Is Secondary Prevention of Alzheimer's Disease Possible?

A Discussion of Studies in the Alzheimer's Disease Field

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ABSTRACT

Alzheimer's disease is a growing epidemic. More than 5 million Americans live with Alzheimer's disease today, and more than 15 million Americans provide care for a family member or friend with Alzheimer's or related dementia. Evidence continues to accumulate suggesting the biological processes associated with Alzheimer's disease begin two or three decades prior to clinical manifestation of cognitive and functional symptoms such as challenges with memory. This suggests a window of opportunity for therapeutic intervention to slow or halt disease progression, also known as secondary prevention. There are several secondary prevention efforts for Alzheimer's disease in different stages of planning or execution; examples include the Dominantly Inherited Alzheimer's Network (DIAN) Trials Unit (DIAN-TU), the Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's disease Treatment Trial (API), the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease Study (A4) and the TOMMORROW trial. Each trial focuses on volunteers with a potentially increased risk or certainty for developing Alzheimer's disease (i.e., accumulation of beta amyloid in the brain, a familial genetic mutation or a genetic variation that may increase risk). Although each study is distinct, there is cooperation to harmonize protocols and data collection to allow the cross comparison of information between studies. This paper provides an overview of the studies.

BACKGROUND

Estimates suggest dementia affects nearly 36 million people worldwide, and the prevalence of dementia is expected to rise as the global elderly populations increase to 66 million by 2030 and over 115 million by 2050 (Wimo and Prince 2010). Alzheimer's disease (AD) accounts for about 60 to 70 percent of all dementias and is the most common type of age-related dementia (Barker et al. 2002; Fratiglioni et al. 2000). In 2010, the global costs of dementia was estimated to be over $600 billion (USD), about 1 percent of the world's gross domestic product (Wimo and Prince 2010). The increasing number of people with dementia will strain world governments and public health systems. AD and related dementias represent a global public health crisis of immense proportions, and demand a massive integrated, multidisciplinary and global response. Development of new technologies and treatments has resulted in significant progress in advancing our understanding of the pathophysiology and molecular mechanisms underlying the disease processes. Despite these developments, there is currently no effective treatment to slow or stop the progression of AD, while the urgent need to accelerate advances with the goal of stopping or slowing AD-related brain changes continue to escalate (Hampel and Carrillo 2012, 1–14).

The Alzheimer's Association is the world's largest voluntary health organization dedicated to care, support, advocacy and research related to AD. As such, we are committed to strengthening and supporting AD clinical study-related activities, including Alzheimer's Association TrialMatch, a service that matches individuals with current clinical trials in their community. Recognizing the importance of diverse therapeutic approaches, the Alzheimer's Association supports ongoing efforts through both directly funding research and convening platforms to enable sharing of scientific information (i.e., the Alzheimer's Association International Conference (AAIC), *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* and the Alzheimer's Association Research Roundtable). The association is committed to finding better treatments and therapies for Alzheimer's disease and related disorders while continuing to provide support for people and families facing AD today.

NEW GENERATION OF ALZHEIMER'S DISEASE CLINICAL STUDIES

Mounting evidence supports the idea that the brain changes underlying Alzheimer's disease begin long before the appearance of clinical Alzheimer's dementia symptoms as currently

defined (Bateman et al. 2012; Lo et al. 2011). The National Institute on Aging-Alzheimer's Association (NIA-AA) revised diagnostic guidelines provide a new framework that expands the definition of Alzheimer's disease from the current National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS ADRDA) definition of frank dementia (McKhann et al. 1984) to a broader timeline consisting of a "silent" phase referred to as preclinical AD and mild cognitive impairment (MCI), reflecting the development and progression of the disease in the absence of clinical symptoms that are sufficient for a diagnosis of dementia (Sperling, Aisen, et al. 2011). Presymptomatic identification of people with AD continues to be a challenge, although this model suggests there may be a window of opportunity to identify and treat individuals at high risk for Alzheimer's disease before the clinical onset of Alzheimer's dementia, similar to treatment of HIV that reduces/eliminates AIDS (Sperling, Jack, et al. 2011).

This theoretical concept is beginning to be reflected in novel secondary prevention trials in AD. Secondary prevention is defined as stopping or slowing the progression of a disease process for people expressing early stages (i.e., early pathology or biological changes). Currently, there are several secondary prevention studies in AD at different stages of development or enrollment: the Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU) (Bateman et al. 2011), Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's disease Treatment Trial (API) (Reiman et al. 2011), the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease Study (A4) (Jack et al. 2013) and the TOMMORROW trial (Roses et al. 2012). Each of these studies is using specific criteria for participant selection that enrich the study population for people at the highest risk for developing AD and who may in fact be in the presymptomatic phase of Alzheimer's disease development.

DIAN Trials Unit (DIAN-TU)

The Dominantly Inherited Alzheimer's Network (DIAN) Observational Trial is an international research partnership to study the adult children of parents with early-onset AD (EOAD) resulting from rare genetic mutations in either amyloid precursor protein (APP), presenilin 1 (PSEN1) or presenilin 2 (PSEN2), also known as familial Alzheimer's disease (FAD). The mutations that cause FAD are dominantly inherited, meaning that if an individual is born with one of these mutations, he or she is guaranteed to develop AD. The DIAN Observational Trial was

established by the National Institute on Aging of the National Institutes of Health (NIH) in 2008, and currently engages 11 research institutes in the United States, the United Kingdom and Australia. The affected parent's age of onset for clinical symptoms is used to estimate the age of onset for the offspring who carry the same genetic mutation. Recent analysis of data from DIAN shows that cognitive, imaging and biochemical markers can change a decade or more before the estimated age of clinical symptom onset (Bateman et al. 2012). The DIAN cohort is ideal for investigating preventative therapies due to the certainty of developing AD and the ability to estimate the age of onset (Bateman et al. 2011), as well as the strong motivation of these individuals to participate in clinical studies.

