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Clinical trial methodologies for disease-modifying therapeutic approaches

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Abstract

In recent years, advances in Alzheimer's disease (AD) biomarker research have provided powerful tools to improve trial design. In particular, biomarkers provide powerful methods for the selection of individuals with AD prior to the onset of dementia. Data suggests that neuroimaging biomarkers will be useful as endpoints for trials in very early, even asymptomatic disease, though further work is necessary to establish validity for regulatory purposes.

Keywords

Alzheimer's disease; biomarkers; clinical trials

Overview

AD is not directly observable. The pathological changes, amyloid plaques, neurofibrillary tangles and loss of neurons and synapses, can be observed histopathologically post-mortem but not directly during life. Physical and neurological examinations are usually of limited or no use. The pathology causes progression from an asymptomatic state, through syndromes of mild cognitive impairment to progressive dementia and death. Symptoms cannot be adequately observed during limited clinical encounters; they are generally deduced from interviews with family members.

Biomarkers, objectively measured indicators of the disease, therefore are useful for diagnosis, longitudinal assessment, and evaluation of therapeutic response. They are essential to clinical trial design, particularly for disease-modifying interventions. Biomarkers can provide indirect indications of pathology, brain function and symptomatology, aiding diagnosis and evaluation and providing quantitative assessment of drug effects.

1. Biomarkers for pharmacodynamics mechanism, proof of concept and dose selection

At early stages of clinical drug development, there are specific examples of utility of biochemical biomarkers in establishing target engagement and potentially in dose selection.

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The strongest examples involve the measurement of amyloid-beta (Aβ) peptides to indicate amyloid binding activity or reduction in peptide generation. For example, the activity of solenazumab, a monoclonal anti-amyloid antibody thought to reduce brain amyloid by binding and sequestering amyloid in the peripheral circulation, activity can be assessed by measurement of Aβ peptides in plasma. This method guided initial clinical studies in this program (Siemers, et al., 2010). Measurement of cerebrospinal fluid levels of amyloid peptides can indicate the extent of peptide generation and clearance in the brain, particularly in radiolabeled amino acid infusion studies (Bateman, et al., 2006). This technique supported dose-selection of the gamma secretase inhibitor semagacestat (Bateman, et al., 2009).

2. Biomarkers for subject selection

It is generally estimated that 10–20% of participants in AD trials do not have AD. Without a validated antemortem diagnostic test, and particularly when site expertise may vary substantially, identification of subjects according to standard clinical and psychometric criteria is imperfect, leading to dilution of observable treatment effects on the disease. While not yet done for pivotal trials, addition of a biomarker assessment would be expected to significantly reduce the diagnostic inaccuracy at enrollment. For example, requiring an amyloid signal by amyloid PET scanning or low CSF $A\beta_{42}$ would reduce the number of individuals with cognitive symptoms caused by conditions other than AD enrolling in trials (Aisen, et al., 2010).

As drug development programs move into the pre-dementia population, this issue becomes much more important. Mild cognitive impairment is a heterogeneous clinical syndrome, with 30–40% of individuals amyloid-negative and not destined for Alzheimer dementia. Predictors of progression include APOE genotype, cognitive and clinical scores, imaging measures and cerebrospinal fluid markers; these can be used to enrich a population of individuals with MCI for rapid progression (Aisen, et al., 2010,Petersen, et al., 2010). Particularly for anti-amyloid therapeutic programs, it seems appropriate to select individuals for trials on the basis of amyloid PET imaging and/or low CSF $A\beta_{42}$; presumably, amyloid biomarkers not only enrich for progression, but also for potential response to anti-amyloid intervention.

APOE genotyping can also be used for selecting pre-dementia subjects more likely to progress to Alzheimer dementia. An advantage of this method is its low cost. However, selecting subjects on the basis of genotype excludes the large portion (30–50%) of individuals with AD who do not carry the ε4 allele. Further, it may raise regulatory difficulties in late stage development, as it would be necessary to establish efficacy in ε4 carriers as well as lack of efficacy in non-carriers.

3. Biomarkers as covariates

Within any stage of Alzheimer dementia, biomarkers can be useful in defining the level of impairment, which in turn predicts subsequent decline, thus reducing unexplained variance in the modeling of trajectories of outcome measures. For example, baseline hippocampal volume can contribute to characterization of disease severity in individuals with MCI; including this as a covariate can increase study power with reduction of sample sizes by 5–15% (Aisen, et al., 2010).

4. Biomarkers to support proposed mechanism of action

Regulatory agencies currently require that pivotal trials demonstrate drug efficacy on the primary disease symptoms, and establish the clinical relevance of the effect; this has been

accomplished using co-primary outcomes, specifically a cognitive performance test such as the ADAScog plus a clinician's global impression of change. But regulators may consider treatment effects on biomarkers as indicators of impact on the underlying neurobiology (ie, a disease-modifying effect) rather than just a symptomatic effect. For example, regulators have been willing to assess treatment effect on volumetric MRI measures as evidence that symptomatic benefit reflects an effect on the neurobiology of AD. Since no putative disease-modifier has yet had a successful pivotal trial, there are no examples of this use of biomarker data. In a small Phase II trial, however, it was possible to show an impact of anti-amyloid immunotherapy on brain amyloid-load, though the small size did not allow association of this effect with cognitive performance (Rinne, et al., 2010).

5. Surrogate outcome measures

In Alzheimer dementia and mild cognitive impairment, pivotal trials can rely on standard cognitive and clinical assessments to demonstrate efficacy and clinical relevance. But AD neurobiology, including the accumulation of amyloid in brain, begins many years before symptoms. Consensus holds that anti-amyloid therapy and other disease-modifying interventions may have the greatest clinical impact if initiated at an early stage. Obviously cognitive and clinical assessments are not useful in this early asymptomatic phase of disease. Evaluation of drugs at this stage will require the use of biomarkers as surrogate outcome measures (Aisen, 2009). Candidate biomarkers for this purpose include volumetric MRI and FDG-PET measures, as these seem to be dynamic indicators of disease progression even in the asymptomatic stage (Aisen, et al., 2010,Jack, et al., 2010).

However, regulatory agencies require that treatment effects on such biomarkers be reasonably likely to predict later clinical effects. To establish this validity, it is important that biomarker measures be included at all stages of clinical development. An association between a treatment effect on biomarkers and on cognitive and clinical assessments can be demonstrated at a symptomatic stage of disease will provide support for the validation of the biomarkers at an asymptomatic stage.

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