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The Potential and Limits for Clinical Trials for Early Alzheimer's Disease and Some Recommendations

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Abstract

Recommendations for clinical trials methods for 'pre-dementia,' 'prodromal,' or early Alzheimer's disease are discussed. Early AD can be considered as subsets of both 'amnestic MCI' and 'probable AD.' In principle, it can be operationalized using recently proposed, new research criteria for AD that specifically does not require impairment in non-memory cognitive function and activities of daily living, and consequently does not require the presence of dementia. The criteria also require patients to show abnormal putative biomarkers but require validation. Trials in early AD should be done when models of drug action and response suggest that the drug in development likely would be effective in early AD and clinical effects could be expected in a relatively short time.

Biomarkers should be used as stratification or explanatory variables that may help to explain clinical outcomes from early AD trials rather than as inclusion/exclusion criteria in order to avoid pseudospecificity.

Trials should be multicentered, double-blinded, randomized, placebo-controlled, generally with dose-ranging of two doses if indicated. Duration of trials should be based on expected onsets and durations of effects, and generally should be less than one year. Crossover trials should be considered when appropriate.

Primary outcomes should specifically assess memory and include repeated assessments. Potential secondary outcomes could include self- and observer-rated health-related quality of life and global impressions of change in lieu of activities of daily living. Onset of dementia should not be an endpoint because many patients would be on the cusp of dementia and dementia onset is influenced by numerous biological and environmental factors. Inferences that can be made from trials results will likely involve the effects of the test drug on memory and self-rated global function. Disease modification is not likely to be inferred except in trials over two years in duration in which a change in a biomarker can be used as an adjunctive assessment. Models and simulations using existing clinical trials databases would be helpful in planning early AD trials.

Keywords

Early Alzheimer's disease; clinical trials; methodology

Introduction

Ideas, recommendations, potential inclusion criteria, methods and limitations for clinical trials for 'pre-dementia,' 'prodromal,' or early Alzheimer's disease are discussed.[1] We wish

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to be able to study AD treatments before the onset of a dementia syndrome which is an essential criterion required for the clinical diagnosis of NINCDS-ADRDA probable or possible AD (1).

Including patients with mild probable AD in clinical trials is unsatisfactory because the disease process may be too advanced to detect substantial clinical benefit from treatment as is illustrated by the small clinical effects seen with the marketed cholinesterase inhibitors and memantine. Despite use of the adjective 'mild,' patients with mild AD have dementia and have been significantly impaired for about 2 to 4 years on average prior to diagnosis if not longer.

Studying patients with mild cognitive impairment or amnestic MCI has been considered an unsatisfactory approach to AD clinical trials because most patients do not progress to dementia over the 1 to 4 year trial periods (2), and because of those that develop dementia about 30% do not meet neuropathological criteria for AD (3). Trials that include patients with amnestic MCI include unknown proportions of patients with and without AD or the neuropathology of AD.

Accurately identifying early AD will allow the testing of treatments that may be effective earlier in the illness when there are fewer signs and symptoms and presumably less underlying neuropathological substrate, and that might have both greater immediate and continuing effects over the course of illness. Improving cognitive function during the pre-dementia phase of the illness might substantially improve health-related quality of life and mitigate the progression of illness when it may matter most. It is also possible to test treatments that might be effective at an early, pre-dementia stage of illness but not later on when there may be too much neuronal degeneration to overcome and loss of therapeutic drug targets.

One caveat in this discussion is that 'early' AD as described here means clinical signs and symptoms of AD before dementia but still might not mean early in the neuropathology of the illness. Effectively treating early AD should not be considered primary or secondary prevention, but rather 'tertiary' prevention or treatment of the symptoms and disease itself.

Thus, by definition, the ability to do clinical trials in early AD rests entirely on being able to accurately diagnose it. Part of the diagnostic process is the ability to accurately identify a person who does not have early AD, i.e., is normal, has MCI (and not early AD), has mild probable AD (not early AD), or has another intercurrent cognitive-impairment syndrome such as one due to cerebrovascular disease. Complicating this effort is the lack of an ante mortem 'gold standard' for an AD diagnosis and lack of validated drug targets for therapeutic drug development.

