ALZHEIMER'S DISEASE

Testing the Right Target and Right Drug at the Right Stage

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Alzheimer's disease (AD) is the only leading cause of death for which no disease-modifying therapy is currently available. Recent disappointing trial results at the dementia stage of AD have raised multiple questions about our current approaches to the development of disease-modifying agents. Converging evidence suggests that the pathophysiological process of AD begins many years before the onset of dementia. So why do we keep testing drugs aimed at the initial stages of the disease process in patients at the end-stage of the illness?

Alzheimer's disease (AD) remains one of the most feared consequences of aging, affecting more than 1 out of every 10 individuals over the age of 65. With more than 10,000 baby boomers turning 65 every day in the United States alone, we are truly facing an AD epidemic. Over the past decade, a string of disappointing clinical trial results have raised concerns about our current strategy for development of AD-modifying therapies. Three hypotheses can explain these recent AD trial failures: (i) We are targeting the wrong pathophysiological mechanisms; (ii) the drugs do not engage the intended targets in patients; and (iii) the drugs are hitting the right targets but are doing so at the wrong stage of the disease.

Here, we address the third supposition and suggest that specific amyloid-based therapies be directed at much earlier stages of AD—perhaps even before the emergence of clinical symptoms. Furthermore, we argue that the field has sufficient tools to begin secondary prevention trials—those conducted after the disease process has begun in hopes of preventing the emergence of symptoms—in asymptomatic individuals who are at high risk for progression to cognitive impairment and AD dementia.

THE RIGHT TARGETS

The majority of current AD clinical trials target brain amyloid-β (Aβ) accumulation, and the recent trial failures have been viewed by some as "nails in the coffin" of the amyloid hypothesis (*1*). In contrast, mounting evidence from natural history studies supports Aβ accumulation in the brain as an early biomarker and critical event in the early progression of AD. Nearly all of the major genetic risk factors of AD also point toward Aβ accumulation as a critical pathogenic factor in the disease. Multiple studies based on cerebrospinal fluid (CSF) assays or imaging of brain amyloid with positron emission tomography (PET) in patients suffering from mild cognitive impairment (MCI) now suggest that positive amyloid markers confer a three- to fivefold higher likelihood of progression to AD dementia (*2*–*9*).

Similarly, recent cross-sectional studies of presymptomatic subjects who carry deterministic autosomal dominantly inherited mutations [such as those in the genes that encode presenilin-1, presenilin-2, or amyloid precursor peptide (APP)] have demonstrated evidence of Aβ accumulation in the brain at least a decade before the predicted age of onset of dementia, accompanied by "downstream" markers of neuronal injury—for example, tau and phospho-tau proteins in the CSF, alterations in functional brain imaging, and brain atrophy and cortical thinning seen with volumetric magnetic resonance imaging (MRI) (*10*, *11*).

Consonant with these findings in genetic at-risk populations are multiple recent reports of an "AD-like endophenotype"—a pattern of abnormalities characterized by functional and structural imaging markers—detected in clinically normal amyloid-positive older individuals (*12*–*17*). A few studies have also reported that, even within the range of normal cognitive performance for age, greater amyloid burden is associated with subtle decreases in performance on neuropsychological tests and these amyloid-positive normal individuals have a significantly greater risk of cognitive decline (*18*–*24*).

However, the consistent reports of amyloid positivity in one third of the normal older human population has been interpreted as a double-edged sword for the amyloid hypothesis. Indeed, the clinical implications of brain amyloidosis in clinically normal older individuals is one of the crucial outstanding questions in AD research. How do older individuals spend years with a "head full of amyloid" and remain apparently healthy? Is amyloid "necessary but not sufficient" to result in cognitive impairment?

Two types of investigations are required to disambiguate this conundrum. First, we need decades-long cohort studies of aging that are rich in sensitive cognitive, clinical, and biomarker assessments in order to elucidate the trajectories and relations among various markers of AD pathology and symptom progression. Second, we need studies of effective anti-amyloid therapies to determine whether early intervention in the process of amyloid accumulation will alter long-term cognitive and clinical outcomes in these asymptomatic subjects.

THE RIGHT DRUGS

The results of clinical trials in patients at the mild to moderate stages of dementia with a number of agents that target the reduction of amyloid burden (Table 1) have been discouraging. Tramiprosate—a glycosaminoglycan mimetic that was believed to block aggregation of Aβ in vitro—was moved into large clinical trials after a small phase II study suggested that the drug also reduced $Aβ_{42}$ peptide concentrations in the CSF of AD patients with mild to moderate dementia. The pivotal trial results failed to demonstrate efficacy with respect to improvements in cognitive or functional outcome measures. Tarenflurbil—the enantiomer of a nonsteroidal antiinflammatory drug shown to have γ-secretase activity in vitro and in transgenic mice models of AD—entered phase III clinical trials without clear evidence of target engagement in the central nervous system (CNS) of humans, and findings from these trials also failed to support efficacy in AD patients.

