Is “Secondary” Prevention of Alzheimer's disease Possible?”

Perspective from the Alzheimer’s Association

Heather Snyder¹*, Dean Hartley¹, Maria Carrillo¹

¹ Medical and Scientific Relations, Alzheimer’s Association, Chicago, IL, USA

* Corresponding Author:
Heather Snyder, Ph.D.
Alzheimer’s Association
225 North Michigan Avenue, Suite 1700
Chicago, IL 60601
Phone: (312) 335-5184
E-mail: hsnyster@alz.org
Alzheimer’s disease is a growing epidemic. More than 5 million Americans are living with Alzheimer’s disease today, and more than 15 million Americans are providing care for a family member or a 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. This suggests a window of opportunity for therapeutic intervention to slow or halt disease progression, also known as secondary prevention. There are currently several secondary prevention clinical trials in different stages of planning; examples include Dominantly Inherited Alzheimer’s Network (DIAN) Trials Unit (DIAN-TU), Alzheimer’s Prevention Initiative (API), AntiAmyloid Asymptomatic Alzheimer’s disease Trial (A4), and TOMMorrow trial. Each trial focuses on volunteers with a potentially increased risk for developing Alzheimer’s disease (i.e. accumulation of beta amyloid in the brain, a familial genetic mutation, or a genetic variation that increases risk). Although each trial 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 these trials including the compounds to be tested and the trials designs.
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 [1]. Alzheimer’s disease (AD) accounts for approximately 60-70% of all dementias and is the most common type of age-related dementia [2, 3]. In 2010, the global costs of dementia was estimated to be over $600 billion (U.S. dollars), about one percent of the world’s gross domestic product [1]. The increasing number of people with dementia will strain world governments and public health systems. AD and related dementias signify a global public health crisis of indescribable proportions, and demand a massive integrated, multi-disciplinary and global response. Development of new technologies and treatments has resulted in significant progress to advance understanding 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 neurodegeneration continues to escalate [4].

The Alzheimer’s Association is the world’s largest voluntary health organization dedicated to the care, support, advocacy and research of AD. As such, we are committed to strengthening and supporting AD clinical trial-related activities, including Alzheimer’s Association TrialMatch™, a service that matches individuals with current clinical trials in their local community. Recognizing the importance of a diverse therapeutic approaches, the Alzheimer’s Association supports on-going efforts through direct research funding and convening platforms to enable sharing of scientific information (i.e. the Alzheimer’s Association International Conference (AAIC), the 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 Alzheimer’s disease today.
NEW GENERATION OF ALZHEIMER’S DISEASE CLINICAL TRIALS

Mounting evidence supports the current hypothesis that underlying Alzheimer’s disease pathology begins long before current clinically-defined Alzheimer’s dementia symptoms appear [5, 6]. 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 NINCDS ADRDA definition of frank dementia [7] to a broader timeline consisting of a more “dormant” phase referred to as preclinical AD and MCI, reflecting the development and progression of the disease in the absence of clinical symptoms sufficient for a diagnosis of dementia [8]. Pre-symptomatic identification of people with AD continues to be a challenge although this phase suggests there is a window-of-opportunity to identify individuals and treat those who are at risk for Alzheimer’s disease before the clinical onset of Alzheimer’s dementia, similar to the treatment of HIV reduces/eliminates AIDS [9]. Translation of this theoretical concept is reflected in these novel secondary prevention trials in AD. Secondary prevention is defined as stopping or slowing the progression of a disease for persons expressing early stages of disease process (i.e. early pathology). Currently, there are several secondary prevention trials at different stages of development or enrollment: Dominantly Inherited Alzheimer’s Network Trials Unit (DIAN-TU) [10]; Alzheimer's Prevention Initiative (API) [11]; Anti-Amyloid Treatment in Asymptomatic Trial (A4) [12]; and the TOMMorrow trial [13]. These trials use specific criteria for participant selection which allows each trial to enroll volunteers that meet these criteria and will then target a selected therapeutic strategy.

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 EOAD resulting from rare genetic mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2) or familial Alzheimer’s disease (FAD). FAD represents dominantly inherited genetic mutations; if an individual is born with one of these mutations, the individual will develop AD. The DIAN Observational Trial was established by the National Institute on Aging (NIA) of the National Institutes of Health (NIH) in 2008, and currently engages eleven research institutes in the United States, the United Kingdom, and Australia. The parent’s age of onset of clinical symptoms is
used to estimate the age of onset for the offspring who are carrying this same dominant genetic change. Recent analysis of data from DIAN shows that cognitive, imaging and biochemical markers can change at a decade or more before the estimated age of clinical onset [5]. 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 [10], as well as the strong motivation by this group of individuals.

