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Perspectives

Optimal design of clinical trials for drugs designed to slow the course of Alzheimer's disease

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Abstract Compounds now in clinical development are hypothesized to slow the clinical progression and pathogenesis of Alzheimer's disease (AD) by their effects to diminish production, increase clearance, or decrease aggregation of amyloid β protein. Options for investigating the effects of these and other drugs on clinical progression and pathogenesis of AD were examined at a conference that included: (1) a review of experimental methods used to investigate disease-modifying drugs for multiple sclerosis, rheumatoid arthritis, cardiovascular disease, and osteoporosis; (2) discussion of possible study designs and outcome measures for trials in patients with AD; and (3) discussion of biomarkers available for AD. There is no uniformly best way to investigate a drug's impact on AD progression but characteristics of studies supportive of a disease-slowing effect can be specified. Relevant clinical outcomes in drug-treated patients versus placebo-treated patients should be compared over at least 1 and possibly as long as 2 years with biomarkers reflective of pathogenesis and of the drug's mechanistic effects measured concurrently.

Keywords: Trial design; Disease modification; Biomarkers; Drug treatment

1. Background

Advances in understanding of the pathogenesis and genetic risk factors for Alzheimer's disease (AD) have led to the discovery of drug candidates that could potentially slow the pathogenesis of AD, decrease the progressive loss of neurons associated with AD, and improve patient outcomes. Both the mechanism of action and the clinical benefit that might be derived from these disease-modifying therapies are different from those associated with currently available therapies designed to lessen disease symptoms by augmenting neurotransmitter activity. Consequently, the clinical trials supporting the registration and use of these disease-modifying drugs would be different from those supporting symptomatic therapies. Currently, there is no general agreement among investigators about how these newer therapies should be tested. To help inform the discussion of study design options for these drugs, the Alzheimer's Association Research Roundtable sponsored a workshop held in Washington, DC on November 23 and 24, 2005. Present at the symposium were researchers from academic medicine, the National Institute on Aging (NIA), the pharmaceutical industry, regulatory staff from the U.S. Food and Drug Administration (FDA), and representatives of the Alzheimer's Association including caregivers and patients. The meeting included presentations by clinical researchers from other therapeutic areas in which drugs with disease-modifying properties have been investigated as well as presentations by AD researchers with expertise in trial design, clinical outcome assessment, and biomarkers. The overall aim of the meeting was to identify both the strengths and limitations of the possible study designs, available clinical outcome measures, and biomarkers for investigating these newer treatment agents. This report provides a perspective on the data, issues, and discussion topics that emerged from that meeting.

The impetus for the meeting is that several commercial sponsors now have clinical drug candidates that are directed toward biologic targets thought to be part of the primary

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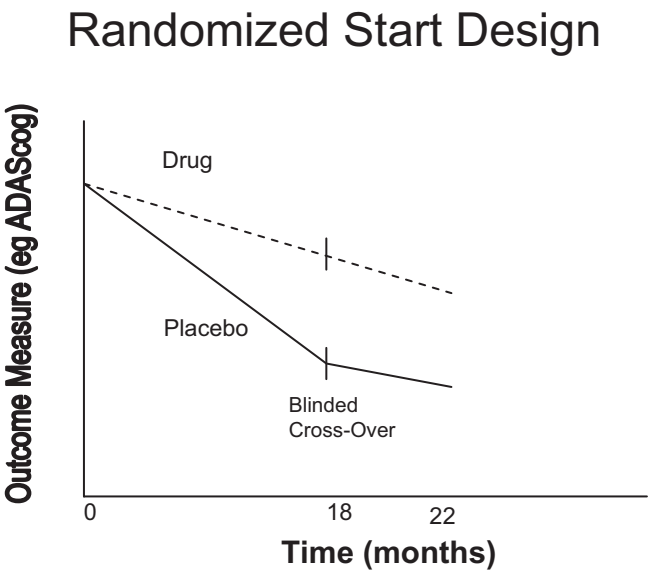

Fig. 1. Graph shows hypothetical effects on a drug that slows the clinical progression of Alzheimer's disease investigated over an 18-month treatment period versus placebo with a blinded follow-up of placebo patients during a 4-month delayed-start period. Cognitive function as measured by the ADAS-Cog declines more slowly in drug-treated patients than in those receiving placebo. When placebo-treated patients are given active drug from month 18 to month 22, their rate of decline appears to slow, but cognitive function in these patients remains below that of patients receiving continuous treatment.

pathology of AD. In particular there are several clinical candidates designed to slow the production, decrease the aggregation, or enhance the clearance of amyloid β protein in brain. A substantial body of genetic, neuropathologic, and clinical evidence [1] implicates this protein in the pathogenesis of AD. Although these anti-amyloid therapies are the most advanced of the potential disease-modifying therapies for AD, the perspectives described in this report are intended to be relevant to the development of any therapy directed at the underlying pathogenesis of AD, including antioxidants, drugs directed at neurofibrillary tangles, or other biologic processes leading to neuronal dysfunction and clinical symptoms [2].