Most recently, the phase III development program for semagacestat, a γ-secretase inhibitor, was halted early because of adverse effects on cognition (and other safety concerns) in AD dementia patients. This result was particularly discouraging to the AD

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field because semagacestat had the strongest phase II evidence to date of CNS target engagement with clear dose-related reduction in $A\beta_{42}$ peptide generation in CSF from trial subjects (*25*).

Recent reports of small studies with monoclonal antibodies against Aβ have shown a reduction in fibrillar (or plaque) Aβ burden in AD patients, as quantified by ^{11}C PIB-PET (Pittsburgh Imaging Compound B Positron Emission Tomography) imaging (*26*, *27*); however, thus far this reduction has not correlated with any clear clinical benefit in the limited number of patients treated at the stages of mild to moderate dementia. A very small number of autopsies performed on brain tissue from AD patients who demonstrated evidence of antibody response to active immunization with AN-1792, a vaccine against the Aβ peptide, demonstrated signs of plaque clearance but no apparent effect on the clinical course of their dementia, as measured with cognitive and functional outcomes (*28*).

THE RIGHT STAGE

A number of trials of promising agents are ongoing in AD patients who are at the stage of mild-to-moderate dementia, and we hope that these studies will demonstrate some efficacy. However, the lack of clinical benefit seen in the aforementioned clinical studies raises the possibility that we are attempting intervention too late in the course of the disease, especially with anti-Aβ therapy.

Several pharmaceutical companies have begun phase II testing of therapeutic agents in patients who are at the predementia (prodromal) stage of AD, which is defined by clinical symptoms of MCI combined with evidence of amyloid accumulation in the brain, as assessed by CSF assays or PET amyloid imaging. But intervention at this stage with anti-amyloid therapy also may be too late to be effective. Recent hypothetical models based on the AD biomarker data available to date suggest that Aβ accumulates for well over a decade, and the neurodegeneration that occurs downstream of Aβ accumulation is well entrenched by the stage of MCI (*29*, *30*).

Therefore, it is possible that treatments that remove all toxic Aβ species from the brain still will not alter the clinical course of the disease after substantial neuronal injury has occurred. Triple–transgenic mouse models suggest that anti-Aβ intervention is less likely to succeed once the down stream neurodegenerative process has begun (as evidenced by early neurofibrillary pathology) (*31*). Indeed, some researchers have postulated that later stages of the AD pathophysiological process may become increasingly independent of the toxic effects of Aβ, so that other mechanisms predominate (for example, calcium dyshomeostasis, tau-mediated neurodegeneration, and mitochrondrial dysfunction) (*32*). This line of thinking has been controversial because clearly there is evidence of deteriorating synaptic function and ongoing neuronal loss throughout the course of AD dementia; thus, one might argue that a biologically active treatment for AD should demonstrate efficacy at all stages of the illness. However, there is analogous evidence for stage-dependent treatment success in other chronic diseases, such as cancer or cardiovascular disease. Lowering of serum cholesterol reduces morbidity and mortality if administered before or even after a single myocardial infarction but has very little effect if administered at the stage of heart failure that results from coronary artery disease when the myocardium is irreversibly damaged. If more than 50% of critical neurons in the medial temporal lobe memory circuits are already lost by the MCI stage of AD (*33*), it seems unlikely that anti-amyloid therapy alone could fully rescue memory function at the dementia stage of AD.

Table 1. Current and future disease-modifying therapeutic targets for AD.

Decrease Aβ production
• β-secretase inhibition
• γ-secretase inhibition or modulation
• α-secretase enhancement
Decrease Aβ aggregation
• Decrease metal ion–mediated fibrilization
• Decrease oligomer formation via reduction of Aβ monomers
• Decrease plaques by blocking β-pleated sheet formation
Increase Aβ degradation
• Insulin-degrading enzyme (IDE) activation
• Neprilysin activation
Increase Aβ clearance
• "Active" vaccination with truncated Aβ peptide
• Passive immunization with monoclonal antibody against Aβ epitope
• Passive immunization with antibody against specific confirmational forms of Aβ (such as oligomers, protofibrils, or plaque)
Decrease tau and neurofibrillary tangle formation
• Prevent tau hyperphosphorylation
• Decrease tau aggregation
• Stabilize microtubules
• Active and passive immunization against tau
Neuroprotection or neuroregeneration
• Antioxidant and other agents to preserve metabolic and/or mitochondrial function
• Antiapoptotic agents
• Decrease inflammatory damage
• Nerve growth factor enhancement
• Stem cell–based neuron replacement