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 [24]. DIAN-TU will test three experimental compounds simultaneously using a unique adaptive trial design to determine whether they affect biomarkers thought to be associated with AD. The ability to study three 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, who 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 - such as amyloid imaging, cerebrospinal fluid (CSF) proteins, volumetric magnetic resonance imaging (MRI) - will be assessed over a six month period. These markers have demonstrated changes in protein levels associated with AD before symptoms occur in several trials [6, 12, 14]. After six months, the experimental compound(s) will be assessed for their ability to change in these biomarkers. Experimental drugs demonstrating a positive biomarker change will be considered for a continuation of 12 to 18 months. Continuation trials will include a cognitive assessment with the goal of demonstrating the biomarker changes observed in the first 6 months correlate with a clinical benefit [10].

In October 2012, DIAN scientists announced their decision to use two investigational monoclonal antibodies—Gantenerumab (Roche) and Solanezumab (Eli Lilly)—a third experimental compound will be determined by the end of 2013. The DIAN-TU has launched and is in process at Washington University, St Louis as well as other sites around the world.

Alzheimer’s Prevention Initiative (API)
The Banner Alzheimer's Institute (Phoenix, Arizona) has launched a clinical trial in cognitively healthy individuals who have a dominantly inherited early onset AD gene / FAD similar to the DIAN-TU study and thus are predetermined to develop AD This population from a single
family or kindred lives in Antioquia, Columbia and carries a rare mutation in the PSEN1 gene causing AD symptoms by approximately age 45, making them the largest descendant FAD population in the world [11]. API will enroll volunteers from this kindred at an age prior to their estimated age of onset in a secondary prevention trial using Crenezumab (Genentech), a monoclonal antibody that targets beta amyloid.

The trial design is a three year randomized control trial with a cognitive battery of tests to assess changes in memory and function, the primary outcome measures. Trial participants will also be assessed by a variety of biomarkers including amyloid PET imaging, MRI, FDG-PET, and plasma and CSF biomarkers. Like the DIAN-TU, this study design may have added benefit of qualifying biomarkers for use as reasonable surrogate endpoints for AD, in addition to assessing the efficacy of treatment and giving access to investigational treatments to those at highest imminent risk. The API study is expected to launch late 2013/early 2014 [15].

**TOMMorrow Trial**

TOMMorrow is sponsored by the Zinfandel-Takeda Pharmaceuticals Alliance and is a phase 3 primary 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 age and cognition at entry [13, 16]. 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 predict the age of onset [17]. Approximately 5,800 cognitively normal individuals aged 65-83 will be enrolled randomly 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. The primary outcome measure will be cognitive impairment, as measured by a neuropsychological battery of tests [16]. This trial will be conducted in the US, Europe, Australia, Russia and Israel [16].

**Anti-Amyloid Treatment for Asymptomatic AD (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 (Lilly), a monoclonal antibody targeting beta
amyloid. The study aims to enroll 1,000 clinically normal, beta amyloid PET-positive individuals over the age of age 65, who will be randomized to receive the therapy or placebo for up to a three-year period [18]. The A4 trial outcome measures will include the treatment effect on rate of cognitive decline and amyloid burden with an anti-amyloid treatment aimed at secondary prevention of AD [19].
DISCUSSION

Secondary prevention trials target individuals in the earliest stages of AD under the new framework proposed by the NIA-AA criteria, in order to delay or halt disease progression. To encourage and facilitate standardization and harmonization across these efforts, the Coalition for Alzheimer’s Prevention (CAP), sponsored in part by the Alzheimer’s Association and FBRI, was formed. CAP brings together leadership from these secondary prevention trials, representatives from the NIA and US Food and Drug Administration Division of Neurologic Products (DNP) to discuss common challenges and opportunities to share resources and use common protocols that will enable comparisons. One of these challenges/opportunities has focused on the difficulty of measuring reliable and meaningful cognitive change in populations with normal memory when measured with traditional neuropsychological testing. A new more sensitive measure of the most subtle changes in cognition may indeed be possible at the earliest biological signs of Alzheimer’s disease (detectable with biomarkers). New cognitive assessments are being developed and tested through a cooperative effort within CAP for these trials thus providing a significant contribution to the field. Additional challenges are to identify people with asymptomatic signs of Alzheimer’s disease and being able to demonstrate the clinical efficacy of a treatment which would necessitate demonstration of clinical benefit, such as delay or halting of the cognitive decline at these early stages of the disease.

The urgency is clear, the scientific community must intensify efforts to accelerate Alzheimer’s disease research. The National Plan to Address Alzheimer’s Disease [20, 21] 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, convening collaborations -like CAP- to support the international community in our collective effort of eradicating AD [21]. The global community must intensify efforts to leverage resources and increase collaborations to address and reverse this rising epidemic
CITATIONS


22. [http://www.dianexpandedregistry.org/Pharma.htm](http://www.dianexpandedregistry.org/Pharma.htm)