After Disappointments, Alzheimer’s Researchers Seek Out New Paths

Biomarkers and Combination Therapies May Lead To Disease-Modifying Treatments, Experts Say

Susan Worley

To date, all efforts to develop a disease-modifying treatment for Alzheimer’s disease (AD) have been unsuccessful. Consequently, the treatments available to address the disease treat only the symptoms (Table 1). However, the many clinical trials that have ended in disappointment may yet prove to have a silver lining, as a critical and collaborative re-examination of premises that guided earlier research is taking place in their aftermath.

Experts have long agreed on two primary neuropathological hallmarks of AD: beta-amyloid (Aβ) plaques and hyperphosphorylated tau in the form of neurofibrillary tangles, both of which are present in the brains of individuals with AD. Most efforts to develop a disease-modifying treatment have focused on Aβ-related interventions. Reports on phase 3 trials of two such interventions, anti-Aβ antibodies bapineuzumab (Jannsen/Plizer) and solanezumab (Eli Lilly), which involved more than 4,000 patients, appeared in a January 2014 issue of the New England Journal of Medicine.

Both agents were tested in patients with mild-to-moderate AD, and although both successfully reached their targets and showed evidence of clearing or modifying Aβ deposits in the brain, neither agent significantly improved clinical outcomes in AD patients.

Among the lessons learned from these and other failed clinical trials, including those of an active anti-Aβ vaccine, John Trojanowski, MD, PhD, Director of the Institute on Aging and the Alzheimer’s Disease Core Center at the University of Pennsylvania, says three are most important.

“First, we know that we must intervene at an earlier stage of the disease,” Dr. Trojanowski says, “so it is now essential to design prevention trials or clinical trials that address prodromal AD. Second, we must use biomarkers in all patient populations to increase confidence in diagnosis and also to monitor target engagement, as well as response to therapy. And third, we must develop drugs that address other AD targets, such as tau tangles.”

Reisa Sperling, MD, Director of the Center for Alzheimer’s Research and Treatment at Brigham and Women’s Hospital and Massachusetts General Hospital and Professor of Neurology at Harvard Medical School, cites these same lessons, with an emphasis on the need to treat the right target at the right stage of disease.

“Phase 3 trials with both bapineuzumab and solanezumab suggest that it’s more likely that we will have success with anti-amyloid therapies at earlier stages of the disease,” Dr. Sperling says. “The solanezumab trials, in particular, showed a benefit in patients with mild dementia, but none of the studies shows statistically significant effects clinically or on biomarkers in the moderate dementia groups. Another lesson we learned is that we need to be able to give enough of these antibodies to increase binding enough to remove amyloid. In the bapineuzumab studies, dosing was limited by side effects; that wasn’t true in the solanezumab studies, which may be why they were able to see some evidence of a clinical effect in a subgroup.”

RETHINKING AD PATHOPHYSIOLOGY

Puzzling to many inside and outside of the field of AD research is the fact that some individuals with significant beta-amyloid accumulation can remain cognitively normal. Moreover, studies have shown that AD-like neurodegenerative patterns can occur in patients without any beta-amyloid accumulation.

“We don’t have all the answers about amyloid yet and we don’t yet have enough data,” says Dr. Sperling. “But the preponderance of data so far suggests that people who have evidence of amyloid accumulation over time show a faster rate of decline than people who do not.

“That does not mean that everyone with amyloid accumulation will develop Alzheimer’s disease,” she adds. “Most likely there are factors that confer resistance to amyloid, and as with high cholesterol and heart disease, amyloid most likely is only one part of the AD puzzle. We know, for example, that the vast majority who have high cholesterol will never have a heart attack or stroke, so cholesterol is only one contributing factor to heart disease.

“Even if amyloid is only a contributing factor to Alzheimer’s disease, intervening at the right stage may prove to be beneficial,” Dr. Sperling says. “I do think there are many other factors to consider, some of which may prove to be synergistic among individuals who are amyloid positive. For example, for a given amount of amyloid, we know that APOE4 [the gene apolipoprotein E4] can further influence the rate of cognitive decline.”

Although it is well established that amyloid accumulation occurs early in the AD process, many experts agree that it is only part of the puzzle, in part because its correlation with cognitive decline and disease progression so far remains weak.

“The cascade hypothesis posits that Aβ in some way trig-

Disclosure: The author reports that she has no commercial or financial relationships in regard to this article.

