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Estimating sample sizes for predementia Alzheimer's trials based on the Alzheimer's Disease Neuroimaging Initiative

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Abstract

This study modeled predementia Alzheimer's disease clinical trials. Longitudinal data from cognitively normal (CN) and mild cognitive impairment (MCI) participants in the Alzheimer's Disease Neuroimaging Initiative were used to calculate sample size requirements for trials using outcome measures, including the Clinical Dementia Rating scale sum of boxes, Mini-Mental State Examination, Alzheimer's Disease Assessment Scale-cognitive subscale with and without delayed recall, and the Rey Auditory Verbal Learning Task. We examined the impact on sample sizes of enrichment for genetic and biomarker criteria, including cerebrospinal fluid protein and neuroimaging analyses. We observed little cognitive decline in the CN population at 36 months, regardless of the enrichment strategy. Nonetheless, in CN subjects, using Rey Auditory Verbal Learning Task total as an outcome at 36 months required the fewest subjects across enrichment strategies, with apolipoprotein E genotype $\varepsilon 4$ carrier status requiring the fewest (n = 499 per arm to demonstrate a 25% reduction in disease progression). In MCI, enrichment reduced the required sample sizes for trials, relative to estimates based on all subjects. For MCI, the Clinical Dementia Rating scale sum of boxes consistently required the smallest sample sizes. We conclude that predementia clinical trial conduct in Alzheimer's disease is enhanced by the use of biomarker inclusion criteria.

Keywords: Alzheimer's disease; Clinical trials; Mild cognitive impairment; Preclinical; Predementia; Sample size; Enrichment

1. Background

Studies of the biology of Alzheimer's disease (AD) have identified an array of targets for potential disease-modifying therapies (Mangialasche et al., 2010), but clinical trials in patients with dementia have been unsuccessful so far (Green et al., 2009; Sabbagh, 2009; Cummings, 2010; Quinn et al., 2010; Samson, 2010). Biological substrates of AD can be identified before patients become demented (Morris et al., 2009), and some AD biomarkers reach peak levels of abnormality before diagnosis (Jack et al., 2010; Lo et al., 2011). It is possible that failed dementia trials may have intervened too late in the disease process to be effective (St. George-Hyslop and Morris, 2008).

Clinical trials of investigational drugs targeting AD biology can enroll patients earlier in the disease, before criteria for dementia are fulfilled. Primary prevention trials enroll volunteers with no clinical or biological signs of AD at baseline but require thousands of participants and take

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many years to complete, as only a fraction of participants will develop AD (DeKosky, 2006). To date, few primary AD prevention trials have been conducted, and no agent has been shown to delay or prevent dementia onset. Secondary prevention trials can enroll participants at increased risk for dementia, affording decreased sample sizes and trial lengths. Secondary prevention trials have included individuals with mild cognitive impairment (MCI), a clinical syndrome defined by memory impairment or other cognitive problems, when compared with age- and education-matched norms, in the absence of functional decline (Petersen et al., 1999). Even some trials enrolling MCI participants have encountered low rates of disease progression (Feldman et al., 2007).

Biological markers of AD predict clinical progression and may be used to identify potential trial participants at greatest risk for dementia. Low levels of beta-amyloid (Aβ) or elevated levels of total tau (tTau) or tau phosphorylated at threonine 181 (pTau) in the cerebrospinal fluid (CSF; e.g., [Mattsson et al., 2009]), evidence of cerebral atrophy on magnetic resonance imaging (MRI; e.g., [Apostolova et al., 2006]), and brain glucose hypometabolism observed with fluorodeoxyglucose positron emission tomography (FDG-PET) (e.g., [Landau et al., 2010]) identify MCI patients at increased and more immediate risk for AD dementia. Even in asymptomatic individuals, the presence of biological evidence of AD significantly increases the risk for future cognitive impairment and AD dementia (Mosconi et al., 2009; Apostolova et al., 2010; Dickerson et al., 2011).

Thus, it is likely that using AD biomarkers as enrollment criteria can reduce the number of participants needed and study duration for AD prevention trials. Using AD biomarkers as outcome measures in AD trials can similarly improve trial efficiency (Jack et al., 2004; Hua et al., 2009; Schuff et al., 2009; Chen et al., 2010; Kohannim et al., 2010; Leung et al., 2010; Schott et al., 2010). The U.S. Food and Drug Administration (FDA), however, has not accepted any biomarker as a surrogate suitable for use as a primary outcome measure in AD trials. Moreover, FDA guidance outlines the use of clinical measures to achieve marketing approval (Leber, 1996; Katz, 2004). Therefore, registration trials, even those conducted in very mild disease, continue to use the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and other clinical scales as primary outcome measures.

The statistical power of predementia trials may be improved by population enrichment strategies using biomarkers. These trials might be able to use a single primary outcome measure (rather than dual primary outcomes, as is the case in dementia trials [Aisen et al., 2011]). Using the Alzheimer's Disease Neuroimaging Initiative (ADNI) data set, we sought to identify the best enrichment strategies for predementia trials in relation to outcome measures to optimize statistical power. We hypothesized that enriching cognitively normal (CN) and MCI trial populations through biomarker criteria would reduce required sample sizes.

2. Methods

2.1. Alzheimer's Disease Neuroimaging Initiative

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering, the FDA, private pharmaceutical companies, and nonprofit organizations as a $60-mn, 5-year public–private partnership. 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. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The principal investigator of this initiative is Michael W. Weiner MD, VA Medical Center and University of California–San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from $>$ 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 adults, 55–90 years of age, to participate in the research: approximately 200 CN older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years. For up-to-date information, see www.adni-info.org.

The current analyses focused on the first iteration of ADNI, which enrolled a cohort of volunteers who were CN, had MCI, or had AD dementia at baseline. Clinical and biological data were collected, including MRI volumetric measures, FDG-PET, and CSF protein analysis. The current analyses focused on data from CN and MCI ADNI subjects. CN subjects had no subjective memory complaints at baseline. CN and MCI subjects scored between 24 and 30 on the Mini-Mental State Examination (MMSE). CN subjects had a global Clinical Dementia Rating scale score of 0 at baseline. MCI subjects scored 0.5, with a required memory box score of 0.5 or higher at baseline. Subjects were also required to meet criteria for memory performance on the Wechsler Memory Scale-Revised Logical Memory II subscale: CN subjects: $\geq$ 9 for 16 years or more of education, $\geq$ 5 for 8–15 years of education, and $\geq$ 3 for 0–7 years of education; MCI subjects: $\leq$ 8 for 16 years or more of education, $\leq$ 4 for 8–15 years of education, and $\leq$ 2 for 0–7 years of education. ADNI CN subjects could not have impairment in activities of daily living and MCI subjects could not meet criteria for dementia.

All ADNI participants had a modified Hachinski scale score of $<$ 4, a Geriatric Depression Scale (abbreviated 15-item version) score of $<$ 6, were fluent in English or Spanish, had a suitable study partner who could accompany