This report gives a high level overview of the way disease modification has been approached in other therapeutic areas and then provides a discussion of key issues involved in the development and testing of potential disease modifying therapies for AD. Although there is no established way of demonstrating a disease-modifying effect of a therapy, the drugs referred to by this name are thought to share certain characteristics. First is that the therapeutic benefits of proposed disease-modifying therapies are not short term or short lived; rather, these drugs are expected to have a relatively persistent and increasingly positive effect on the long-term course of chronic disease. This hypothesized effect is depicted in the left hand portion of Fig. 1 with clinical course of symptoms over time measured by some relevant outcome measure such as the Alzheimer's Disease Assessment Scale-Cognitive Portion (ADAS-Cog). Given the natural history of symptom progression in AD, the separation of drug-treated patients versus placebo-treated patients shown in Fig. 1 could probably only be observed over periods of greater than 1 year. A second characteristic of proposed disease-modifying therapies is the hypothesized link between the effect of the drug on some aspect of disease pathogenesis and observed clinical benefit, a link supported by biomarker data from the clinical trials. Investigations of the clinical utility of any disease-modifying therapy for AD would require studies over relatively long-term periods relative to placebo or other comparator. Claims that long-term clinical benefit is related to a drug effect on a specific aspect of pathogenesis would require supportive data showing a link between clinical measures and action of the drug on relevant biomarkers.

2. Symptomatic and Disease-Modifying Effects in Clinical Trials: Examples from Other Therapeutic Areas

Novel drugs with disease-modifying properties have been evaluated and approved in several therapeutic areas but not for AD or other type of dementing illness. The standards used to support registration and use of drugs currently approved for the treatment of AD are well known [3–5]. Each of the approved drugs has been shown to improve both cognition and global clinical function over periods of 3 to 6 months relative to placebo in double-blind trials [6,7]. Cognition is measured by a performance-based test in which patients are asked to complete tasks taxing learning, memory, language, judgment, praxis, and other cognitive abilities known to be impaired in AD; the test most widely used in clinical trials of antidementia drugs is the cognitive portion of the ADAS-Cog [8]. The coprimary clinical measure in these trials is usually a clinician-rated global assessment such as the Clinician's Interview-Based Assessment of Change (CIBIC) [9] or a scale that provides a quantitative assessment of the patient's ability to perform activities of daily living (ADL) [10]. Both measures, the CIBIC and ADL, are completed by trained clinical raters with input from both the patient and a caregiver who has frequent contact with the patient.

There is no adequate definition of a disease-modifying treatment that is universally applicable. Current discussions of disease modification in AD do not contemplate 2 of the potential objectives of drug treatment for AD, namely, prevention and cure. The investigations required to show either primary prevention of AD or cure of AD are, although difficult to perform in practice, fairly straightforward to design. The aims of most of the potential disease-modifying drugs for AD currently in development are more modest, and the studies under discussion are designed to investigate claims other than prevention or cure. Specifically, most anti-amyloid drugs are being studied for their possible long-

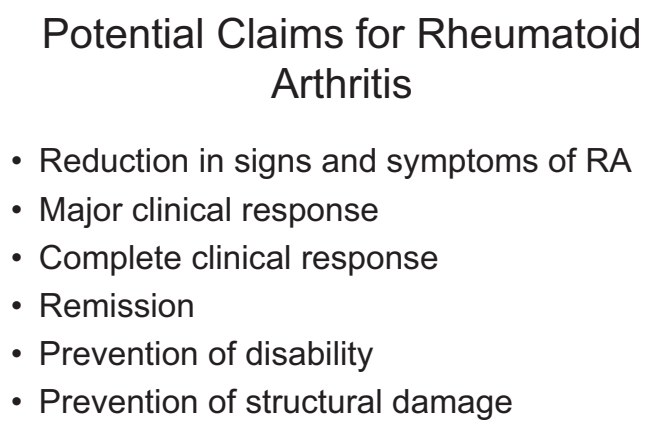

Fig. 2. A list of potential claims for drugs used to treat rheumatoid arthritis. Note that each type of claim requires different supporting clinical data and some require biomarker data as well. (Courtesy of Marc Hochberg, MD.)

term benefit on symptoms of disease and on the progression of underlying pathogenesis in patients with diagnosed AD.

