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PRE-DEMENTIA ALZHEIMER'S TRIALS: OVERVIEW

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Abstract: A series of negative clinical trials of disease-modifying agents for Alzheimer's disease has increased pessimism regarding the prospects for important therapeutic advances. But limited efficacy may be attributed in part to the advanced degree of neurodegeneration present at the onset of dementia. To optimize the likelihood of success, it is essential to develop the methodology to allow testing of disease-modifying treatments at an early stage of pathology, when modulation of pathophysiologic mechanisms may yield major clinical benefits.

Alzheimer's disease (AD) is among the major health problems worldwide, and is growing in impact as populations age. Intensive therapeutic research over the past three decades has produced modestly effective symptomatic treatments. In recent year, the focus has shifted to disease modification, that is, slowing the progression of the underlying neurobiology of AD. Promising targets have been identified, and candidate agents aiming to reduce amyloid load or toxicity, slow tau phosphorylation and tangle burden, or otherwise provide neuroprotection, have moved forward in clinical development. But none has yet proven efficacy. Indeed, there is general frustration following a series of unsuccessful clinical development programs. While it may be that the agents tested had insufficient efficacy, there is also substantial concern that methodological issues may be slowing progress.

In AD, pathology likely precedes dementia onset by a decade or longer, with dementia representing a late stage along the neurobiological pathway. It is plausible that effective disease-modifying interventions for AD might be only minimally effective or even futile at the dementia stage; neuroprotection or favorable effects on amyloid or tau pathways might be overwhelmed by extensive neuronal/synaptic degeneration and plaque pathology. For this reason, to optimize the impact of disease-modifying treatments, they must be initiated at the earliest possible stage of disease.

Most efforts to conduct therapeutic trials in a pre-dementia population have enrolled subjects with amnestic mild cognitive impairment (MCI), with the primary analysis assessing impact of treatment on time to consensus diagnosis of AD. This design has the advantage of clear clinical validity, a desirable feature in consideration of the uncertain regulatory status of the MCI designation. At least one set of MCI criteria seems to predict a high likelihood of AD diagnosis (approximately 15% per year), so that such a trial can have a reasonable size with adequate power to demonstrate a treatment effect. But progression from MCI to AD is not a discrete event; the loss of function necessary to meet criteria for dementia occurs gradually, and it is challenging to assign a specific date to dementia onset. This subjectivity may be aggravated in large international trials. The progression of cognitive and functional impairment caused by AD pathobiology is insidious; defining a discrete disease onset seems arbitrary.

The community of AD clinical investigators is strongly weighing alteration of the diagnostic criteria for AD to include individuals with amnestic MCI plus biomarker evidence of AD neuropathology. The Alzheimer's Disease Neuroimaging Initiative (ADNI) has demonstrated that subjects with "early AD" defined in this way have accelerated decline on continuous measures of cognition (ADAS-cog) and clinical status (CDR-SB). Thus it may now be feasible to test disease-modifying interventions in early AD using standard outcome measures; trial power can be increased by using biomarker covariates, and disease-modification can be supported by neuroimaging outcomes such as volumetric MRI (1-7).

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