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Perspective

Ethical challenges in preclinical Alzheimer's disease observational studies and trials: Results of the Barcelona summit

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Abstract Alzheimer's disease (AD) is among the most significant health care burdens. Disappointing results from clinical trials in late-stage AD persons combined with hopeful results from trials in persons with early-stage suggest that research in the preclinical stage of AD is necessary to define an optimal therapeutic success window. We review the justification for conducting trials in the preclinical stage and highlight novel ethical challenges that arise and are related to determining appropriate risk-benefit ratios and disclosing individuals' biomarker status. We propose that to conduct clinical trials with these participants, we need to improve public understanding of AD using unified vocabulary, resolve the acceptable risk-benefit ratio in asymptomatic participants, and disclose or not biomarker status with attention to study type (observational studies vs clinical trials). Overcoming these challenges will justify clinical trials in preclinical AD at the societal level and aid to the development of societal and legal support for trial participants.

Keywords: Alzheimer's disease; Preclinical AD; Ethics; Asymptomatic

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1. Introduction

By the year 2030, 76 million people worldwide will suffer from dementia, with most cases being caused by Alzheimer's disease (AD) [1]. Despite the considerable advances in our understanding of the neuropathologic processes that underpin AD, academic and industry research programs that develop mechanism-based therapies, including those directed against β-amyloid have yet to produce meaningful clinical benefits [2]. Consequently, one of the biggest questions that the AD research community faces is whether clinical trials have so far included participants who have already surpassed the optimal therapeutic window for intervention, together with the need to ensure the presence of AD pathology through biomarkers.

In 1984, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA, now the Alzheimer's Association) published for the first time the clinical diagnostic criteria for AD [3]. Almost 30 years later, the progress in our scientific understanding of the neuropathology that precedes clinical symptoms prompted the scientific community to redefine AD as a pathologic continuum. Both the International Working Group and the US National Institute of Aging with the Alzheimer's Association (NIA-AA) released revised guidelines that incorporated biomarkers to identify individuals at risk of developing AD dementia [4–8]. Both criteria subdivide AD development into three stages: preclinical (abnormal biomarkers and no or only subtle cognitive impairment), mild cognitive impairment (MCI) due to AD or prodromal AD (defined as the presence of abnormal pathophysiological biomarkers and episodic memory impairment) and dementia (abnormal biomarkers and clear cognitive and functional impairment).

One significant advance in our understanding of AD is that it has two components: a neuropathologic one, which remains asymptomatic during years, and a clinical one, which starts with a MCI stage followed by a dementia one. Convergent biomarker and imaging findings from autosomal dominant AD mutation carriers, genetic at-risk and age at-risk cohorts suggest that the pathophysiological process of AD starts over a decade before the dementia stage [9–14]. This asymptomatic phase, referred to as preclinical AD, has given us an unprecedented opportunity to perform observational studies and trials to intervene at earlier stages of the continuum and delay the onset of clinical decline and ultimately dementia. In this scenario, trials in mild moderate AD have been consistently negative during the last decade [15], and although we are still waiting for the results of ongoing prodromal AD trials, intervention studies on asymptomatic individuals appear as highly relevant and promising, before substantial irreversible neuronal network dysfunction and loss, associated with overt clinical symptoms, have occurred.

Conducting preclinical AD trials gives rise to a variety of novel ethical and policy challenges. These include whether to disclose genetic and/or biomarker results to an individual, the need to determine an acceptable risk-benefit ratio in asymptomatic participants and the legal protection of participants from insurance policies. The ethical framework that guides clinical research can be seen as a balancing among the interests of the participants and society on one side, as well as the research challenges on the other [16]. To review and discuss the novel ethical challenges that need to be overcome for successful performance of trials in the preclinical stage of AD, a multistakeholder group met in a 1-day summit entitled "Ethical challenges of future Alzheimer's disease clinical research" held in Barcelona in October 2014. This reunion was organized by the Barcelona-βeta Brain Research Center, the research institute where the Pasqual Maragall Foundation conducts all its scientific activities devoted to clinical research for the prevention of AD. This discussion group included experts from academia, including AD researchers and bioethicists, patients' organizations and regulatory agencies. This article summarizes the outcome of that meeting, where these ethical and policy challenges were debated and recommendations to address them throughout the research process were proposed, discussed, and agreed.

2. The scientific basis of the preclinical stage and prevention strategies

The prevailing hypothesis for AD pathogenesis, the amyloid cascade hypothesis, assumes several causal events that begin with the accumulation of β-amyloid in the brain followed by tau hyperphosphorylation and then neuronal degeneration. In addition to advanced age, the risk of developing AD is increased among persons with certain genetic variants. Autosomal dominant AD (ADAD), characterized by pathogenic mutations in one of three genes—the β-amyloid precursor protein (*APP*), Presenilin 1 (*PSEN1*), and Presenilin 2 (*PSEN2*)—provide almost certain risk (~100%) of developing symptomatic AD [17]. In addition, apolipoprotein E ε4 (*APOE* ε4) allele carriers have a significantly higher risk of developing symptomatic AD when compared to noncarriers [18]. Specifically, the risk of AD has been shown to be 2.6 times higher for people with the *APOE* ε2/ε4 genotype relative to *APOE* ε3/ε3 individuals and 3.2 and 14.9 times higher for *APOE* ε3/ε4 and *APOE* ε4/ε4 persons, respectively [19].

Our understanding of preclinical AD indicates that biomarker abnormality occurs in a temporal manner where it has been demonstrated that abnormally low cerebrospinal fluid (CSF) β-amyloid 42 ($A\beta_{42}$) and cerebral amyloid deposits precede elevated CSF tau, topographical cerebral injury, and cognitive decline [20]. New data from recently initiated studies such as EPAD (European Prevention of Alzheimer's Dementia), PREVENT Research Programme