Report of the task force on designing clinical trials in early (predementia) AD

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ABSTRACT

Background: A large number of promising candidate disease-modifying treatments for Alzheimer disease (AD) continue to advance into phase II and phase III testing. However, most completed trials have failed to demonstrate efficacy, and there is growing concern that methodologic difficulties may contribute to these clinical trial failures. The optimal time to intervene with such treatments is probably in the years prior to the onset of dementia, before the neuropathology has progressed to the advanced stage corresponding to clinical dementia.

Method: An international task force of individuals from academia, industry, nonprofit foundations, and regulatory agencies was convened to discuss optimal trial design in early (predementia) AD.

Results: General consensus was reached on key principles involving the scope of the AD diagnosis, the selection of subjects for trials, outcome measures, and analytical methods.

Conclusion: A consensus has been achieved in support of the testing of candidate treatments in the early (predementia) AD population. *Neurology*® 2011;76:280–286

GLOSSARY

AD = Alzheimer disease; **ADAS-cog** = cognitive subscale of the Alzheimer's Disease Assessment Scale; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **aMCI** = amnestic mild cognitive impairment; **CDR-SB** = Clinical Dementia Rating Scale sum of boxes; **EMA** = European Medicines Agency; **FDA** = Food and Drug Administration; **MCI** = mild cognitive impairment.

It has been over a century since Alois Alzheimer's first report, and a third of a century since Robert Katzman demonstrated the enormous and growing prevalence of Alzheimer disease (AD).[1] Estimates of the impact of world population aging on the scope of the problem continue to grow, with a recent projection of over 100 million cases by 2050.[2] While the past 2 decades have seen the approval of a handful of modestly effective symptomatic treatments for this disease, there is still no available disease-modifying therapy. Highly promising targets have been identified, and, particularly in the area of anti-amyloid interventions, plausible treatments have been developed.[3] Yet efficacy trials have largely disappointed. Indeed, there is now evidence that effective elimination of amyloid plaques may fail to halt fatal progression when administered to individuals with dementia.[4] Consensus has been growing that it may be necessary to initiate effective disease-modifying treatment before the onset of clinical dementia in order to demonstrate efficacy.[5] This would be consistent with the medical approach to other chronic diseases such as diabetes and congestive heart failure, i.e., not waiting until there is significant organ failure before initiating therapy.

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Following earlier efforts to establish consensus viewpoints on AD biomarker research,[6,7] a task force of drug development specialists from academic medical centers, pharmaceutical companies, regulatory agencies, and a nonprofit foundation convened for a 1-day meeting in Las Vegas, Nevada, on October 31, 2009, to discuss the design of clinical trials in early AD. This article summarizes the presentations, discussion, and final consensus of this group.

PRIOR EXPERIENCE IN EARLY AD TRIALS: MCI TRIALS During the past 15 years, there have been a number of efforts to test AD treatments in early symptomatic patients without dementia. In general, these trials have enrolled subjects with amnestic mild cognitive impairment (aMCI), selected using the Petersen criteria.[8] The primary analysis in most of these trials has been a survival-type analysis of time to the onset of dementia. One important reason for this choice of analysis has been that it is readily acceptable to the Food and Drug Administration (FDA).

The mild cognitive impairment (MCI) trials have been largely negative, which may be a reflection of the drugs tested, but the outcomes may also have been related to methodologic issues with the trial design (discussed below). The Alzheimer's Disease Cooperative Study tested vitamin E and donepezil in MCI, and found no delay in diagnosis of AD associated with donepezil or vitamin E over 3 years, though the donepezil group had a reduced likelihood of progression to AD during the first 12 months of treatment.[9] Subsequent trials of rivastigmine,[10] galantamine,[11] and rofecoxib[12] failed to demonstrate delay to progression to dementia.

Operationalization of aMCI and dementia diagnosis has been problematic. Progression from MCI to dementia is indolent; it is challenging to assign a specific time to conversion even with the use of expert consensus review of each case. Inclusion/exclusion criteria utilized in those studies have not identified populations with consistent rates of conversion from aMCI to dementia; in these trials, conversion rates varied from 5% to 15% per year.

One approach to these difficulties is to abandon the distinction between MCI and dementia in describing study populations and endpoints in therapeutic research (without necessarily reducing use of the terms to describe syndromes); that is, expand the diagnosis of AD to include the subset of subjects with MCI who have AD neuropathology and are likely to progress to AD dementia. This approach obviates the need for elaborate and subjective procedures for establishing the time of dementia onset. However, this strategy requires accurate identification of individuals predementia with AD pathology and a very high risk of cognitive and clinical progression. Biomarkers reflecting AD neurobiology offer a potential means of early subject identification. Indeed, there has been a large collaborative effort to define the predictive value and relationships among various candidate biomarkers to aid subject identification and facilitate trial design.