2.1. Disease modification in multiple sclerosis

Some of the drugs available for the treatment of multiple sclerosis such as type 1 interferons and glatiramer acetate, are thought to have disease-modifying effects as well as effects on symptoms of disease. The effects of these drugs in patients with multiple sclerosis (MS) have been evaluated in randomized, placebo-controlled clinical trials with treatment for 1 to 2 years [11]. Clinical measures, primarily the Expanded Disability Status Scale (EDSS), and biomarkers, primarily magnetic resonance imaging (MRI) visible lesions, have been used to evaluate the currently available therapies. Psychometric limitations of the EDSS have prompted clinical investigators to develop newer, more sensitive and widely applicable clinical measures [12] such as the Multiple Sclerosis Functional Composite (MSFC). MRI visible lesions correlate poorly with clinical outcomes in MS; hence, there is considerable research investigating other brain imaging measures that can provide evidence of relevant drug effects, including effects on brain atrophy. Longitudinal relationships among clinical and imaging biomarkers for MS progression are not precise with only low correlations between progression of disability and MRI visible lesions [12]. Also, the current standard clinical assessment (EDSS) correlates poorly with brain atrophy at follow-up over a clinically relevant period; the correlation with a more refined clinical measure (MSFC) is somewhat better [12]. Although there are limitations to both the clinical and imaging biomarkers used to evaluate treatments for MS, the data validating these measures are sufficiently robust to support their routine use in the evaluation of new therapies. Refinements in both clinical and biomarkers of drug effect are still needed to drive development and testing of new therapies for MS.

2.2. Disease modification in rheumatoid arthritis

Several therapies are approved for this chronic condition, and labeling varies substantially to reflect the range of clinical and biomarker effects that have been shown for each therapy (Fig. 2) Nonsteroidal anti-inflammatory drugs (NSAIDS) are used routinely for management of disease symptoms, whereas disease-modifying antirheumatic drugs (DMARDs) are aimed at different levels of the underlying pathophysiology of rheumatoid arthritis (RA) and provide additive, or possibly synergistic, efficacy. Examples of DMARDs are methotrexate [13] and newer biologic agents such as tumor necrosis factor (TNF)-α antagonists [14]. Relevant clinical parameters measured to assess efficacy include signs and symptoms of disease, disability, and extent of therapeutic response [15]; use of these measures can lead to specific claims including major clinical response, complete clinical response, remission, and prevention of disability. Radiographic measures reflecting structural damage associated with RA can also be used to support claims of disease modification, with the provision that positive radiologic changes are observed over a 1-year treatment period. No single outcome measure can substitute for others, however, and labeling as well as clinical use depend on the specific types of outcome seen and the period over which that outcome is observed.

2.3. Disease modification in cardiovascular disease

Evaluation of drugs for the treatment of cardiovascular disease routinely involves measurement of both clinical endpoints and biomarkers that are mechanistically related to the underlying pathogenesis of disease. The utility of serum cholesterol as a surrogate marker for clinical efficacy in cardiovascular disease is supported by a very large volume

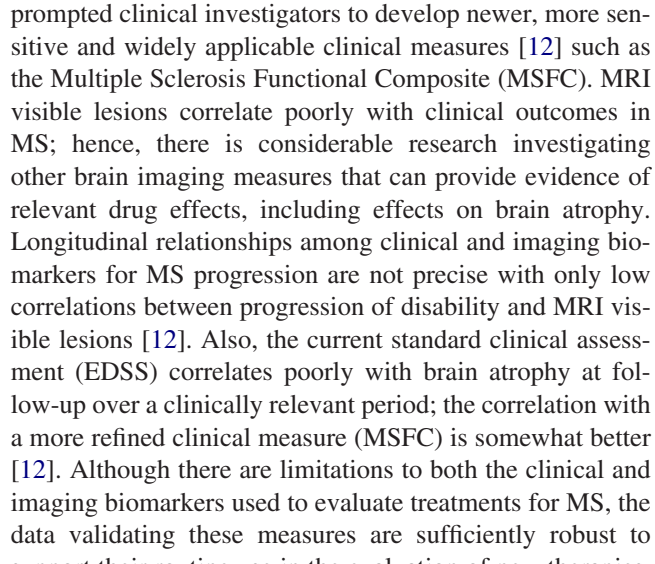

Fig. 3. A list of potential considerations for trials of drugs used to treat cardiovascular disease. Note that each of the different trial types involves a specific patient group, study design, supporting biomarker data, and clinical indication. (Courtesy of Gregg Larson, PhD.)