The clinical border between MCI and mild AD is not sharp. Although considered a risk or transitional state to AD (4), a proportion of patients diagnosed with MCI can be diagnosed as AD by their physicians. Thus many patients with MCI could be perceived to have mild AD and entered into AD trials; and a proportion of mild AD patients could be perceived to have MCI and entered into MCI trials. Specifically, AD trials that allow patients to enter with Mini-Mental State Examination (5) scores of 26 and below can include some patients with MCI; and MCI trials that allow patients to enter with MMSE scores of 24 and higher

[1]The following conventions are used: MCI or aMCI means amnestic MCI; early AD means the same as 'pre-dementia' AD or 'prodromal' AD and refers to the concept of identifying patients with AD prior to their fulfilling criteria for probable AD, or having a dementia. 'Mild AD' means possible or probable AD (McKhann et al 1984) with relatively mild cognitive impairment and dementia. 'Biomarker' is used loosely as a biological measure that is associated with AD, and is not meant to convey diagnostic marker, validated or un-validated surrogate markers

could include patients with mild AD. A practical effect for MCI trials is to enrich a sample for the development of probable AD over a 2 to 4 year period (2). Consequently, a group of amnestic MCI patients likely includes the subset 'pre-dementia AD,' prodromal AD, or early AD. Moreover, some patients considered to have mild probable AD could also qualify for early AD using proposed research criteria, and early AD can include both MCI and mild AD within its criteria.

Criteria for MCI, early AD and probable AD

The following table displays differences and similarities among MCI, proposed research criteria for early AD, and probable AD by current research criteria. The essential distinction between the proposed research criteria (when specifically applied to early AD) and either amnestic MCI or probable AD is the requirement for a biomarker as a supportive feature. Clearly early AD criteria occupy a position between MCI and mild AD criteria (1, 4, 6).

Enrichment and biomarkers

The current biomarkers under discussion (6) are state markers that can vary with illness, may not always be expressed, and may be influenced by factors other than disease progression. It has not been determined whether the biomarkers under consideration are necessary diagnostic markers that – along with other characteristics – can be used to make an accurate AD diagnosis or are biomarkers that serve to increase the likelihood for an AD diagnosis or enrich the study sample for the subsequent development of probable AD.

Early AD as it is formulated here could be considered a more advanced risk state for AD than amnestic MCI. An implication is that episodic memory impairment coupled with a biomarker increases the likelihood for AD to near the level as the current criteria for probable AD that requires the presence of more severe clinical features (but no biomarkers) as discussed by the authors of the proposed new research criteria (6).

The use of biomarkers as supportive features or enrichment of proposed research criteria is associated with both advantages and issues. The most obvious of which is that if early AD participants in trials are limited to those with abnormal MRI, PET, or CSF studies (presumed to be associated with AD pathology) the results will not be generalizable to broader AD samples. For example, clinical trials results could not be generalized to biomarker-negative patients who are likely to constitute a substantial proportion of a clinically relevant study sample. Another limitation to biomarkers as entry criteria is that their significance in a general population, including people who do not have AD, are not cognitively impaired, or who are clinically normal is not known. People who do not have symptoms and who score positive on the biomarkers cannot be thought necessarily to have AD or be expected to progress to a state of cognitive impairment.

Finally, if the biomarkers enrich the sample for AD diagnoses but do not meaningfully differentiate the sample from another group of AD patients, e.g., a group for example without the abnormal biomarkers, then the clinical sample identified may represent a pseudospecific subgroup. Other factors may interact with the biomarker-defined sample to affect the results of the trials. For example age and APOE ε4 carrier status may affect the identification of early AD patients and their inclusion in a trial, and affect the course of cognitive change as they do with MCI (7). Although treatment bias is attenuated by randomization the effects of treatment may differ depending on APOE genotype or age.