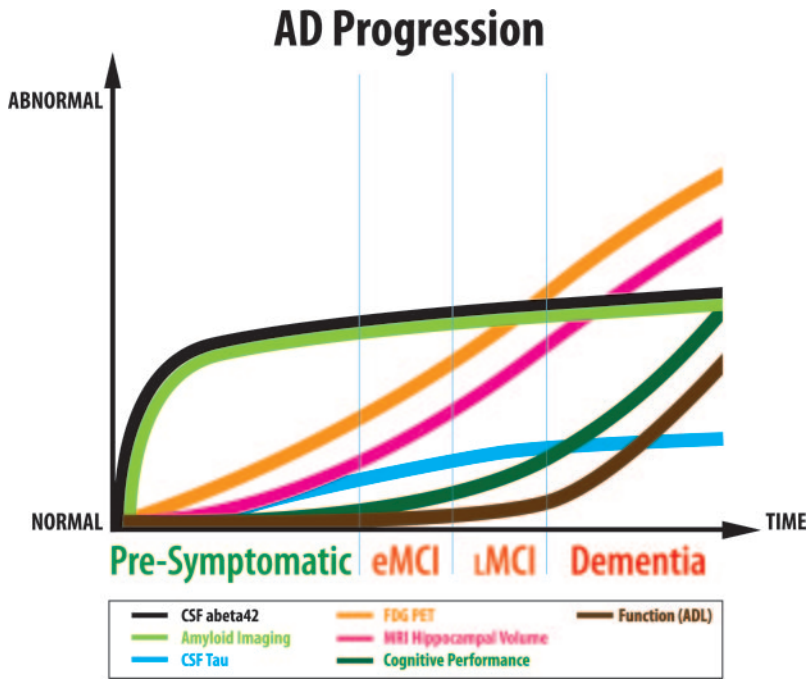
The Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset,[13] all of which is publicly shared, has provided the means to begin mapping the interrelationships among biomarkers and cognitive and clinical disease features, facilitating early AD diagnostic efforts as well as other aspects of trial design. Work by these and other[14] groups have provided information that can be used for furthering trial design in the early, predementia AD population.

The research criteria for AD proposed by Dubois and colleagues[15] are consistent with this strategy. Rather than requiring documentation of the functional impairments that define dementia, these criteria rely on gradual and progressive change in memory reported by patients or informants, objective evidence of episodic memory impairment, and at least one of several imaging or CSF biomarkers that have been associated with an AD diagnosis. These criteria define a population that includes patients both predementia (aMCI) and with dementia on the AD spectrum.

PARTICIPANT SELECTION FOR EARLY AD TRIALS There are a number of candidate selection biomarkers that can be used to increase the likelihood that patients who fulfill MCI criteria have predementia AD (figure). These include genetic markers such as *APOE* genotype,[16] structural imaging markers such as hippocampal, whole brain, or regional cortical atrophy,[17] functional imaging change such as decrease of posterior cingulate activity measured by FDG-PET,[18] as well as CSF biochemical markers such as Aβ42, tau, and phospho-tau,[19] among others.

Longitudinal studies demonstrate the value of biomarkers in selection of subjects with MCI who are more likely to progress in severity. CSF aβ and tau measurements[20,21] or amyloid brain imaging[22] might be particularly interesting selection tools. In addition to selecting subjects likely to progress, they may allow selection of subjects particularly appropriate for specific pharmacodynamic approaches to amyloid or tau dysregulation. Several groups have demonstrated the utility of such an approach. Hansson et al.[23] show excellent stratification of an MCI population into

Figure Hypothetical depiction of biomarker changes during the progression of Alzheimer disease (AD) from onset of pathology through dementia prepared by Alzheimer's Disease Neuroimaging Initiative investigators



Modified and reproduced (with permission) from reference 28. ADL = activities of daily living; MCI = mild cognitive impairment.

groups that will and will not progress to dementia using CSF measurement of tau and Aβ42. Similar results from an independent cohort have been reported by Fagan et al.[20] Although use of such measures can help to select subjects with MCI who are likely to progress within a defined time interval, it remains possible that this approach risks excluding cases who may have AD (clinically indistinguishable though biomarker negative); further study of the issue is necessary.

