HHS Public Access

Author manuscript

J Clin Psychiatry. Author manuscript; available in PMC 2015 June 08.

Published in final edited form as:

J Clin Psychiatry. 2014 June ; 75(6): 661–662. doi:10.4088/JCP.14com09235.

Endpoints in Preclinical Alzheimer's Disease Trials

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Researchers, pharmaceutical companies, funders, regulators, and other stakeholders in the scientific fight against Alzheimer's disease (AD) have expressed great interest in the evaluation of putative "preclinical AD treatments," interventions that are initiated in cognitively unimpaired persons and intended to postpone, reduce the risk of, or completely prevent progression to the clinical stages of AD. Thank goodness. With the growing number of persons living to older ages, preclinical AD treatments are urgently needed to avert a catastrophic public health problem, and at least some of the proposed treatments may need to be initiated before the mild cognitive impairment (MCI) or dementia stages of AD, when the pathology is already extensive, to be most efficacious.

As we have previously noted, the field needs both the scientific means and financial incentives to rapidly evaluate putative preclinical AD treatments in cognitively unimpaired persons at risk for AD. The trial endpoints need to help reduce the number of research participants and time it takes to evaluate putative preclinical AD treatments, for the world cannot afford to await the results of one large, expensive and time-consuming trial at a time and sponsors are unlikely to provide investigational drugs or much support for preclinical AD trials that last longer than the drug's patent life. What's more, the endpoints need to be sufficiently compelling to regulators, such that an investigational drug's effects on the endpoint could lead to marketing approval. Under standard regulatory agency provisions, the treatment would need to have "clinically meaningful" effects, including evidence that it impacts relevant cognitive features of AD and the ability to function (e.g., activities of daily living). An impact on functional performance is a high bar for a preclinical AD trial to reach. Fortunately, regulatory agencies also have accelerated approval provisions for the approval of certain treatments, including those for AD. Under these provisions, it is possible to approve a treatment if its effects on the primary endpoint are "reasonably likely" to predict a clinically meaningful benefit and then to acquire the post-marketing data needed to support a clinically meaningful effect. With those criteria in mind, the search is on for efficient preclinical trial endpoints with sufficient "theragnostic value" in preclinical AD trials, such that a treatment's effects on the endpoints are at least reasonably likely to predict a clinical benefit.

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In the Alzheimer's Prevention Initiative (API), we and our colleagues have been interested in finding a suitable primary endpoint for potentially license-enabling preclinical AD trials in cognitively unimpaired persons who, based on their genetic background and age, are at the highest imminent risk for progression to the clinical stages of AD(1;2). Utilizing a strategy first proposed by Suzanne Hendrix, Jessica Langbaum and our colleagues first used a longitudinal data set from the Rush University AD Center to exhaustively search for the combination of cognitive test scores with the greatest power to track cognitive decline in unimpaired older adults, who subsequently progressed to the clinical stages of AD, while controlling for practice and aging effects in other persons who remained cognitively unimpaired over the same time frame. A combination of 7 test scores was found to provide the best power to the track cognitive decline associated with preclinical AD—though the results depended in part on the studied test battery and there are other combinations that proved to be almost as good(3). How could a composite cognitive test score have better power to track preclinical AD than the most sensitive individual test in the composite? By capturing an additional aspect of preclinical AD decline and not adding to measurement noise. Since it is difficult to know how well any tests might do in that regard, we have made the case for the use of empirically generated and independently confirmed composite cognitive test scores in the preclinical tracking of AD and the evaluation of preclinical AD treatments.

In this issue of the Journal of Clinical Psychiatry, Napatkamon Ayutyanont and our colleagues describe the effort to characterize the composite cognitive test score that was selected for the evaluation of an investigational amyloid-β modifying treatment in the API autosomal dominant AD (ADAD) trial(4). The analysis capitalized on longitudinal data acquired by Dr. Francisco Lopera and his colleagues in PSEN1 E280A mutation carriers and non-carriers from the world's largest ADAD kindred in Antioquia, Colombia. Data from initially unimpaired PSEN1 E280A mutation carriers at least 30 years of age were used to provide an indicator of preclinical AD decline and data from the non-carriers in that age group were used to control for practice and aging effects. Despite differences in language, test batteries, frequency of follow-up assessments, and application to a younger cohort, the analysis found a roughly similar combination of cognitive test scores had the best power to track preclinical ADAD decline, and it permitted us to estimate the number of mutation carriers needed for our five-year preclinical ADAD trial now in progress using the API composite cognitive test score as the primary endpoint (Clinicaltrials.gov identifier NCT01998841).