Methodological considerations and outcomes

The overall clinical course of early AD would be expected to be slower on average than mild AD. Even in mild to moderate AD trials a substantial proportion of the sample remain

stable or improve over 18 months (8). It is difficult to detect a drug effect that might moderate clinical course if the course of worsening without treatment is slight. Moreover, a treatment intended to mitigate clinical course may not show a discernable effect until much later. More sensitive cognitive outcomes are not likely to be practically helpful because the mean change is very small. On the other hand, treatments that have a relatively acute effect on memory may be more precisely assessed in early AD because of the expected stable course over the short term.

Outcome measures for trials need to reflect the actions of the drug in the sample selected. Because early AD is mainly defined by episodic memory impairment and self-identification, change in memory should be the primary outcome. Self- and observer- rated impressions of change (9) and health-related quality of life assessments may be particularly sensitive and clinically meaningful. Activity of daily living scales that are under development for use in prevention trials might also be useful in the future (10).

Medication considerations

Earlier diagnosis leads to a better ability to study illness course, clinical heterogeneity, predict the future, and allows for clinical trials to be done earlier in the illness. This depends, however, on the models for action of the particular drugs, the relevant drug targets, and how they might exert their clinical effects. It is possible that a drug that is effective as a primary preventative will not be effective in people with early AD, and that other drugs may be only discerned to be effective later in the course of illness. Moreover, from a social, economic and medical perspective drugs may have demonstrated effects in early AD but may not have a measurable practical effect later in the illness because of loss of neuronal substrate on which the drug acts or neurodegeneration of other systems.

The risk to benefit profile of a drug needs to taken in to account for a trial in early AD or MCI. A drug with significant adverse events risks may not be suitable for an initial early AD trial. For example, the possibly greater safety risks of active vaccines or monoclonal antibodies need to be considered differently in an early AD sample where progression is slower and patients are not as impaired than in mild to moderate AD.

Recommendations for early AD trials

The new AD research criteria could be applied to early AD and clinical trials in the following way: (A) Include all patients who fulfill the core diagnostic criteria, i.e., an episodic memory deficit, do not have dementia, and do not have significant problems in everyday functioning. (B) Note whether individual patients also fulfill criteria for amnestic MCI. (C) Characterize patients on the basis of their MRI, CSF, or PET supporting features. The biomarkers could be used as stratification variables in the randomization scheme in order to assess for the possibility of differential drug response based on biomarkers. Patients then need to be reassessed by clinical examination and using the selected episodic memory tests to ensure the reliability and short-term stability of an early AD diagnosis, that patients have not either improved or have not progressed to problems in everyday functioning.

The initial uses of early AD criteria for clinical trials could be considered an enhancement technique. But the decision to employ a pre-dementia, early AD trials strategy should depend on the mechanism of action of the candidate drug, its target and available substrate, and on pre-clinical models for its potential efficacy in humans.

Table 2 lists some recommendations for criteria, methods, outcomes and rationales for their inclusion. If there is an evidence-based hypothesis that a particular biomarker predicts response to the test drug, then that biomarker should be used as a stratification or predictor variable to assess clinical outcomes. Because the biomarkers currently being considered are

state markers and may change over time they should be assessed during the trials course as well.

The need for clinical trials modeling

Conducting AD trials is a large and expensive undertaking. In addition to relying on experts and consensus opinion to plan trials, especially in new areas such as early AD, statistical modeling of proposed trials could be a useful and efficient endeavor. Given the relatively large amount of individual patient data from MCI trials, mild to moderate AD trials, and from databases such as the AD Neuroimaging Initiative, clinical trials simulations can be undertaken. Even with relatively small databases, bootstrapping the very mild subsamples that may correspond to early AD could generate larger simulated patient samples. Samples from the databases of some prevention trials such as ADAPT (11), GEMS (12) and GuidAge (13) could be used as well since many participants have MCI and progress to dementia. Simulating early AD trials using available memory test scores and biomarkers at baseline would provide substantial information for designing future trials and better inform clinical trialists.