Most disease-modifying drug development programs in the late stages of clinical development target brain amyloid synthesis or clearance, not only because it is a tractable target but also because of its early derangement in the disease. Thus, a reasonable hypothesis is that selection of trial subjects with biomarker evidence of amyloid accumulation will enroll an enriched population that is most likely to demonstrate the presumed benefits of an anti-amyloid strategy. Amyloid PET imaging and measurement of CSF Aβ42 provide roughly equivalent selection of such subjects.[22] The recent demonstration that an anti-amyloid therapy can reduce amyloid accumulation as measured by PIB-PET[24] further supports this rationale for treatment with an anti-amyloid intervention. It should be noted, however, that selection of early subjects using amyloid biomarkers may be useful for therapeutics targeting mechanisms unrelated to amyloid, and that there are plausible biomarkers unrelated to amyloid (for example, CSF tau levels) that may also be useful for drug development; the amyloid hypothesis remains unproven.

If this suggested approach to subject selection for AD trials gains regulatory acceptance, that is, if subjects with MCI with biomarker evidence of amyloid dysregulation will be considered to have an early stage of AD, then such subjects can be assessed using rate of change of continuous clinical and cognitive measures rather than time to dementia onset. This should provide a gain in power, taking advantage of the greater information captured by such measures and avoiding some pitfalls of survival-type analyses. Although in a sense any criterion that reduces or splits a sample, including biomarker-based selection criteria, could reduce the generalizability of the study results, in this case an amyloid biomarker may be identifying the appropriate target population for treatment (that is, a cognitively impaired sample defined by an etiologic marker, for whom the test drug might be more likely to work).

It is important to note that there are special genetically defined populations at particularly high risk of AD that may be appropriate for prevention or early treatment studies. Examples include presenilin 1 mutation carriers, individuals with Down syndrome, and individuals who are homozygous for the *APOE* ϵ4 allele. Efforts are underway to conduct trials of disease-modifying agents in each of these groups.

STATISTICAL ANALYSIS OF EARLY AD TRIAL DATA Analysis of ADNI data, which includes multiyear follow-up of subjects with aMCI with neuroimaging and biochemical biomarkers as well as cognitive and clinical measures, has allowed evaluation of this approach to subject selection and analysis of disease progression. The 12- or 13-item version of the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog)[25] appears to be the most efficient measure among those assessed in ADNI of longitudinal cognitive change in this group (in terms of the ratio of annual change to the SD of that change), while the Clinical Dementia Rating Scale sum of boxes (CDR-SB)[26] is a powerful indicator of overall clinical progression.[27] Simulations utilizing ADNI data indicate that linear mixed model analysis of ADAS-cog or CDR-SB provides adequate statistical power to detect slowing of progression with manageable group sizes, while analysis based on time to dementia diagnosis requires larger trials (Donohue et al., manuscript submitted). Group sizes are reduced when subjects with aMCI are selected on the basis of

amyloid dysregulation using a cutoff level of CSF Aβ42. Whether the gain in specificity comes at the cost of sensitivity, i.e., excluding subjects who would benefit from the therapy, remains to be seen.

It may also be fruitful to evaluate novel approaches to survival analyses, using more statistically efficient endpoints than time to diagnosis. The CDR-SB, shown by ADNI to be efficient in tracking progression of subjects with MCI (in terms of annual change divided by SD of change), provides a candidate endpoint for such analyses. Since each CDR box point (or, in the case of the memory domain, half point) represents clinically notable decline in a primary domain of AD symptomatology, reduction by 0.5 or 1 on the mean change in CDR-SB would seem to capture both efficacy and clinical relevance (alternatively, a global clinical impression of change measure might be used to demonstrate clinical relevance). The CDR-SB may also be used in responder analyses.

PHARMACEUTICAL COMPANY VIEWS Company representatives were encouraged that it may be feasible to study anti–amyloid disease-modifying drugs and perhaps other strategies at predementia stages of AD at which they may be most effective. They agreed that the analyses of ADNI data support the use of LMM analyses of continuous measures in preference to previously used time-to-dementia analyses. They remained concerned, however, that efficacy trials will need to be large and long, a formidable barrier to drug development. They point out, for example, that regulatory agencies typically favor pivotal studies with multiple active arms (to allow dose-response assessment) and that 90% power is considered appropriate. Further, it may be unrealistic to expect effect sizes as large as 40%. Moreover, there is a perceived need to include a more liberal estimate of endpoint variability in power calculations than has been seen in focused clinical trial consortia such as ADNI; that is, ADNI sites may not be representative of the international sites participating in current AD drug development programs. Drug companies continue to seek both enrichment strategies for subject inclusion and more efficient tools for the development of disease modifiers. While pharmacodynamic markers, for example CSF measurement of Aβ42 for secretase inhibitors, may be very useful for confirmation of target engagement and dose selection, the uncertain translation of biomarker movement into eventual cognitive and clinical benefits leaves substantial risk to this strategy. Robust surrogate markers and acceptance of assessment of clinical benefit using continuous or ordinal measures such as the CDR-SB as a single primary endpoint would be enormously useful.