of data from epidemiologic studies, animal models, mechanistic studies, and many clinical trials showing a predictable relationship of serum cholesterol to morbidity and mortality owing to cardiovascular disease in primary prevention, secondary prevention, and acute coronary syndrome trials [16]. Figure 3 presents some of the considerations behind studies done to support current and future therapies for cardiovascular (CV) disease. Despite the success in developing both therapies and biomarkers for cardiovascular risk, the search for new therapies in this area is facing significant challenges. Serum cholesterol accounts for only a portion of the entire risk for CV disease and thus, other biomarkers of risk are under investigation [17]. Additionally, new cholesterol-lowering regimens are being evaluated against the current standard of care so that any additional clinical benefit of further lipid lowering will require renewed examination of lipid/cardiovascular risk relationships in extremely large patient populations [18].

2.4. Disease modification in osteoporosis

Drugs have been approved for both the treatment and for the prevention of osteoporosis, and some agents have both indications [19]. The primary clinical endpoint for these agents is a reduction in the risk of vertebral fracture, but several secondary endpoints including nonvertebral fractures and quality of life are examined in many trials. Bone Mass Total (BMT), Bone Mineral Density (BMD), and biochemical markers of bone resorption are useful biomarkers of drug effects, but their relationship to clinical outcomes is not uniformly linear [20] and not always predictable. Long-term clinical benefits coupled with positive effects on BMD are characteristic of therapies for the prevention of osteoporosis [21], whereas biomarker effects are less important for symptomatic drugs. Randomized, placebo-controlled trials with clinical endpoints remain the gold standard in osteoporosis research, whereas biomarkers are helpful in understanding mechanism in secondary indications and in bridging studies.

2.5. Clinical and biomarker data needed to support disease modification

Drugs designed to slow or modify the pathogenesis of a chronic disease with a clinical course lasting for several years are difficult to study. The clinical benefit of some drugs used to treat the chronic diseases described above are only discernable when drug-treated patients are compared with placebo-treated patients over periods of at least a year and often, as is the case in CV disease and osteoporosis, over much longer periods of time. Additionally, if the clinical benefit is evident only in the lessened likelihood of some relatively rare events such as fractures or cardiovascular events, the number of patients required to show a clinical benefit owing to drug may be very large, possibly in the thousands. Long clinical trials involving drugs with no immediate symptomatic benefit also entail the risk of high subject dropout rates and low treatment compliance. There is a tendency in the face of such difficulties to give

Compounds Being Tested as Disease-Modifying Drugs for AD

Compound	Sponsor	Proposed Mechanism
AB001	Elan Pharmaceuticals	Monoclonal N-Terminal Antibody to Aβ
LY450139	Lilly Pharmaceuticals	Functional γ-Secretase Inhibitor
Alzemed	Neurochem, Inc.	Promote Clearance and Reduce Fibrilization of Aβ
R-flurbuprophen	Myriad Pharmaceuticals	Functional γ-secretase Modulator

Fig. 4. A partial list of potential disease-modifying drugs currently in clinical development for Alzheimer's disease. All of these drugs are thought to diminish the pathogenic effects of amyloid β protein.

credence to biomarkers that show an effect of drug that is either more immediate or more reliably than is the effect on clinical measures. The difficulties that can arise from too great a reliance on biomarkers, however, have been well documented [22]. There are many examples of cases in which a biomarker thought to be related to disease pathogenesis responded in an apparently positive way to a new treatment when clinical outcomes were either unaffected or actually changed in an unexpected direction. One recent example from the AD field was observed in a trial involving active immunization against the amyloid β protein with AN-1792. The study was designed to measure the effects of active immunization on the progression of clinical symptoms and effects on brain atrophy as measured by volumetric MRI. Among patients who showed a substantial immunologic response, there was some evidence for slowing of cognitive decline but, contrary to expectations, a decrease in brain volume [23].

Although there is no adequate substitute for showing the impact of a new drug on relevant clinical parameters over clinically relevant time periods, the use of biomarkers can affect both regulatory decisions and clinical practice as shown by the examples reviewed at the symposium. Biomarkers that have some relationship to disease pathogenesis but are poorly correlated with clinical outcomes can still be used to help clinicians understand the drug's mechanism of action and to support the claim of an effect on disease pathogenesis. The measurement of brain lesions by MRI in the evaluation of drugs for MS and the measurement of BMD in the evaluation of treatments for osteoporosis are examples. Drugs for the treatment of RA are differentiated in part by the extent to which their effects can be measured by radiographic measures of structural damage. In the case of drugs for CV disease, lipid measures serve several functions. They are a way of assessing risk, a way of showing

the mechanism of drug action, and are surrogates for risk reduction. Biomarkers for AD could eventually serve one or more of these functions in support of labeling or in clinical practice depending on the data presented to support such use.

