Medical News & Perspectives

Researchers Test Strategies to Prevent Alzheimer Disease

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A decade of disappointing clinical trial results for Alzheimer disease (AD)-modifying therapies in people suggests that treatment should be targeted at earlier stages in the disease—even before overt symptoms arise.

Profound brain alterations—such as accumulation of the protein fragment called beta-amyloid—are found 10 to 20 years before dementia or even mild cognitive impairment is diagnosed. Alzheimer disease investigators estimate that by the time memory begins to erode and other cognitive problems emerge, too much damage has occurred in the brain to be reversed by the experimental treatments.

In response to this idea, researchers have moved toward designing trials of therapies to delay or prevent the onset of AD in cognitively healthy but at-risk volunteers. As a number of researchers noted, because there may well be differences between people with early-onset AD and those with sporadic, late-onset disease, it will be crucial to carry out these studies in different risk groups.

Several such trials, referred to variously as secondary prevention trials or preclinical or presymptomatic treatment trials, are either under way now or will begin soon. These trials emerged from a unique collaborative effort among AD researchers. In 2012, 3 prevention initiatives—Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4), Dominantly Inherited Alzheimer Network (DIAN), and Alzheimer's Prevention Initiative (API)—formed an umbrella group called the Collaboration for Alzheimer's Prevention to maintain a regular dialogue among themselves as well as with regulatory groups, stakeholders, and pharmaceutical representatives as they plan and implement preclinical treatment trials.

"An even modestly effective preclinical treatment could have a profound public health effect," noted Eric Reimer, MD, of the Banner Alzheimer's Institute, Phoenix, Arizona, and co-director of the API. "It's been commonly cited that since AD risk doubles every 5 years after the age of 65, if we could delay the onset of AD by only 5 years without increasing lifespan we could reduce disease frequency by half," said Reimer. "And the goal is to do even better than that."

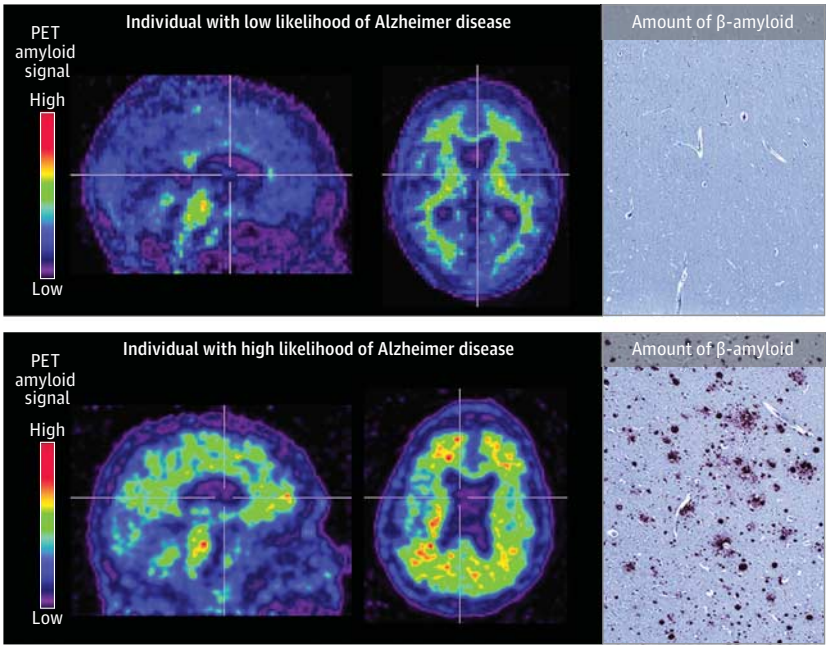
Several of the preclinical AD trials will test investigational antiamyloid treatments in at-risk patients before the disease has ravaged the brain. The trials will use agents that target various toxic forms of the amyloid protein. Many researchers think this approach will provide a better test of the amyloid hypothesis—which holds that buildup of amyloid is a primary driver of AD—because the failure of so many antiamyloid therapies in clinical trials has called this theory into question.