REGULATORY VIEWS Dr. Russell Katz from the US FDA and Dr. Cristina Sampaio from the European Medicines Agency (EMA) provided unofficial comments on the meeting attendees' discussion of early AD trial design considerations.

The notion of extending the diagnosis of AD to the predementia population, utilizing aMCI criteria plus 1 or 2 biomarkers or similar implementations of the Dubois research criteria, did not raise any particular concerns, as long as the criteria were consistent with expert opinion. Trial designs could then be similar to those currently accepted for the approval of treatments for AD dementia. Most likely, long trial durations (at least 18–24 months) will be required for medications that slow the rate of symptom progression. (Conversely, to evaluate the impact of treatments on potential surrogate neuroimaging endpoints, power is substantially greater and shorter trial durations are feasible.) Drs. Katz and Sampaio encouraged the idea that predementia AD trials and mild to moderate AD trials could be jointly submitted for regulatory consideration of a claim for the treatment of AD.

Primary analyses can utilize change on continuous outcome measures. As one illustrative example, a broad measure of cognition such as the ADAS-cog-12 plus the CDR-SB as coprimary outcomes can demonstrate benefit on primary symptoms and clinical relevance. While coprimary measures have proven feasible in AD dementia trials, in principle a single outcome measure such as the CDR-SB might adequately capture primary symptoms and clinical relevance. For the EMA, an approach to use a single primary endpoint would require a formal application by academic experts; a mechanism for such application is available.

The FDA generally recommends inclusion of more than one dose of medication in pivotal trials, so that the safest effective dose can be established. But this is not an absolute requirement. Particularly when there are no substantial toxicity concerns, a pivotal trial might compare a single dose to placebo.

Drs. Katz and Sampaio share the view that disease-modifying treatments might be most effective at the earliest stage of disease, and that it therefore may be advisable to study drugs at a presymptomatic phase of AD. If expert consensus is established in support of specific diagnosis of AD at a presymptomatic stage, and if a surrogate endpoint can be validated against clinically relevant endpoints at a later

(symptomatic) stage, such a surrogate might reasonably be utilized in presymptomatic subjects.

CONCLUSIONS: TRIAL DESIGN IN EARLY AD

This task force on early AD trial design established substantial consensus on key issues.

1. The optimal stage for efficacy trials of disease-modifying interventions may be prior to dementia onset.
2. The selection of AD cases can be extended to patients predementia using amnestic MCI criteria plus one or more biomarkers.
3. CSF Aβ42 or amyloid PET imaging may be optimal biomarkers for selecting subjects for anti-amyloid interventions.
4. Analysis of continuous clinical and cognitive measures is likely to be more efficient than survival analysis.
5. It may be reasonable and acceptable to use a single primary outcome measure to establish both benefit on primary disease symptoms and clinical relevance.
6. Validation of surrogate endpoints in symptomatic patients may eventually provide a mechanism for developing treatments at the asymptomatic stage of AD.

Much remains to be done to facilitate early AD trials. Cognitive outcome measures can be improved, for example using item-level analyses of existing instruments to construct better tools. Various clinical measures, perhaps based on the CDR or an activities of daily living scale, also warrant further exploration for use as endpoints or continuous outcome measures. In addition to achieving consensus validity regarding the diagnosis of early AD, it is essential that the community of experts establish guidelines for the clinical relevance of treatment effects in this population. The methodology developed for early AD studies, including the utilization of biomarkers, can be expected to provide trial design advances applicable to the dementia stages of AD; development programs involving multiple disease stages will provide the best guidance for clinical use of new treatments across the disease spectrum.

While AD drug development continues to face high barriers and risks, these points of agreement provide a new path that may improve the likelihood of success in bringing the next generation of treatments to the clinic. Continued cooperation among companies, academic investigators, nonprofit organizations, and government regulators will facilitate the optimization of trial designs.