Therefore, the accumulated evidence suggests that researchers should begin to (i) target selected therapies to specific stages of AD and (ii) think about the disease in terms of primary, secondary, and tertiary prevention rather than lumping together all disease-modifying treatments across the disease spectrum (Fig. 1). Although primary prevention would be ideal, the prospect of large primary prevention trials for late-onset sporadic AD remains daunting and likely unfeasible given the length of treatment required to achieve a clinical endpoint. Furthermore, there is considerable concern over the cost and safety of treating thousands of individuals who may never develop AD pathology. At present, the earliest feasible stage for therapeutic trials in sporadic AD is likely to be at the stage of asymptomatic amyloid accumulation, on the basis of the (still unproven) hypothesis that brain amyloidosis is indeed indicative of early-stage AD. These studies may be considered secondary prevention trials aimed at preventing or slowing the progression of the clinical syndrome in patients in which the pathophysiological process of AD has already begun.

ARE SECONDARY PREVENTION TRIALS FEASIBLE?

A number of secondary prevention trial initiatives are already in the planning stages for several at-risk populations: (i) individuals who carry autosomal dominant mutations, a very small population (less than 2% of all AD) with virtually 100% likelihood of early-onset AD dementia; (ii) individuals who are homozygous for the *APOE ε4* allele, a somewhat larger population with a less-certain

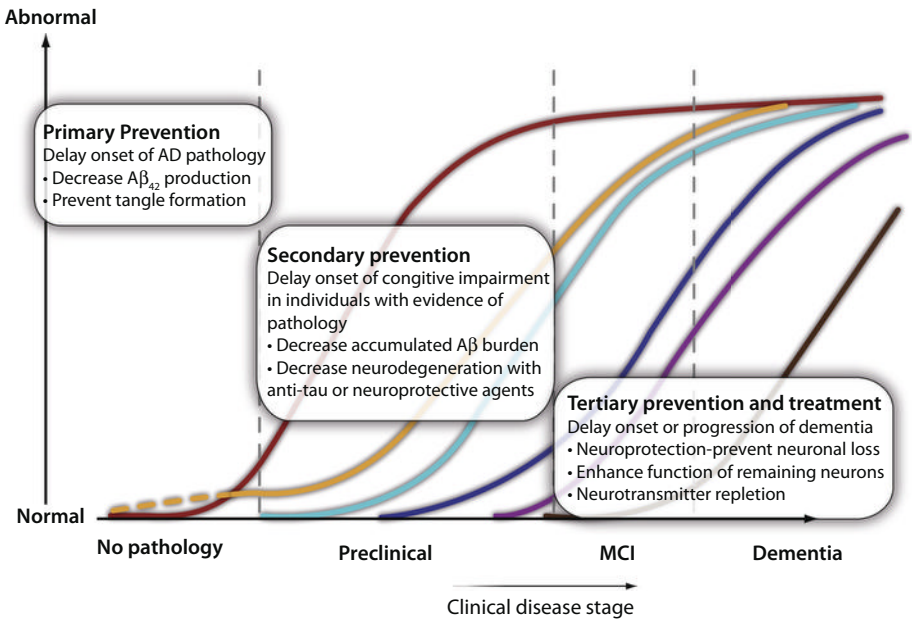

Fig. 1. Optimal stage for intervention? Shown is a scheme of the proposed stages of AD with potential prevention and treatment targets. We have depicted the hypothetical dynamic trajectories of currently available biomarkers of the AD pathophysiological process over the clinical course of the disease by plotting biomarker measurements (from normal to abnormal ranges) on the *y*-axis versus the defined clinical stages of AD on the *x*-axis [adapted from Jack *et al*. 2010 (*29*), with permission]. Primary prevention trials would occur in individuals who do not yet have evidence of AD pathology, whereas secondary prevention trials would occur in individuals who have evidence of early pathology, as assessed with AD biomarkers, but do not yet have clinically evident symptoms, meeting criteria for MCI. Red, amyloid β accumulation (CSF, PET); yellow, synaptic dysfunction (FDG-PET, fMRI); turquoise, tau-mediated neuronal injury (CSF); blue, brain structure (volumetric MRI); purple, cognition; brown, clinical function. [Adapted from Jack *et al.* 2010 (*29*), with permission]

risk of clinical progression and a potentially increased risk of amyloid-related imaging abnormalities (ARIA), as suggested by recent findings in ongoing trials (*34*); and (iii) asymptomatic amyloid-positive older individuals who are at risk by virtue of advanced age, the largest target population for eventual secondary prevention therapy but with relatively little long-term data to determine the risk of progression on an individual basis.