Another aim of these studies is to determine whether the established brain imaging and cerebral spinal fluid biomarkers used in the trials are related to clinical outcome, a quality referred to as the theragnostic utility of a biomarker, said API co-director Pierre Tariot, MD, also of the Banner Alzheimer's Institute. And as this article goes to press, it looks like another new marker—positron emission tomography (PET) tau imaging—will be added to several of the trials, allowing researchers to follow the spread of the tau protein, the other major hallmark of AD.

If a treatment's biomarker effects prove reasonably likely to predict a clinical benefit, the biomarkers could potentially be used as surrogate end points for future trials, producing results faster, said Tariot.

Targeting Early-Onset Disease

In the first trial, begun last year by API and set to run 5 years, Reimer and colleagues are collaborating with a Colombian team headed by Francisco Lopera, MD, at the University of Antioquia, Medellín. For decades Lopera has focused his research efforts on a huge extended family living in the Abrurrá Valley, in the northern reaches of the Andes Mountains near Medellín. Among an estimated 5000 living members, about 1500 carry an autosomal-dominant mutation in the presenilin 1



Positron emission tomography (PET) amyloid imaging has been associated with the presence and density of beta-amyloid at autopsy (*JAMA*. 2011;305[3]:275-283). Researchers in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) trial are using PET imaging to help identify individuals at risk for Alzheimer disease to test amyloid-modifying therapy.

(*PSEN1*) gene, one of 3 genes in which mutations are known to cause alterations in amyloid-beta processing that lead to early-onset AD.

The API researchers have amassed a registry with detailed cognitive assessments of more than 3400 members of this kindred, including more than 800 mutation carriers, who usually develop dementia before they turn 50 years old.

The API trial will enroll 300 cognitively healthy individuals who are at least 30 years of age from this family to test the antiamyloid monoclonal antibody crenezumab: 200 people with the mutation will be randomly assigned to receive injections of crenezumab or the placebo every 2 weeks for 260 weeks, while 100 noncarriers will also receive the placebo to ensure that study participants will not learn whether they carry the mutation. The vast majority of autosomal-dominant mutation carriers do not want to know their mutation status, noted Reimer.

Another AD prevention trial—the DIAN-Trials Unit (DIAN-TU), which launched in December 2012—also focuses on asymptomatic individuals at risk for early-onset AD. This 4-year, multisite international trial is enrolling people who are either known to carry or are at risk for carrying any of the 3 genes linked to autosomal-dominant AD: *PSEN1*, carried by the Colombian group, presenilin 2 (*PSEN2*), and amyloid precursor protein (*APP*).

The DIAN observational study (Bateman RJ et al. *N Engl J Med*. 2012; 367[9]:795-804), a separately funded study, helped provide the rationale and justification for the DIAN-TU study, noted DIAN-TU's director, Randall Bateman, MD, of Washington University Medical School, St Louis, Missouri. The observational study put researchers in close touch with these families and helped them work together in a cohesive fashion that led to discussions about doing an intervention trial, said Bateman.

DIAN-TU investigators will test 2 antiamyloid interventions: gantenerumab and solanezumab, which are monoclonal antibodies directed at different forms of amyloid-beta. A third yet-to-be-determined drug may be added to the trial. The study includes a pooled placebo group shared by all the treatment groups, which lowers the number of people needed in the trial, an important factor given the limited population of carriers of autosomal-dominant AD mutations, said Bateman.

During the first stage of the trial—the biomarker phase—researchers will monitor the response of imaging and fluid biomarkers to the drugs to assess which agent or agents look most promising for the follow-up second phase to examine cognitive effects of the drugs. The trial is evolving toward an adaptive design in which additional drugs can enter the biomarker part of the trial for evaluation, added Bateman.

Preventing Late-Onset Disease

A third prevention trial, A4, focuses on a different, much more common group—older adults who are at risk for AD not because of an autosomal-dominant mutation but because their brain scans show evidence of amyloid accumulation (Sperling RA et al. *Sci Transl Med*. 2014;6[228]:228fs13).