3. Ongoing Studies of Disease-Modifying Agents in AD

Some of the drugs currently in clinical development for slowing the progression of AD are presented in Fig. 4. AB001 is a monoclonal antibody directed toward the N-terminal of Aβ. Preclinical data suggest that monoclonal antibodies to Aβ can sequester this protein in the periphery where it is eliminated, thereby reducing levels of soluble Aβ in brain [24]. AB001 is a follow-up compound to AN-1792, which was designed to stimulate the production of antibodies to Aβ 1-42. AN-1792 administration was associated with encephalitis in 18 of 298 patients with mild to moderate AD given active immunization in a planned 24-month comparison with placebo [25]. The newer study of AB001 is similar in design to the study of AN-1792. Patients are assigned randomly to AB001 or placebo and are to be followed up with clinical measures of cognition and function for 18 months. At regular intervals patients also receive MRI scans of their brain to enable brain volumetric measures. Additionally, a positron emission tomographic (PET) measure of brain metabolic activity and cerebrospinal fluid (CSF) measures of tau protein and phosphorylated tau are obtained.

Compound LY 450139 is a γ-secretase inhibitor being developed by Eli Lilly and Company. Gamma-secretase is one of the enzymes required for the production of Aβ protein from the amyloid precursor protein (APP) [1]. Gamma secretase inhibitors have been shown to decrease the production of Aβ centrally [26] and decrease formation of brain amyloid plaques in a mouse model genetically engineered to overproduce human Aβ. When given to humans, the γ-secretase inhibitor produces a dose-dependent reduction in plasma Aβ similar in magnitude to that observed in transgenic mice [27]. The compound will enter clinical trials versus placebo over 1 to 2 years with clinical and biomarker measures similar to those described for the compounds from Elan.

Alzemed is a CNS active nonimmunologic binding agent being developed by Neurochem Inc. This is a low-molecular-weight compound designed to reduce fibrilization and promote clearance of Aβ [28]. The compound reduces Aβ toxicity in cell models and, in a 12-week study of 58 AD patients assigned to one of three doses of Alzemed or placebo, was associated with some reduction in CSF Aβ [28]. Two doses of Alzemed are now being compared with placebo in a double-blind study of more than 1,000 patients with AD treated for 18 months. Clinical outcome measures are the cognitive portion of the ADAS-Cog [5], and the Clinical Dementia Rating (CDR) [29] along with MRI brain volumetric measurements and CSF Aβ measures.

R-flurbiprofen is a functional γ-secretase modulator that is related to a class of nonsteroidal anti-inflammatory drugs. R-flurbiprofen has been shown to lower Aβ both in vitro and in animal models [30]. A Phase II study in patients with mild to moderate AD treated for 12 months found an effect to improve scores on the ADAS-Cog and a functional measure only in patients with mild AD with high blood levels of drug. A Phase III study in mild AD patients will compare a high-dose versus placebo over 12 months with clinical outcome measured by the ADAS-Cog, a functional assessment and the CDR. Biomarkers will also be evaluated.

4. Strategic Issues in Clinical Development of Disease-Modifying Agents for AD

4.1. Study designs to investigate disease modification

There is no study design that can unambiguously determine that a drug has an effect to slow the progression of AD, but there are some design features that would be at least consistent with such an effect. More importantly, those designs could help clarify the clinical implications of a disease-modifying effect in that they would show the consequences of delaying or interrupting treatment. In most clinical drug trials, patients are assigned randomly to receive either active drug or placebo, and clinical outcomes in both groups are measured at regular intervals for a clinically relevant period. The left-hand portion of Fig. 1 shows hypothetical results that might be obtained with a clinically effective drug for AD evaluated in this way. Using traditional clinical measures of cognition and disability, a disease-modifying effect would most likely manifest itself as a change in the slope of a line showing cognitive or functional change (usually decline) over an extended period of at least 1 and preferably 2 years.