Recent longitudinal data from natural history studies suggest that it is now feasible to conduct secondary prevention trials over a time frame (3 to 5 years) that is realistic for studies that require clinical monitoring, but there are important trial-design considerations. In particular, it is likely that regulatory authorities will require evidence of an effect on a cognitive outcome in addition to evidence of biomarker change as measures of efficacy. Thus, the best chance of detecting efficacy may depend on defining a relatively homogeneous population of subjects who will demonstrate evidence of clinical progression in this relatively short time frame, but who are not at a clinical disease stage at which it is too late to intervene with anti-amyloid therapy. Individuals who show evidence of amyloidosis and neurodegeneration in biomarker and imaging studies—and perhaps very subtle cognitive symptoms (stage 3 of the recently proposed National Institute on Aging–Alzheimer's Association framework for the preclinical stages of AD) (*35*)—may be mostly likely to demonstrate clinical decline toward MCI and dementia over a few years' time; however, intervention at this stage might still be suboptimal for slowing disease progression with only an amyloid-modifying therapeutic agent. In the future, it may be ideal to combine anti-Aβ and anti-tau therapies once individuals become symptomatic.

These secondary prevention trials should embed a variety of fluid biomarkers and imaging measures to help determine whether decreasing amyloid burden can slow down stream neurodegeneration and whether the success of anti-amyloid therapy is dependent on the degree of neurodegeneration at baseline. Unfortunately, although a number of these biomarkers have shown great promise at identifying individuals at risk for progression, the use of biomarkers to track therapeutic response has been rather problematic. The most well-known example of a paradoxical biomarker response is the MRI result from the AN-1792 vaccine trial. Individuals who mounted an immune response to anti-Aβ vaccination showed greater rates of brain shrinkage despite some evidence of modest cognitive benefit on a subset of memory measures (*36*). As mentioned above, the semagacestat phase II trials demonstrated a decrease in CSF $A\beta_{42}$, but it remains unclear whether an increase or decrease in this biomarker is associated with therapeutic benefit. For immunotherapy agents aimed at reducing fibrillar Aβ burden, such as monoclonal antibodies and newer vaccine approaches, PET amyloid imaging may be the best marker of target engagement (*26*), but it remains unknown to what extent reduction in fibrillar Aβ is indicative of decreases in other potentially more-toxic forms of Aβ. The results from recent clinical trials underscore the need to better characterize the "theragnostic" response of multiple biomarkers in these early AD trials.

Perhaps the most daunting challenge is to identify a clinically relevant change that defines the stage at which an individual tips from cognitively normal to subtly abnormal, which may be years before a formal diagnosis of MCI is made. The cognitive measures that may be most sensitive to the very earliest symptomatic phases of AD are likely to differ from those currently used in trials with subjects who are in the late MCI and AD dementia stages (*22*, *23*). Moreover, clinical decline is thought to be nonlinear over the course of AD, as cognitive decline is most rapid and most easily detected (at least with current tools) during the moderate stages of dementia. Indeed, researchers and patients are caught "on the horns of a dilemma," because the most efficacious time for intervention with currently available anti-amyloid therapies may be in the early pathophysiological stages of AD, but this is also the stage at which it will be particularly difficult to detect clinical decline over a short time frame. Although a number of studies have demonstrated evidence of subtle cognitive decline in amyloid-positive normal individuals (*21*, *23*, *24*), it remains unknown whether measuring change in a single domain, such as episodic memory, or a newly developed composite measure will be most useful for tracking

very early progression that is specific to AD-related pathology.

Even with well-characterized at-risk populations, better-validated biomarkers, and more sensitive clinical measures, prevention trials are likely to be expensive, and partnerships between academia, government, industry, and philanthropic organizations will be required to fund these efforts. However, the expense of these prevention studies will pale in comparison with the cost of caring for an ever-expanding number of AD dementia patients if we do not find a successful disease-modifying therapy.

Lastly, there are important ethical considerations in planning these secondary prevention trials. The enrollment process for such trials may require researchers to reveal to subjects the results of biomarker or genetic screening. Given the incomplete knowledge to date, it will be difficult but crucial to explain to subjects the uncertainty regarding the likelihood that a clinically normal individual with high amyloid burden will indeed progress toward AD dementia. In addition, on the basis of results with the current set of drugs being tested in large-scale clinical trials, it is likely that biologically active medications will carry some risk. We must decide whether it is reasonable to expose asymptomatic individuals to drugs with a small but important risk of adverse events, even if some of them will not develop the clinical symptoms of AD. If we can better assess the risks for an individual participant, these cognitively intact individuals can make an informed decision, which some would argue is more ethical than our current practice of asking patients with mild dementia to fully assess the risk-benefit ratios. The potential benefits to society are high, and we believe that many individuals will volunteer for these studies in the hope that their children's generation will see AD dementia as a preventable illness.

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