PERSISTENT FAILURE OF "DISEASE-MODIFYING" DRUGS TO BENEFIT ALZHEIMER DISEASE: NOW WHAT?

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On May 7, 2013, Baxter International reported that the Phase III trial of intravenous immunoglobulin (IVIG; Gammagard®) failed to demonstrate benefit for reducing cognitive decline or preserving functional activities in persons with mild to moderate Alzheimer disease (AD) dementia. Owing to the lack of a positive outcome, Baxter announced that it was discontinuing its other studies of immunoglobulin therapy in AD. This disappointing outcome was followed by Eli Lilly and Company's announcement on June 13, 2013, that it was stopping its Phase II trial of LY2886721, a beta secretase inhibitor, in individuals with AD dementia because of apparent hepatotoxicity (toxic damage to the liver).

Such discouraging results unfortunately are not new to the AD field. Since 2001 there have been seven Phase III and two Phase II clinical trials in individuals with symptomatic AD of therapeutic agents that target amyloid-beta (Aβ). Aβ is a brain peptide that when dysregulated is believed by many investigators to be central to the pathogenesis of AD.[1] All of these trials have failed due to either lack of efficacy, development of adverse events, or both. The continuing failure of these therapeutic agents understandably has produced reluctance in some investors to continue to underwrite the high costs involved in finding truly effective therapies for AD.[2]

Why have these drugs failed? There are many possibilities, but three major factors are addressed here. First, perhaps the drugs are unable to "engage" their target, Aβ. Many of these drugs, however, do appear to successfully interact with Aβ, as deduced from their effect on Aβ biomarkers in treated individuals.[3,4]Indirect evidence for "target engagement" by a vaccine directed against Aβ also was reported in 2008, when individuals with AD dementia who years earlier had been immunized with the vaccine died and were autopsied. They had much less cerebral Aβ burden than autopsied AD individuals who had not been in the trial.[5] However, the participants with the active immunization had no clinical benefit despite their reduced Aβ load, when they were compared with trial participants receiving placebo.

The above findings lead to the second factor: Is Aβ the right target? Although there is strong scientific support for the amyloid hypothesis of AD, not all investigators accept that it plays a major role in causing or exacerbating the illness. In part, this is because the symptomatic stage of AD is characterized by other active pathologies in the brain in addition to Aβ dysregulation. These pathologies include neurodegeneration, activated microglia and neuroinflammation, insulin resistance, altered levels of neurotransmitters and neurotrophins, oxidative stress, and several more. The severity of AD dementia, moreover, correlates much better with tau pathology (often considered to be a marker of neurodegeneration) than with Aβ pathology. Even if there is merit to the amyloid hypothesis, it may be overly simplistic to expect an Aβ monotherapy (or any drug that is

directed at a single mechanism) to be efficacious in the face of the multiple pathophysiological processes present in symptomatic AD. Consistent with this idea, it is important to note that drugs targeting mechanisms other than Aβ also have all failed as monotherapies in persons with symptomatic AD (See Table 1). (Author note: Combination therapy with several drugs, each targeting different mechanisms, should be considered for future clinical trial designs).

Agent	Target/Mechanism	Outcome
Non-Aβ		
Atorvastatin; Simvastatin	Cholesterol (HMG CoA reductase inhibitor)	Negative
NSAIDs	Inflammation	Negative
Rosiglitazone	Insulin (PPAR gamma agonist)	Negative
Latrepirdine	Mitochondrial function	Negative
Aβ		
AN1792	Amyloid immunoRx	Negative (AEs)
Tramiprosate	Amyloid aggregation	Negative
Tarenflurbil	Gamma secretase	Negative
Semagacestat; Avagacestat	Gamma secretase	Negative
Bapineuzumab	Amyloid immunoRx	Negative
Solanezumab	Amyloid immunoRx	Negative (+/-)
IVIG	Nonselective immunoRx	Negative
LY2886721	Beta secretase	Negative (AEs)
AE = adverse event		

Table 1. Failure of AD Candidate "Disease Modifying" Therapeutics. Modified with permission from a presentation by Laurie Ryan, PhD, Division of Neuroscience, National Institute on Aging, Bethesda, Maryland.

We come to the third factor: Perhaps anti-Aβ therapies are being administered too late in the course of the disease. There now is ample evidence from clinicopathological studies and from *in vivo* molecular biomarker studies that cognitively normal individuals can and do harbor the pathological lesions of AD. These observations led to the concept of preclinical AD,[6] where the pathophysiological process of AD is underway but has yet to result in cognitive decline and impaired functional abilities (i.e., the symptoms of AD). This concept increasingly has been adopted in the field[7] and has led to proposals that AD is characterized by two major stages: One in which the brain lesions accumulate in the absence of symptoms (preclinical AD), and the other in which AD symptoms are manifest (See Table 2). The symptomatic stage of AD, encompassing mild cognitive impairment due to AD[8] and AD dementia,[9] likely represents the end stage of the pathophysiological disorder. Symptomatic

▯ "Alzheimer disease" (AD) refers to the neurodegenerative brain disorder, regardless of clinical status, representing a continuous process of synaptic and neuronal degeneration
▯ AD has two major stages: ○ Preclinical (presymptomatic; asymptomatic) ○ Symptomatic (clinical)
▯ Symptomatic AD is defined by intraindividual cognitive decline, from subtle to severe, that interferes with daily function, and can be subclassified on symptom severity ○ Incipient (prodromal; mild cognitive impairment) ○ Dementia

Table 2. Stages of Alzheimer disease. Modified with permission from Table 4 in Morris JC, Arch Neurol 2012.[15]

AD is marked, in comparison with preclinical AD by extensive neuronal injury and loss in selected brain regions that are highly vulnerable to the disorder[10] even in the earliest symptomatic stage of AD.[11]With this in mind, perhaps it is not surprising that all trials of "disease-modifying" agents have failed as they have used cohorts that are limited to individuals with symptomatic AD, who thus already have substantial and irreversible brain damage.