Thanks to the generosity of several research groups, we have begun to extend our findings to a growing number of longitudinal cohorts and to prepare for the use of a similar composite cognitive test score in the API APOE4 preclinical AD trial, which is planned in cognitively unimpaired apolipoprotein E4 (APOE4) homozygotes, 60–75 years of age, who have a particularly high imminent risk of progression to the clinical stages of late-onset AD. Looking ahead, we anticipate that different composite cognitive test scores will be used in preclinical AD trials, depending in part on the longitudinal data needed to characterize the optimal test combination and statistical power in the at-risk group being considered for study. Some groups have expressed interest in using computational test batteries or more difficult cognitive tests to further optimize the power to track preclinical AD decline, again

depending in part on the longitudinal data needed to demonstrate their added value in the relevant at-risk population. Others are using other endpoints, such as frequency of or time to progression to MCI or dementia, whichever comes first. While it would seem prudent support have flexibility in the selection of the preclinical AD endpoint at this time, it also seems prudent for different trials to acquire the data needed compare findings across trials. What about using brain imaging or other biological measurements as endpoints in preclinical AD trials? While they do have the potential to track AD and evaluate preclinical AD treatments with improved statistical power, they are not yet ready to serve as primary endpoints in license-enabling trials. Additional data from preclinical AD trials themselves are needed to determine the extent to which a preclinical AD treatment moves different biomarkers, whether it does so in a way that is free from a potentially confounding effect unrelated to disease-slowing and, most importantly, to establish the relationship between the treatment's biomarker and clinical effects. For this reason, the API trials are specifically designed to embed the most promising biomarkers in the trials and relate a treatment's 2-year biomarker effects to its 5-year effects on the composite cognitive test score.

The advancement of endpoints for preclinical AD trials has benefitted greatly from several factors: The clarity, consistency, and flexibility that the Food and Drug Administration has shown in its public comments and draft guidance statement on the use of endpoints in early clinical and preclinical AD trials(5); similar comments from the European Medicine's Association; progress in the design of several other preclinical AD trials, including the, the Alzheimer's AD Cooperative Study (ADCS) A4 Trial(6), Dominantly Inherited Alzheimer's Network Therapeutic Unit (DIAN-TU) Trial(7–10), and the TOMMORROW trial(11;12); the efforts of several stakeholder groups; the efforts of stakeholders in the Collaboration for Alzheimer's Prevention (CAP) to exchange preclinical AD trial progress, problems, and solutions, encourage the harmonization of preclinical AD trial data, and support data and biological sample sharing after the trials are over; the growing interest of drug sponsors in preclinical AD trials; and the interest of public and private funders in the development of theragnostic biomarker endpoints, as reflected by the Accelerating Medicine's Partnership (AMP), in which NIH and industry funds will be used to include additional exploratory biomarker endpoints in three of the publicly supported preclinical AD trials.

There is much more to do and learn when it comes to the optimization suitability of endpoints in preclinical AD trials. But the recent momentum has been awfully encouraging.

Acknowledgments

Dr. Reiman is Deputy Editor of the Journal of Clinical Psychiatry and Editor of the Journal's Special Section on Alzheimer's Disease. In this commentary, article, he, Dr. Jessica Langbaum, and Dr. Pierre Tariot comment on an article submitted by their own group and reviewed by other Journal editors. They places the article in the context of the Alzheimer's Prevention Initiative (API), an ambitious research program which they and their colleagues have established with support from the NIH, philanthropy, and industry partners.

This work is supported by National Institute on Aging grants RF1 AG041705 (EMR, PNT), UF1 AG046150 (EMR, PNT), R01 AG031581 (EMR), P30 AG19610 (EMR), Genentech, Avid Radiopharmaceuticals, Banner Alzheimer's Foundation, Anonymous Foundation, Nomis Foundation, Arizona Alzheimer's Consortium, and the State of Arizona.

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