Featured Article

The effect of diagnostic criteria on outcome measures in preclinical and prodromal Alzheimer's disease: Implications for trial design

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Abstract

Introduction: We investigated the influence of different inclusion criteria for preclinical and prodromal Alzheimer's disease (AD) on changes in biomarkers and cognitive markers and on trial sample size estimates.

Methods: We selected 522 cognitively normal subjects and 872 subjects with mild cognitive impairment from the Alzheimer's Disease Neuroimaging Initiative study. Compared inclusion criteria were (1) preclinical or prodromal AD (amyloid marker abnormal); (2) preclinical or prodromal AD stage-1 (amyloid marker abnormal, injury marker normal); and (3) preclinical or prodromal AD stage-2 (amyloid and injury markers abnormal). Outcome measures were amyloid, neuronal injury, and cognitive markers.

Results: In both subjects with preclinical and prodromal AD stage-2, inclusion criteria resulted in the largest observed decline in brain volumetric measures on magnetic resonance imaging and cognitive markers.

Discussion: Inclusion criteria influence the observed rate of worsening in outcome measures. This has implications for trial design.

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Keywords: Alzheimer's disease; Longitudinal; Biomarkers; Cognitive markers; Preclinical; Prodromal; Sample size estimates; Clinical trial

1. Introduction

Alzheimer's disease (AD)–modifying therapy, targeting amyloid, is probably most effective when administered early, that is, before the stage of dementia. A number of research criteria have been proposed to identify nondemented subjects with AD based on the presence of AD biomarkers [1–3]. They can be applied in subjects without cognitive impairment (asymptomatic at risk for AD or preclinical AD) and subjects with mild cognitive impairment (MCI) (MCI due to AD or prodromal AD). However, these criteria allow for different combinations of AD pathology biomarkers, and it is unknown whether this impacts on observed changes in outcome measures. For trial design, it is critical to understand how selection criteria for subjects at such early stages of the disease influence change in outcome measures. Previous studies on outcome measures typically had a short follow-up, did not compare the effect of different inclusion criteria, or restricted their analyses to a limited set of outcome measures [4–12].

The aim of our study was to investigate whether changes in outcome measures are dependent on the inclusion criteria for preclinical and prodromal AD used. We studied three definitions for preclinical and prodromal AD: (1) having abnormal amyloid markers; (2) having abnormal amyloid markers and normal neuronal injury markers; and (3) having both abnormal amyloid and neuronal injury markers. As outcome measures, we used biomarkers for amyloid β (Aβ) in cerebrospinal fluid (CSF) or on positron emission tomography (PET), CSF tau, fludeoxyglucose PET (FDG-PET), brain atrophy measured with magnetic resonance imaging (MRI), and measures of cognitive functioning. To study the potential effects of different combinations of inclusion criteria and outcome measures on trial design, we calculated sample sizes for a hypothetical 3-year placebo-controlled trial in subjects at predementia AD stages. To study the additive value of biomarkers to define predementia AD, we also calculated slopes and sample sizes for subjects with normal cognition and MCI, regardless of their biomarker status.

2. Methods

2.1. Alzheimer's Disease Neuroimaging Initiative study

We studied data from subjects that participated in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study (adni. loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

2.2. Participants

We selected all participants with normal cognition (N = 522) or MCI (N = 872) from ADNI-1, ADNI-2, and ADNI-GO who had baseline and follow-up data available for at least one visit within a 3-year period for several biomarkers and cognitive tests (explained in more detail below). The ADNI inclusion criteria for participants with normal cognition were absence of memory complaints, a Mini–Mental State Examination (MMSE) [13] score of 24–30, a Clinical Dementia Rating (CDR) [14] score of 0, and no MCI or dementia diagnosis. The inclusion criteria for subjects with MCI were memory complaints, objective memory loss, an MMSE score between 24 and 30, and a CDR score of 0.5. Exclusion criteria were the absence of an informant, a score of >4 on the modified Hachinski scale [15], and score of >5 on the Geriatric Depression Scale [16], additional diseases expected to interfere with the study, use of investigational agents, multiple trial participation, and findings showing other reasons for cognitive problems. Permitted medication had to be stable for at least 4 weeks before screening. We downloaded ADNI data at 31st March, 2014.

2.3. Subject classification based on AD biomarkers

Subjects were classified as preclinical or prodromal AD with the use of AD biomarkers for amyloidosis and/or neuronal injury (see below), as proposed by International Work Group-2 (IWG-2) or National Institute on Aging and Alzheimer's Association (NIA-AA) research criteria [1–3]. As a marker for amyloidosis we used CSF $A\beta_{1-42}$ or ^{18}F-AV-45-PET, and as marker of neuronal injury we used CSF tau or FDG-PET. If both modalities were present for a given subject, we used their PET measures because they are more commonly used in practice. Subjects with normal cognition were classified as preclinical AD when they had abnormal amyloid, without taking into account neuronal injury markers; as preclinical AD stage-1 if they had abnormal amyloid and a normal injury marker; and as preclinical AD stage-2 if both the amyloid and injury markers were abnormal. MCI subjects were similarly classified as prodromal AD if the amyloid marker was abnormal, without taking into account neuronal injury markers; as prodromal AD stage-1 if the amyloid marker was abnormal but the injury marker normal; and as prodromal AD stage-2 if both the amyloid and injury marker were abnormal. Fig. 1 gives an overview of classification of subjects according to these criteria.

2.4. Baseline assessment and longitudinal assessment

Subjects underwent a standardized assessment that included neurological, physical, and neuropsychological examinations, collection of CSF and blood, and performance of MRI and PET scanning. For 32 cognitively normal and 23 MCI subjects, amyloid assessment was performed at follow-up only; and for these subjects, we used the first follow-up assessment with this measure as the baseline visit. The protocols for data collection are described in detail at http://www.loni.ucla.edu/ADNI/Data/ADNI_Data.shtml. Cognitive measures were collected at baseline and at