In this 3-year clinical trial, which began enrolling earlier this year at sites around the world, the researchers will equally randomize 1000 older individuals into placebo and treatment groups to test whether the amyloid-modifying monoclonal antibody solanezumab can slow the rate of cognitive decline on a composite measure of neuropsychological tests.

"We will be screening a large number of individuals—5000 healthy adults between 65 and 85 years of age—because we know about a third of healthy older individuals have amyloid plaque buildup in their brains sufficient to be what we call elevated amyloid or amyloid-positive on a PET scan," explained one of A4's principal investigators, Reisa Sperling, MD, of Harvard University Medical School, Cambridge, Massachusetts. Because there is a slight increase in AD risk in African American and Latino individuals, A4 is requiring that 1 of every 5 participants comes from one of these groups, who are underrepresented in biomarker studies, said Sperling.

The amyloid status will be revealed to those being screened because, as Sperling noted, "we feel this information is important to these cognitively healthy people in making their decision about participating in the trial." An ethics branch of the trial will study the process of screening and disclosing this information while helping convey the uncertainty about what the scans mean at this point, particularly that not every person with evidence of amyloid buildup in the brain develops AD.

Individuals who do not show evidence of elevated amyloid accumulation on PET scans will be eligible to participate in the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) study, a natural history observational group that will run in parallel to the treatment group of A4. Participants in the LEARN cohort will receive identical cognitive and clinical assessments every 6 months and imaging and biomarker outcomes at the end of the study.

"We know some of the LEARN participants will become amyloid positive during this time," said Sperling, and this cohort will serve as a comparison with those in the placebo group of the A4 trial, helping tease out more aspects of amyloid-related as well as nonamyloid factors that drive cognitive decline.

Reimer and colleagues are planning to launch another study, the API-APOE4 Treatment Trial, in the latter half of 2015. Reimer has carried out longitudinal studies on people with 0, 1, or 2 copies of the *APOE4* gene for nearly 2 decades, work that has served as a foundation for the design of this trial. Older people who carry 2 copies of the *APOE4* allele—2% to 3% of the population—are at high risk of developing AD later in life.

Researchers will enroll cognitively healthy participants between the ages of 60 and 75 years who have 2 copies of the *APOE4* allele. The study will enroll a greater number of people than the Colombian study, and the researchers are still in the process of identifying which drug will be tested. The trial will also investigate the effect of revealing the status of the *APOE* genotype to participants. A previous study (Green RC et al. *N Engl J Med*. 2009; 361[3]:245-254) found that disclosing *APOE4* status was better tolerated than anticipated, but the participants were younger and were not followed up longitudinally, said Reimer.

Also under way this year is the TOMMORROW trial, a large phase 3 clinical AD prevention trial enrolling close to 6000 cognitively healthy participants aged 65 to 80 years in 50 centers around the world. The TOMMORROW trial investigators will assess the status of both *APOE* and another gene, *TOMM40* (translocase of outer mitochondrial membrane 40 homologue), to predict the risk of developing mild cognitive impairment due to AD within a 5-year

period and to evaluate the effectiveness of using a low dose of the currently approved diabetes drug pioglitazone (designated as AD-4833 for this study) to delay onset of mild cognitive impairment.

In addition to being an insulin-sensitizing agent, pioglitazone has a remarkable effect on mitochondrial function, another mechanism implicated in AD pathogenesis, noted Jeffrey Cummings, MD, of the Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, Nevada, who is involved in this trial. "This is one of the first trials to look at the possible benefit of mitochondrial activation in the treatment of AD," he said.

Given the looming health crisis AD presents, these prevention studies are a vital step toward making an impression on the disease, commented Ronald Petersen, MD, of the Mayo Clinic, Rochester, Minnesota, who is not directly involved in any of the studies. He emphasized, however, that "this doesn't mean that we're abandoning people with symptomatic disease, as there is still a good deal of effort going on in drug development for people with AD." ■