Modifications to this standard design that might help show a drug effect on the underlying pathogenesis of the disease have been proposed and include the randomized withdrawal design and the randomized start design [31]. The latter is shown in the right hand part of Fig. 1, with patients initially receiving placebo randomly, under blinded conditions beginning to receive active drug. Assuming that the drug being tested had an effect to slow disease pathogenesis, patients started on active drug after an extended period on placebo would not match the therapeutic response in patients on continuous treatment. A design of this kind has been used recently to study a new treatment for Parkinson's disease [32]. Potential ambiguities in the interpretation of randomized start data result from psychometric properties of the outcome measure, differences in dropout rates between treatment groups, and uncertainty about the length of time required for a newly introduced treatment to have its maximal effect. Most clinical outcome measures do not show linear change over the entire range of disease severity,

so psychometric properties of scales like the ADAS-Cog alone might make comparison of drug response at baseline and after several months on placebo difficult to compare directly [33]. It is likely that the dropout rate in drug and placebo groups during the initial double-blind period would not be the same, and the effect of differential dropout on the magnitude of treatment response during the randomized start period would be difficult to evaluate. Lastly, the time needed to achieve full benefit of a symptomatic drug is often unknown and, thus, even a randomized start period of 1 to 2 months might not be enough time to allow the formerly placebo-treated patients to catch up to those continuously on drug. Despite these limitations, continued separation of clinical outcomes for patients on continuous drug treatment when compared with patients given active treatment only after several months on placebo would provide strong suggestive evidence that the drug had an enduring effect on disease pathogenesis.

Given these considerations, it is unlikely that a study using clinical outcome measures alone could unambiguously differentiate drug effects on underlying pathogenesis from effects that are purely symptomatic. To determine whether a drug has clinical benefit, such a differentiation is not necessary. That is, if administration of a drug to certain patients with AD under well-specified conditions leads to improvements in cognition and function, then that drug is a useful treatment regardless of how the drug works. Statements about clinical efficacy that are devoid of mechanism, however, are not likely to help build a cumulative body of knowledge about how to treat a complex disease such as AD. As indicated by the examples reviewed above, biomarkers can, under some circumstances, be used to indicate that a drug's clinical effects are a result of effects on underlying pathogenesis.

4.2. Biochemical and brain imaging biomarkers in studies of disease modification

A recent conference report presented a very good review of the data relevant to the use of both biochemical and brain imaging measures as biomarkers for presymptomatic AD[34]. Essentially, that review concluded that, although several biochemical and brain imaging markers show some potential as aids to early diagnosis, none has been fully validated, and all require much more evaluation. For current purposes these biomarkers must be considered for their potential to reveal scientifically and clinically relevant information about the effects of proposed drug treatments for AD. As noted above in the review of biomarkers used in other therapeutic areas, very few biomarkers are understood well enough to serve as surrogate markers for clinical efficacy. More realistically, biomarkers might serve to provide either evidence of a drug effect on a specific physiologic target or of a drug effect on some measure correlated with disease progression [35].

Potential biochemical biomarkers for AD trials include several that can be measured in CSF and in blood. Those that appear to be most promising are Aβ, tau, and hyperphosphorylated tau. Recent studies suggest that persons in the very earliest, presymptomatic phase of AD have lower concentrations of Aβ and higher concentrations of tau in CSF [36]; the low levels of Aβ are thought to result from increased deposition of Aβ in brain, whereas the increased levels of tau may reflect neuronal degeneration. Elevated Aβ in plasma is a relatively weak risk factor for AD [37], but plasma Aβ measures do not correlate well with disease progression. The degree to which plasma and CSF measures of Aβ, tau, and hyperphosphorylated tau reflect concentrations in brain, is largely unknown. As a result, these plasma and CSF measures cannot be used as measures of drug effects on disease pathogenesis. They might, however, be used to determine whether a drug has some effect on biochemical measures thought to be relevant to pathogenesis.

Several types of brain imaging measures are correlated with the degenerative processes of AD, but there is no measure that directly reflects pathogenesis. Volumetric brain measures derived from MRI scans show group differences between patients with AD and controls, and there is a progressive loss of brain volume with progression of AD [38]. Brain metabolic activity as measured by fluorodeoxyglucose (FDG) PET scans is also diminished in AD and in patients with mild cognitive impairment (MCI) [39], a state that is often a prodrome of AD [40]. The loss of metabolic activity measured by FDG-PET is progressive with disease, but neither brain volume loss nor diminished metabolic activity is specific to AD, and neither has been shown to correlate with treatment response. Recently, radioligands for deposited amyloid and, possibly, other neuropathologic features of AD have been developed [41,42]. Images with these ligands differentiate AD patients and some MCI patients from normal controls, and longitudinal studies are ongoing.

None of the imaging markers is satisfactory as a surrogate for use in clinical trials but might help in describing the biological correlates of drug effects in disease-modifying trials. In particular, volumetric MRI could be used to determine whether a drug changed the rate of brain volume loss associated with AD, FDG-PET could be used to determine whether a drug changed the rate at which brain metabolic activity is lost with AD, and the newer amyloid imaging techniques could be used to determine whether a drug changed the rate of amyloid accumulation associated with AD.

