the individual ADAS-Cog items were collected or was only the total score captured. If total scores were available, the next question was to determine if the total was calculated using the ADAS-Cog with 11, 12, or 14 items. To allow the assessment of population demographic differences, key descriptive variables were located and extracted from each trial at the subject level: age, gender, race education, and baseline Mini-Mental State Examination (MMSE, if available), investigator and country. Joining of data sets necessitated locating unique subject identifiers and also indicators identifying study populations, for example, intention to treat, per-protocol, or safety. Longitudinal assessment of response measures required determination of the visit schedule and translation of visit codes to common time units. Other challenges included locating Apolipoprotein E (ApoE) status data (there was no standard method of archival) and determining the set of codes used to indicate missing data items.

Longitudinal trajectories were calculated using four methods

1. Observed mean values and standard errors. No imputation was applied for incomplete profiles.
2. LOCF plots. Missing data were imputed using a last observation carried forward single imputation.
3. MMRM slope. Least squares means for change scores were estimated at each 6-month time point using a mixed-model-repeated-measures model with baseline score and time included in model as fixed effects. Time is modeled as a continuous measure. An exchangeable correlation structure was assumed.
4. MMRM categorical time. Least square means for change scores were estimated at each 6-month time point using a mixed-model-repeated-measures model with baseline score and time included in model as fixed effects. Time is modeled as a categorical measure. A first-order autoregressive correlation structure was assumed.

Table 1
Correlations among outcome measures in change from baseline

	6 mo	12 mo	18 mo
ADAS-MMSE	−0.35	−0.56	−0.66
ADAS-CDR-SB	0.27	0.46	0.58
MMSE-CDR-SB	−0.28	−0.46	−0.60

NOTE. Correlations between pairs of outcomes. All correlations significant at $P < .0001$.

3. Results

A total of 4515 placebo-arm subjects, followed for a duration ranging from 12 to 24 months in 20 trials [4–22] were included in the analysis. Line graphs of the three measures of cognitive and clinical status are shown in Figs. 1–3.

Change scores in the outcome measures were correlated, with higher correlations at later time points (Table 1). Correlations were higher among mild subjects than moderate subjects (Appendix, table a-c). Q5

Comparison of the observed case and categorical time modeling to the continuous-time (linear) MMRM model suggests that the trajectories do not depart markedly from linearity (Figs. 4–6). However, there is some acceleration of decline with duration of follow-up; a quadratic term added to the model was highly significant for the ADAScog and MMSE and CDR-SB (data not shown).

We examined data modeled in three ways: by last observation carried forward (LOCF), an MMRM analysis fitting time as a categorical variable and an MMRM using time as a continuous variable. LOCF curves showed blunted decline rates.

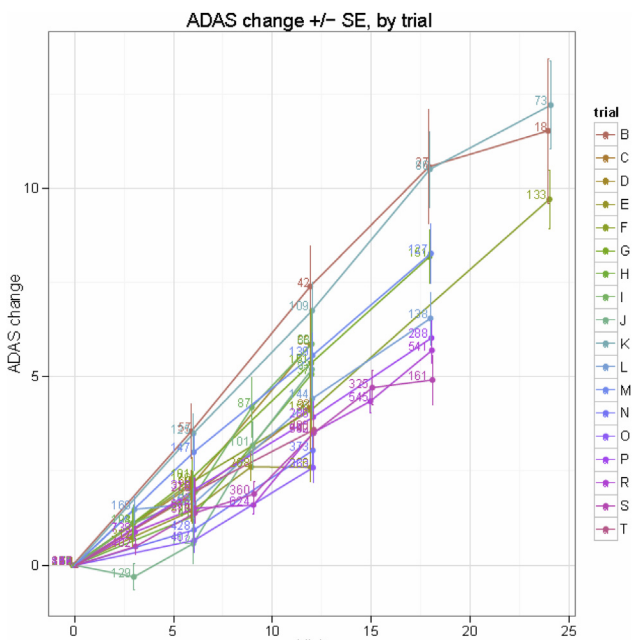

Fig. 1. Observed ADAS data from 18 trials. Abbreviations: ADAS change, Alzheimer's Disease Assessment Scale cognitive subscale, change from baseline score; SE, standard error; Visit, study visit in months from baseline.