Many hypothetical models have been proposed for the continuum of AD from its preclinical (asymptomatic) stage to its symptomatic stage. Studies of individuals in families with rare autosomal dominant mutations causing AD can be informative in this regard. Using cross-sectional data from asymptomatic mutation carriers (MCs), in comparison with sibling non-carriers (NCs), who are participants in the Dominantly Inherited (Alzheimer Network (DIAN; U19AG032438, JC Morris, PI), there now is evidence that altered cerebrospinal fluid (CSF) levels of $A\beta_{42}$, the toxic isoform of Aβ, begin approximately 20 years before the expected age of symptomatic onset. Altered levels of CSF $A\beta_{42}$ are followed by a sequence of pathological changes involving the appearance of Aβ deposits in the cerebral cortex; altered CSF levels of tau; regional brain volume loss and hypometabolism; and finally subtle cognitive decline, all in the preclinical stage of AD (Figure1).[12]

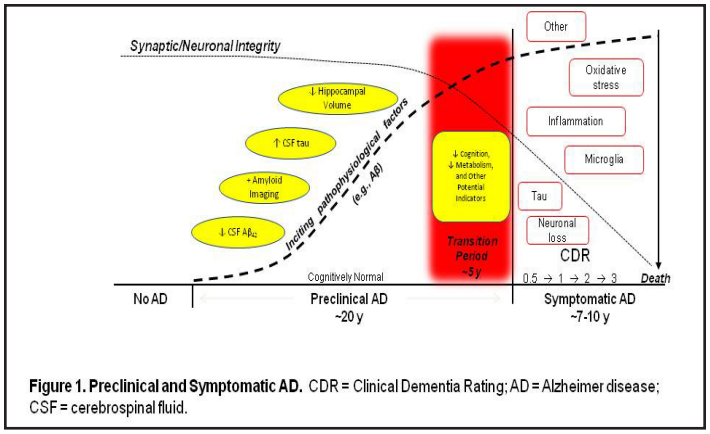

Figure 1. Preclinical and Symptomatic AD. CDR = Clinical Dementia Rating; AD = Alzheimer disease; CSF = cerebrospinal fluid.

(For larger image, click here)

This sequence is consistent with the amyloid hypothesis, which also is supported by stable isotope labeling kinetic studies that demonstrate a ~25% greater production rate of $A\beta_{42}$ in MCs as compared with NCs.[13]The DIAN cohort is ideally suited for these studies because MCs have a virtually certain risk of becoming symptomatic with AD (i.e., the mutations have near-100% penetrance) and at a predictable age (generally when their affected parent became symptomatic). Whether biomarker-positive, cognitively normal older adults meet either of these conditions is not yet known.

It is reasonable to hypothesize that interventions with anti-Aβ monotherapies in asymptomatic MCs may offer the possibility of therapeutic success because extensive neuronal injury and loss have not yet occurred and other pathologies

are not yet established. Under the direction of Randall J. Bateman, MD, at Washington University, the first-ever secondary prevention trial with anti-Aβ "disease-modifying" drugs began on December 31, 2012, when the initial DIAN participant consented to the trial and was randomized to a treatment arm in March 2013. Two treatment arms are being conducted simultaneously, one with a monoclonal antibody targeting soluble Aβ (solanezumab, Eli Lilly and Company), another with another monoclonal antibody targeting fibrillar Aβ (gantenerumab, Roche). The 2 monoclonal antibodies are designed to accelerate Aβ clearance from the brain.

The DIAN trials have pioneered therapeutic intervention in preclinical AD. They soon will be joined by additional "secondary prevention" studies. One will be conducted by the Banner Alzheimer Institute in Phoenix, AZ, in collaboration with investigators at the University of Antioquia in Colombia, South America, where the largest known family with a dominantly inherited form of AD is located.[14] This Alzheimer Prevention Initiative (API) also plans to evaluate an anti-Aβ monoclonal antibody, as does yet another trial sponsored by the Alzheimer Disease Cooperative Study that will enroll cognitively healthy older adults who are biomarker-positive for AD as determined by amyloid imaging. All three of these "secondary prevention" trials face many challenges, including whether results in the rare dominantly inherited form of AD can be extrapolated to the far more common "sporadic", late onset form of AD. These trials nonetheless will provide critical insights into how AD pathophysiology can be modulated or even aborted in the preclinical stage of the illness. For example, even if negative the trials will provide important information as to the role of Aβ in AD as they represent a direct test of the amyloid hypothesis. If they do demonstrate efficacy, they provide much needed hope that one day truly effective therapies for AD can be available. In this way, the current disappointment about failed clinical trials in AD will evolve into "Now What?" strategies that successfully aim to delay or even prevent the appearance of symptomatic AD.

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