4.3. Identifying a strategy

Choice of a strategy for developing a drug thought to slow the underlying pathogenesis of AD will require consideration of the drug's mechanism of action, availability of potential biomarkers, and regulatory standards. All of these factors are evolving. The regulatory standards used to approve the drugs already on the market for AD resulted from intense dialog involving FDA, academic researchers, the

pharmaceutical industry, and representatives of advocacy groups [43]. They were an attempt to accommodate different perspectives and achieve scientific rigor along with clinical relevance and recognized the practical limitations of conducting clinical research. The standard set for approval was one that would not allow marketing of drugs with little or no clinical utility but was not so high as to discourage ongoing efforts to develop incrementally better drug therapies [3,44]. Regulatory standards are flexible enough to allow consideration of a variety of scientifically valid data and clearly allow for the approval of a drug with useful clinical effects regardless of mechanism or supporting biomarker data. The principal barriers to development and approval of disease-modifying agents for AD are more scientific and practical than regulatory.

The discussions at the meeting identified some features that would probably need to be included in any successful plan for development and registration of a drug designed to slow the pathogenesis of AD. First is that the studies comparing drug and placebo would have to be of longer duration than those used to investigate the drugs with symptomatic effects. Basically, this stems from the fact that drug effects on progression are likely to be observable only relative to marked and measurable deterioration in placebo-treated patients; additionally, from a clinical standpoint, it is clear that claims about long-term benefits should be supported by long-term data. Secondly, there should be a strategy to use biomarkers whenever they are available to provide supportive evidence concerning the drug's effect on specific mechanisms of disease and, possibly pathogenesis of disease. As examples, some biomarkers might provide evidence of a drug's effects on amyloid processing or of the drug's effects on brain volume, metabolic activity or amyloid burden. Lastly, design maneuvers such as the randomized start could provide additional data consistent with the view that the drug's effects on disease progression result from slowing of underlying disease pathogenesis. Because no single design, measure, or biomarker provides definitive information about drug effects or efficacy, a combination of factors is probably required for the most compelling strategy.

5. Tactical Issues in the Design of Trials for Disease-Slowing Agents in AD

5.1. Selection of patients

Given that one has selected a general strategy for investigating a proposed disease-slowing drug, there are several specific operational considerations that can have a critical impact on the success or failure of a proposed clinical plan. Chief among these is selection of patients for the trial. Because the overall strategic goal for most of the clinical development programs that are ongoing is to evaluate effects to slow disease progression in patients with established disease, most studies will include patients within the spectrum of mild to moderate AD, similar to those enrolled in trials of symptomatic agents. The expected mechanism of drug action may have an impact on the stage of disease at which patients are selected and may also encourage the use of specific characteristics (eg, disease severity, genotype, measure on a biomarker related to disease) for stratification. Retention of patients to minimize dropouts is critical for longer, disease-modifying trials, and techniques for enhancing retention will have to be considered.

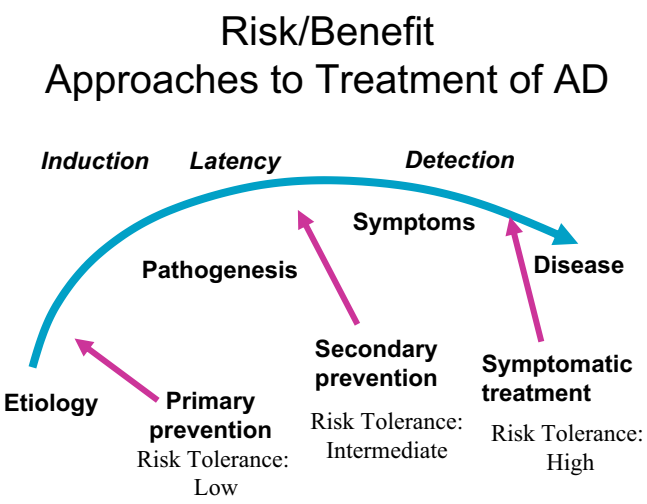

Fig. 5. A diagram of the clinical course of Alzheimer's disease from emergence of the earliest predisposing factors through clinical diagnosis and eventually to end-stage disease. Hypothetical treatment goals and descriptions of risk tolerance for each phase of disease are given. (Courtesy of Mary Sano, PhD.)