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Table 1

Diagnostic criteria for amnestic MCI, new research criteria AD, and probable AD

	Amnestic MCI[1]	**Proposed criteria for early AD**[2]	**Probable AD**[3]
Symptoms and course	Memory complaint reported by patients and informants; of insidious onset and gradual progression	Gradual and progressive change in memory function reported by patients or informants over > 6 months	Progressive worsening of memory and other cognitive functions
Memory impairment	Impaired delayed recall on a paragraph from the Wechsler Memory Scale-R Logical Memory II > 1.5 - 2 SD below education-adjusted norm	Impaired episodic memory: recall deficit that does not improve or normalize with cueing or recognition testing, after effective encoding of information has been controlled	Impaired ability to learn new information or to recall previously learned information
General cognition	Sufficiently preserved so that a diagnosis of AD cannot be made.	Memory impairment can be isolated or associated with other cognitive changes	Dementia confirmed by neuropsychological testing with deficits in ≥ 2 areas of cognition
Functional performance or ADLs	Sufficiently preserved so that an AD diagnosis cannot be made	Not required	Significant problems in everyday functioning
Presence of dementia	Not present	Not required	Established by clinical and neuropsychological examination
MMSE range for trials	24-30	Not specified	Typically, ≤ 26
Clinical brain imaging	CT or MRI to rule out other causes	Requires MRI to assess for vascular lesions	CT or MRI not inconsistent with AD and to rule out other causes
Required supportive features	None required	MTL atrophy (by MRI), or low CSF amyloid-β_{42}, or high CSF t-tau/ p -tau, or reduced glucose metabolism in bilateral temporal parietal regions (PET), or autosomal dominant mutation and FH	None; progressive deterioration of specific cognitive functions, Impaired ADLs, altered patterns of behavior, family history, normal clinical EEG and CSF, cerebral atrophy by CT scans
Age	55 to 90 years	Not specified	40 and 90 years of age
Exclusion criteria	Significant cerebral vascular disease, depression, infarct, infection or focal lesions on CT or MRI, medical or psychiatric disorders that could interfere with study participation	(Selected) sudden onset, gait disturbances, EPS, seizures, behavioral changes, visual field deficits, hemiparesis, other causes for memory and related symptoms, non-AD dementia, depression, cerebrovascular disease, toxic/ metabolic abnormalities, MTL infectious or vascular lesions	Other conditions that cause progressive cognitive decline, including stroke, Parkinson's, and other CNS diseases, or that cause dementia, among them various medical conditions

[1] (4) Petersen et al 2005

[2] (6) modified from DuBois et al 2007

[3] (1) McKhann et al 1984

Table 2

Model criteria and methods for phase II drug development trials for early or prodromal AD

Characteristic	Recommendation	Rationale
Experimental intervention (e.g., drug, antibody, psychotherapeutic, environmental)	Appropriate for MCI, early AD, and non-dementia patients who may not progress or may improve in their symptoms	Expect effectiveness over brief period, should be substantially safe considering participants have few symptoms, slow progression
Participant inclusion criteria	Episodic memory impairment as described (6), repeated memory assessments over several weeks. Trial should include biomarkers as stratification variables.	The need to rely on episodic memory impairment makes diagnosis dependent on actuarial tests. Repeated testing is needed to gain reliability in the diagnosis.
Exclusion criteria	Impairment in activities of daily living or dementia	Without these or similar criteria many would fulfill criteria for probable AD. Operationalization may be difficult
Methods	Multicenter, randomized, double-blinded, placebo-controlled trial. Randomization may be stratified by biomarker or cognitive severity	Needed to control for various known and unknown sources of bias
Durations	Based on expected drug actions. Brief for symptomatic effects, over 2 years for attenuation of progression	Patients with early AD are likely to show less change over time than mild AD patients
Primary outcome	Cognitive outcomes emphasizing memory function, different from tests used for early AD diagnosis	Early AD primarily defined by episodic memory impairment in the absence of many other symptoms
Secondary Outcome	CGIC, self-, informant- and clinician-rated, health-related QoL	Because ADLs are not likely to be impaired, and patients and informants notice impairment, self- and observer-rated global assessments and health-related QoL ratings are needed to assess further clinical significance
Statistics	Analysis based on stratification, repeated assessments of cognitive change over course of trial.	Assess outcomes based on biomarker status; repeated measures of cognitive outcomes to enhance precision and describe drug effects