DIAN-TU is the clinical trials arms of DIAN, and is funded in part by a partnership between the Alzheimer's Association, the DIAN Pharma Consortium and NIH (Washington University School of Medicine, 2014). DIAN-TU will test experimental compounds simultaneously using a unique adaptive trial design to determine whether they affect biomarkers associated with AD. The ability to study multiple compounds in parallel with a single placebo control group provides immense advantages in terms of efficiency and trial size. DIAN TU participants who have inherited an EOAD/FAD gene but do not yet demonstrate symptoms of AD are being recruited from the DIAN observational cohort and will receive either experimental treatment or placebo in the first part of the study. AD-associated biomarkers or measures of biological change—such as amyloid imaging, cerebrospinal fluid (CSF) proteins or volumetric magnetic resonance imaging (MRI) (Lo et al. 2011; Jack et al. 2013; Carrillo et al. 2013)—will be assessed over six months. After this time, if the experimental compound(s) have demonstrated they can effect a positive change in the biomarkers, they will be considered for continuation over a longer time frame to demonstrate efficacy in cognitive measures (Bateman et al. 2011).

In October 2012, DIAN scientists announced their decision to start studies with the use two investigational monoclonal antibodies—gantenerumab (from Roche) and solanezumab (from Eli Lilly). The DIAN-TU has launched and is enrolling participants at Washington University in St. Louis, as well as other sites around the world.

Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's disease Treatment Trial (API)

The Banner Alzheimer's Institute in Phoenix, Ariz., has launched the Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's disease Treatment Trial (API) in a large Colombian family—in cognitively healthy individuals who have a dominantly inherited early onset AD gene/FAD similar to the DIAN-TU study (Clinicaltrials.gov, 2014). This population from a single family or kindred lives in Antioquia, Colombia, and carries a rare mutation in the PSEN1 gene, causing AD symptoms by approximately age 45, and are the largest descendant FAD population in the world (Reiman et al. 2011). API will enroll volunteers from this kindred at an age prior to their estimated age of onset in a study that will examine the therapeutic benefit of crenezumab (from Genentech), a monoclonal antibody that targets beta amyloid.

The study design is a three-year randomized controlled trial with a battery of cognitive tests to assess whether treatment attenuates losses in memory and function, the primary outcome measures, during the time period in which symptoms are expected to develop. Trial participants will also be assessed on a variety of biomarkers including amyloid positron emission tomography (PET) imaging, MRI and fludeoxyglucose (FDG)-PET, as well as plasma and CSF biomarkers. Like the DIAN-TU, this study design may have the added benefit of qualifying biomarkers for use as reasonable surrogate endpoints for AD in clinical trials, assessing the efficacy of treatment, and giving access to investigational treatments to those at highest imminent risk.

TOMMORROW Trial

TOMMORROW is sponsored by the Zinfandel-Takeda Pharmaceuticals Alliance and is a Phase 3 prevention study in elderly participants with normal cognitive abilities. The individual risk of each volunteer will be stratified using an algorithm based on their TOMM40-523 and ApoE genotype, as well as their age and cognition at study entry (Roses et al. 2012; Welsh-Bohmer et al. 2013). The TOMM40 gene codes for a mitochondrial membrane channel that allows proteins and peptides to be transported into the mitochondria. Variants in the TOMM40 gene have been linked to an increased risk of AD and may also be linked to age of onset (Roses 2010). Approximately 5,800 cognitively normal individuals age 65–83 will be enrolled into this five-year study. The study will recruit internationally from large, diverse, community-based

populations. Individuals deemed to be at low risk will receive placebo as control, while high-risk individuals will be randomized to receive either placebo or a low-dose of pioglitazone, an anti-diabetes drug that has shown promise in potentially preventing AD. The primary outcome measure will be cognitive impairment, as measured by a battery of neuropsychological tests (Welsh-Bohmer et al. 2013). This study is being conducted in the United States, Europe, Australia, Russia and Israel (Welsh-Bohmer et al. 2013).

Anti-Amyloid Treatment for Asymptomatic AD Study (A4 Trial)

Funded in part by the NIA and Eli Lilly, the Alzheimer's Disease Cooperative Study (ADCS) will launch the A4 trial to test solanezumab (from Eli Lilly), a monoclonal antibody targeting beta amyloid, in an estimated 1,000 clinically normal, beta amyloid PET-positive individuals older than 65. Volunteers will be randomized to receive the experimental treatment or placebo for up to a three-year period (Brigham and Women's Hospital 2013). The A4 study outcome will measure the rate of cognitive decline (Miller 2012).

DISCUSSION

Secondary prevention trials target individuals in the earliest stages of developing AD. These studies are helped by the new framework put forward in the NIA-AA diagnostic criteria, and take advantage of a window of opportunity to intervene at an earlier time point in order to delay or halt disease progression. The urgency is clear; the scientific community must intensify efforts to accelerate Alzheimer's disease research. The National Plan to Address Alzheimer's Disease (U.S. Department of Health and Human Services 2013; Alzheimer's Association Expert Advisory Workgroup on NAPA 2012) includes milestones to address the looming crisis of Alzheimer's disease, with the goal of effectively treating and preventing Alzheimer's by 2025. The Alzheimer's Association is committed to working with federal agencies, academic research institutions and industry partners to promote collaborations to support the international community in our collective effort of eradicating AD (Alzheimer's Association Expert Advisory Workgroup on NAPA 2012). The global community must increase efforts to leverage resources and support collaborations to address and reverse this rising epidemic.

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