If a drug were shown to slow pathogenesis in patients with mild to moderate AD, then it is quite likely that the drug would also be considered as a treatment for earlier stage patients in either secondary or, possibly, primary prevention trials. Fig. 5 presents a graphic depiction of the relationships among scientific, practical, and ethical issues to be considered as one plans for studies in patients at different stages of AD and in persons with different degrees of risk for AD. The tolerance for risk and study burden will vary with stage of disease and, generally, will be less in persons without symptoms than in those whose disease has already been diagnosed. Among patients with AD, those with severe disease may be less willing to participate in studies of agents that might only preserve them in their current, debilitated state without any actual improvement.

5.2. Selection of outcome measures

The clinical characteristics that need to be evaluated in studies of disease-modifying agents are the same as those that are measured in studies of symptomatic treatments. These include measures of cognition, function, and behavioral or psychiatric symptoms; these are all characteristics of the disease process and should be evaluated in any study of a potential therapy. Additional measures of caregiver burden, health economic impact, and side effects will need

to be included in an overall evaluation of a drug's therapeutic impact. Whereas the domains to be assessed are quite similar for symptomatic and disease-modifying agents, characteristics of the clinical trials dictate that selection of outcome measures may be more difficult for disease-modifying trials. In particular, the length of follow-up in disease-modifying trials will be considerably longer, and psychometric properties of the outcome measures will have to be examined more closely. For example, many of the most commonly used outcome measures such as the ADAS-Cog [33] and Mini-Mental Status Exam (MMSE) [45] show longitudinal change that is nonlinear over time when patients are followed up for more than 1 year.

5.3. Selection of study design and analytic plan

The analytic plan as well as the study design must be consistent with the proposed therapeutic claim for a disease-slowing drug. The hypothesis that a drug slows the rate of progression in symptoms and, possibly in biomarkers related to pathogenesis, seems most consistent with a statistical comparison of rates of change over time, rather than a comparison of baseline to endpoint. Techniques for estimating rates of clinical change over time in AD have been under investigation for some time [46]. Although there is no uniform agreement on how best to calculate such rates, several justifiable plans for estimating change rates have been proposed. The plan for any given trial might depend on the specific outcome measure, the frequency of observation, and the length of the observation period. Because a disease modification trial would involve multiple outcomes, an analytic strategy for dealing with multiplicity would have to be specified in the study protocol. The randomized start design presented previously as a way to support a claim of disease slowing is, from a statistical perspective, a variant of a crossover design. Methods for analyzing such studies have been discussed recently in the statistical literature [47].

Although selection of an appropriate analytic plan will enable hypothesis testing to match the proposed disease modification hypothesis, no analytic technique will correct problems that are inherent in the design or conduct of a study. Problems that could occur easily in a disease modification trial include extensive missing data, poor adherence to treatment, and inadequate statistical power. Investigators planning studies of disease-modifying agents in AD should carefully consider the likelihood of treatment nonadherence and make provisions to investigate whether such events are treatment related. Post-hoc exclusion of patients based on lack of adherence can be misleading. Longitudinal data are available in the literature on rates of change for many of the outcome measures likely to be used in AD progression trials, and these data can be used to estimate required sample sizes. Missing data can never be recreated adequately, so measures must be taken to insure that a very high proportion of planned measures are obtained accurately.

6. Conclusion

There are substantial conceptual and practical difficulties involved in trying to determine whether a drug treatment slows the clinical course and pathogenesis of AD. Nevertheless, there are study designs, clinical outcome measures, and biomarkers that can be used to provide a strong test of the hypothesis that a new drug modifies the course of AD. When used in combination, these designs, outcome measures, and biomarkers can provide meaningful information sufficient to guide clinical practice and to differentiate among drugs with different mechanisms and clinical uses. In designing clinical programs to investigate disease-modifying drugs for AD, the following guidelines should be followed: (1) Clinical benefit must be shown over a period that is relevant to the proposed claim and to the natural history of the disease; (2) treatment effects are often specific to a stage of disease; (3) design maneuvers such as randomized start and randomized withdrawal can help explicate the nature of the drug's effects; (4) biomarkers can be of value in describing and selecting trial participants, in understanding a drug's biologic effects, and in monitoring biologic effects; but (5) the specific utility of any biomarker must be supported by data, and rarely will a biomarker serve as a surrogate for clinical efficacy.

The scientific sessions at the Workshop were followed by a forum involving patients, caregivers, representatives of the Alzheimer's Association as well as clinical researchers, and representatives of the FDA. This session will be the subject of a report to be published separately. An overriding theme of those discussions was a desire on the part of patients, advocates, and caregivers to have a greater role in designing, interpreting, and advocating for more clinical trials of new treatments for AD.

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