Alzheimer's & Dementia: Translational Research & Clinical Interventions 4 (2018) 46-53

Featured Article

A simulation study comparing slope model with mixed-model repeated measure to assess cognitive data in clinical trials of Alzheimer's disease

Yun-Fei Chen[a,*], Xiao Ni[a], Adam S. Fleisher[a], Wei Zhou[a], Paul Aisen[b], Richard Mohs[a]

[a]Department of Neuroscience, Eli Lilly and Co., Indianapolis, IN, USA
[b]Department of Neurology, University of Southern California, Los Angeles, CA, USA

Abstract

Introduction: In clinical trials of Alzheimer's disease, a mixed-model repeated measure approach often serves as the primary analysis when evaluating disease progression; a slope model may be secondary.
Methods: Longitudinal change from baseline (14-item version of Alzheimer's Disease Assessment Scale–Cognitive Subscale) was simulated for treatment/placebo from multivariate normal distributions with the variance-covariance matrix estimated from solanezumab trial data. Type I error, power, and bias were based on 18-month treatment contrast. Sample sizes included 500 and 1000 patients/arm.
Results: The slope model was more powerful in most scenarios. Mixed-model repeated measure was relatively unbiased in parameter estimation. The slope model yielded unbiased estimates whenever the underlying trajectory was not detectably different from linear. Both methods led to similar type I error.
Discussion: In clinical trials of Alzheimer's disease, mixed-model repeated measure analysis with relaxed assumptions on disease progression seems to be preferred. The slope model might be more powerful if the trajectory has little departure from linearity.

Keywords: Clinical trials efficiency; Mixed-effects models; Mixed-model repeated measure (MMRM); Quantitative review

1. Background

Progression of a chronic disease such as Alzheimer's disease (AD), by definition, involves kinetics or dynamics of cognitive change relative to time, or the trajectory and shape of a curve. In clinical trials of drugs intended for the treatment of AD, comparing mean changes (baseline to endpoint) between treatment groups using a mixed-model repeated measure (MMRM) approach often serves as the primary analysis.

The MMRM analysis is a "semiparametric" approach, which treats time as a factor, or a categorical variable, and estimates the mean change from baseline in the outcome in each group treating baseline performance as a covariate [1]. The primary efficacy analysis is pivoted against a single endpoint (e.g., 18 months). Mallinckrodt et al. demonstrated that mixed-effects models, particularly the MMRM with unstructured mean and within-subject error correlation, provide more accurate estimates of treatment effect and its standard error than last observation carried forward analysis of covariance when data are missing at random [2]. Slope model, in contrast, assumes a linear progression model and may often serve as an alternative secondary analysis, which compares the slopes between treatment groups and treats time as a continuous variable.

Y.-F.C., A.S.F., and W.Z. are full-time employees and minor shareholders of Eli Lilly and Company. X.N. was an employee of Eli Lilly and Company at the time of this research and is currently an employee of Novartis. P.A. has served as a consultant to the following companies: NeuroPhage, Elan, Eisai, Bristol-Myers Squibb, Eli Lilly and Company, Merck, Roche, Amgen, Genentech, Abbott, Pfizer, Novartis, AstraZeneca, Janssen, Medivation, Ichor, Toyama, Lundbeck, Biogen Idec, iPerian, Probiodrug, Somaxon, Biotie, Cardeus, Anavex, AbbVie, and Cohbar. P.A. receives research support from Eli Lilly and Company, NIH (NIA U01-AG10483 [PI], NIA U01-AG024904 [Coordinating Center Director], NIA R01-AG030048 [PI], and R01-AG16381 [Co-I]). R.M. was an employee of Eli Lilly and Company at the time of this research and retired in 2015.

*Corresponding author. Tel.: +1-317-292-3994; Fax: +1-317-276-7100.

E-mail address: chen_yun-fei@lilly.com

https://doi.org/10.1016/j.trci.2017.12.002

The objective of this simulation study is to investigate the fixed (treatment) effect via MMRM and slope model using the same unstructured variance-covariance matrix. Herein, to make a fair comparison with the MMRM model, we use the term "slope model" to refer to a linear mixed-effects model that is linear in time without adding random slope or intercept in the model. The slope model described in this analysis uses a single parameter and is based on a simple and intuitive parametric trajectory model that can capture dynamics based on data from multiple visits. Several related types of slope models could also be considered, and similar inferences could be obtained by modeling unadjusted (not change from baseline) scores, using a model with patient-level random effects for slope and intercept. When changes from baseline are modeled, baseline Mini–Mental Status Examination and/or baseline Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) are important covariates for rate of progression [3].