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DISCLOSURE

Dr. Aisen serves on a scientific advisory board for NeuroPhage; serves on the editorial advisory board of *Alzheimer's Research & Therapy*; serves as a consultant to Elan Corporation, Wyeth, Eisai Inc., Schering-Plough Corp., Bristol-Myers Squibb, Eli Lilly and Company, NeuroPhage, Merck & Co., Roche, Amgen, Genentech, Inc., Abbott, Pfizer Inc, Novartis, Bayer Schering Pharma, Medivation, Inc., Daiichi Sankyo, Astellas Pharma Inc., Dainippon Sumitomo Pharma Company Limited, BioMarin Pharmaceutical Inc., Solvay Pharmaceuticals, Inc., Otsuka Pharmaceutical Co., Ltd., AstraZeneca, and Janssen; receives research support from Pfizer Inc, Baxter International Inc., and the NIH (NIA); and has received stock options from Medivation, Inc. and NeuroPhage. Dr. Andrieu serves on scientific advisory boards for Ipsen, Eisai Inc., Pierre Fabre Laboratories, Pfizer Inc, and Eli Lilly and Company; has received funding for travel or speaker honoraria from Eisai Inc., Lundbeck Inc., Ipsen, Pierre Fabre Laboratories, Nestlé, Pfizer Inc, and Novartis; serves on the editorial board of the *Journal of Alzheimer's Disease*; and receives research support from INSERM. Dr. Sampaio reports no disclosures. Dr. Carillo serves on scientific advisory boards for the Alzheimer's Association and Genworth Insurance. Dr. Khachaturian serves on scientific advisory boards and as consultant for the Alzheimer's Association Toyama Chemical Co., Ltd., ExonHit Therapeutics; has received funding for travel and speaker honoraria from the Alzheimer's Association; and serves as Editor-in-Chief for *Alzheimer's & Dementia*. Dr. Dubois reports no disclosures. Dr. Feldman has served on scientific advisory boards for Bristol-Myers Squibb, Elan Corporation, Glia Scientific Communication, Janssen, Pfizer Inc, and Wyeth; has received funding for travel or speaker honoraria from the Academy of Healthcare Education, Alpha Plus, AstraZeneca, Cadmus Medea Inc., Eisai Inc., Glia Scientific Communication, Janssen, Lundbeck Inc., Medical DecisionPoint, LLC, InforMed Direct Plc, MedPlan Communications Inc., Novartis, and Pfizer Inc; serves on editorial advisory boards for *Dementia and Geriatric Cognitive Disorders* and the *Journal of Neurological Sciences*; may accrue revenue on a patent re: Detecting and Treating Dementia; receives publishing royalties for *Atlas of Alzheimer's Disease* (Informa Health, 2007); is a full-time employee of Bristol-Myers Squibb; has served as a consultant for Servier; served as a paid member of steering committees of clinical trials sponsored by Elan Corporation and Pfizer Inc; has received research support from Elan Corporation, Lundbeck Inc., Myriad Genetics, Inc., Eisai Inc., Pfizer Inc, Eli Lilly and Company, Janssen, the Canadian Institutes of Health Research, Pacific Alzheimer Research Foundation, and the NIH; holds stock and stock options in Bristol-Myers Squibb; and has held stock in BioMarin Pharmaceutical Inc. Dr. Petersen serves on scientific advisory boards for Elan Corporation, Wyeth, and GE Healthcare; receives publishing royalties for *Mild Cognitive Impairment* (Oxford University Press, 2003); and receives research support from the NIH (NIA). Dr. Siemers is a full-time employee of Eli Lilly and Company. Dr. Doody has received funding for travel from and served on scientific advisory boards or as a consultant for Medivation, Inc., Sonexa Therapeutics, Inc., Zapaq Inc./CoMentis, Inc./Athenagen, Inc./Astellas Pharma Inc., Debiopharm Group, and GlaxoSmithKline, AC Immune SA, Avanir Pharmaceuticals, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, ExonHit Therapeutics, Fujisawa Pharmaceutical Company, Ltd./Astellas Pharma Inc., Genentech, Inc., Eli Lilly and Company, Merck Serono, Noven Pharmaceuticals, Inc., Ocera Therapeutics, Pfizer Inc, Prana Biotechnology Limited, sanofi-aventis, Schering-Plough Corp., Sepracor Inc., Suven Life Sciences Ltd., Transition Therapeutics Inc., and Varinel; serves on the editorial boards of *Alzheimer's Disease and Associated Disorders*, *Dementia and Geriatric Cognitive Disorders*, and *BioMed Central: Alzheimer's Research and Therapy*; is listed as an inventor on a patent re: a biomarker algorithm to diagnose AD invented by the Texas Alzhei-

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