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EDITORIAL

EARLY ALZHEIMER'S TRIALS: NEW DEVELOPMENTS

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After decades of observational studies it is now time to launch large trials to reduce disability in an aging world. Age-related disability is complex, often involving the interplay of prevalent diseases such as Alzheimer's disease (AD) with various co-morbidities and general frailty. Factors that may mitigate or exacerbate disability are only partially understood. Some patients with biomarker indicators of amyloid accumulation in brain will never develop Alzheimer's dementia, while frail individuals may be particularly prone to decline. Even as we proceed with therapeutic trials, we must continue to study the many important interrelated factors influencing outcomes.

A large number of promising candidate disease-modifying treatments for AD have advanced into Phase II and Phase III testing. However, most completed trials have failed to demonstrate efficacy, and there is growing concern that methodological difficulties may slow progress. The optimal time to intervene with such treatments is probably in the years prior to the onset of dementia, before the neuropathology has progressed to the advanced stage corresponding to clinical dementia (1).

Data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and elsewhere suggest that AD begins with amyloid β peptide (Aβ) accumulation in the brain, which leads ultimately to synaptic dysfunction, neurodegeneration, and cognitive/ functional decline (2). This predicts that the earliest detectable changes are those related to Aβ (cerebrospinal fluid (CSF) assays and PET amyloid imaging). Subsequently, neurodegeneration is reflected in a rise of CSF tau species, synaptic dysfunction by FDG-PET, and neuron loss indicated by atrophy most notably in medial temporal lobe (measured with MRI). These changes ultimately lead to memory loss, general cognitive decline and eventually dementia. Expression of each element of AD pathology (e.g. Aβ and tau deposits, atrophy) is influenced by many modifying factors including age, APOE genotype, and cerebrovascular disease.

Most disease-modifying drug programs in the late stages of clinical development target brain amyloid accumulation by inhibiting secretase cleavage of the amyloid precursor protein or by directly interacting with amyloid peptides in the brain or the periphery. It is reasonable to assume that selection of trial subjects with biomarker evidence of amyloid accumulation will enroll a population likely to demonstrate the presumed benefits of these treatment strategies. Amyloid PET imaging and measurement of cerebrospinal fluid Aβ42 provide roughly equivalent selection of such subjects (3). The Clinical Dementia Rating Sum of Boxes (CDR-SB), as shown by ADNI in the US and Real.fr in Europe, is a candidate endpoint for such studies.

We are please to present in this JNHA issue the papers that were presented at the EU / US Task Force on Designing Pre-Dementia Alzheimer's Trials in Las Vegas, November 2009. Recommendations for clinical trial methods for "pre-dementia", "prodromal AD" or "early AD " are discussed by L.S Schneider (4); R.S. Doody (5), R. Peterson (6), J. M. Cedarbaum (7), W.Z. Potter (8) and R. Schindler (9), reflecting their experience from academic and industry perspectives. After discussion with Task Force participants from academy, industry and regulatory agencies some consensus was reached regarding such trials. This consensus will be published soon and will continue our task force series. Another important point to be discussed is the difficulty conducting such complex trials when current pivotal studies may involve 200 centers in 20 different countries. The heterogeneity and variability of participation sites resulting from cultural and language differences may mask the efficacy of a drug. We need to re-evaluate our practice, and consider a shift toward the conduct of trials in a relatively small number of large highly-qualified centers. Because AD is a prevalent disease, this approach may be feasible if we can maintain such centers with adequate staffing as well as regional networks for recruitment.

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