In AD, it is often hypothesized that for a disease-modifying drug assumed to slow disease progression, the treatment group compared with the placebo group should shift the slope of decline on a given clinical outcome. It is important to note, however, that this is only one hypothesis among many regarding the accrual of treatment benefit that might be observed under an efficacious disease-modifying therapy. The gradual accrual of apparent treatment benefit (e.g., as would arise with diverging slopes) may be suggestive of permanent benefit, but continued and gradual accrual of apparent treatment benefit is neither sufficient nor necessary to establish the permanency of the benefit [4]. With this in mind, it can be interpreted that a slope model may provide a more intuitive and clinically meaningful way of demonstrating a disease-modifying effect than MMRM. Although MMRM analysis is an approach accepted by regulatory agencies to examine treatment efficacy, the slope model is required by the European Medicines Agency and has been proposed as an alternative approach, given its usefulness in consideration of possible disease-modifying effects [5].

Typically, a disease-modifying intervention is considered to be one that can slow disease progression by altering the neurobiology of the disease. While AD placebo trajectories are generally nonlinear because of an evident placebo effect occurring in the first 12 weeks or a finer time resolution assessment (e.g., every 6 weeks) [3], the disease trajectory often appears linear after the 1- to 2-year time course of initial improvement [6]. An expert group advocated the use of longer trials for disease modification coupled with slope models and biomarkers, specifically recommending that trials of 18-month duration be used [7]. This group also suggested that slope models be used from the perspective that diverging slopes of decline between drug and placebo groups can provide evidence for disease modification. The merits of slope model include it being a simpler model with a clear clinical interpretation, pertinent to the disease progression and modification concept, and potential efficiency gain. As is typical of more parsimonious models, a more favorable bias-variance trade-off may potentially be obtained, whereby the negative consequences of increased model bias are offset by the benefit of stabilized (reduced variance) estimation. One risk of the slope model is an incorrect model specification due to a strong linear assumption that could lead to a bias in estimation.

Due to the nature of AD, clinical trials are often plagued with high rates of missing data and highly variable clinical assessments underscoring the importance of efficient study design and analysis. In a chronic condition like AD, a linear model for progression is probably not an unreasonable approximation within a short window. Given the value of a slope model as a secondary analysis, it would be valuable to benchmark against the more general MMRM analysis and evaluate the trade-off, as well as the risk, of bias under varying degrees of departure from linearity. Here, we conducted a simulation study to compare the slope model and MMRM analysis based on various scenarios to better understand the performance of each method.

2. Methods

2.1. Study design

The design of EXPEDITION2 (NCT00904683) has been described previously [8]. Briefly, EXPEDITION2 was a multinational, randomized, double-blind, placebo-controlled, phase 3 study of solanezumab, an immunoglobulin G subclass 1 anti-amyloid monoclonal antibody that binds to the mid-domain of the amyloid-β peptide and is thought to increase clearance of soluble amyloid-β. Solanezumab was given intravenously 400 mg every 4 weeks into outpatients with mild-to-moderate AD dementia. Patients were at least 55 years of age and met criteria for probable AD dementia based on National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria [9]. Patients with Mini–Mental Status Examination [10] scores of 16 to 26 were allowed to participate. Mild AD dementia was defined as screening visit Mini–Mental Status Examination scores of 20 to 26; moderate AD dementia was defined as screening visit scores of 16 to 19. Randomization to treatment was stratified by AD severity to ensure a balance of treatment assignment within both the mild and moderate AD dementia patient groups. Patients were allowed to continue treatment with stable doses of standard-of-care AD treatments (e.g., acetylcholinesterase inhibitors and memantine) throughout the studies.

Institutional review boards at all participating sites approved the study. The study was conducted in accordance with ethical principles of Good Clinical Practice and the Declaration of Helsinki and its guidelines.

2.2. Statistical methods

Simulations were performed to compare the statistical properties of the slope model and MMRM analysis. Longitudinal change from baseline of the ADAS-Cog 14 for six