John Trojanowski, MD, PhD

Susan Worley is a freelance medical writer who resides in Pennsylvania.
After Disappointments, Alzheimer’s Researchers Seek Out New Paths

Table 1 Current Treatments for Symptoms

<table>
<thead>
<tr>
<th>Generic Name (Brand)</th>
<th>Manufacturer</th>
<th>Postulated Mechanism of Action</th>
<th>Approximate Cost for 30 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galantamine (Razadyne)</td>
<td>Janssen Pharmaceuticals</td>
<td>Enhances cholinergic function by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. The effect of galantamine may diminish with disease progression, as fewer cholinergic neurons remain functionally intact.</td>
<td>$265 to $550 depending on dosage and formulation</td>
</tr>
<tr>
<td>Rivastigmine (Exelon)</td>
<td>Novartis Pharmaceuticals</td>
<td>Enhances cholinergic function by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. The effect of rivastigmine may diminish with disease progression, as fewer cholinergic neurons remain functionally intact.</td>
<td>$310</td>
</tr>
<tr>
<td>Donepezil (Aricept)</td>
<td>Eisai</td>
<td>Enhances cholinergic function by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase.</td>
<td>$340 to $380 depending on dosage and formulation</td>
</tr>
<tr>
<td>Memantine (Namenda)</td>
<td>Forest Pharmaceuticals</td>
<td>N-methyl-D-aspartate (NMDA) receptor antagonism; memantine preferentially binds to the NMDA receptor-operated cation channels.</td>
<td>$290</td>
</tr>
</tbody>
</table>

The FDA has approved five treatments for symptoms of Alzheimer’s disease, but one of them, tacrine (Cognex, Sciele Pharma) has been discontinued in the U.S. Use of these interventions can result in moderate but temporary improvement in cognitive function in individuals with mild-to-moderate dementia.

Reisa Sperling, MD

Indeed, Dr. Sperling, who is co-lead investigator of the A4 trial (see “Current Clinical Trials” later in this article) intends to pursue nonamyloid as well as amyloid targets, expecting that the A4 trial design will serve as a platform for future secondary prevention trials with other agents, and ultimately for combinations of agents. In addition, individuals screened for the trial who do not show evidence of elevated amyloid accumulation may be eligible to participate in LEARN, a companion observational study. The LEARN study will seek to quantify amyloid-related cognitive decline and obtain data on nonamyloid factors that contribute to AD.

**IMAGING TECHNIQUES AND NONIMAGING BIOMARKERS**

Because a successful treatment for AD may require intervention prior to the emergence of symptoms, early identification of pathology that indicates an increased likelihood of developing AD dementia is critical. Imaging and nonimaging biomarkers, as well as genetic information, are necessary to improve the sensitivity and specificity of all assessments, from those undergone at presymptomatic stages of the disease to those associated with the monitoring of treatment. The field has seen remarkable growth in all of these areas.

“We now have three FDA-approved amyloid imaging agents, including florbetapir (Amyvid, Avid Radiopharmaceuticals, approved in 2012) followed by flutemetamol (Vizamyl, GE Healthcare) and florbetaben (Neuraceq, Piramal Imaging), that build on the foundation of the research tracer [11C] Pittsburgh Compound B (PiB) for the detection of cerebral amyloid burden in individuals with cognitive changes,” says Andrew Saykin, PsyD, ABCN, Director of the Indiana Alzheimer Disease Center at Indiana University School of Medicine and Genetics Core Leader at the Alzheimer’s Disease Neuroimaging Initiative (ADNI). “These F18-labeled PET [positron-emission tomography] tracers are an important improvement over the first generation of experimental amyloid tracers labeled with C11, which has a very short half-life.

“Another major development has been the standardiza-
After Disappointments, Alzheimer’s Researchers Seek Out New Paths

Andrew Saykin, PsyD, ABCN

New developments in the realm of tau imaging, although still in the early stages, also have been very encouraging. Many outside of the field, including patients and their families, hope that sophisticated imaging techniques may eventually replace the more invasive collection of cerebrospinal fluid (CSF) via lumbar puncture, but for now researchers still depend on CSF assays.

“Advances in imaging already provide noninvasive means for detecting AD-related changes or heightened risk for progressive cognitive decline,” says Dr. Saykin. “However, as with all methods, imaging has limitations. For example, despite the great progress in PET tracers for amyloid and tau, PET cannot yet detect several other important proteins that cause neurodegenerative changes leading to other forms of dementia. Unlike CSF, where multiplex assays can search for a range of abnormal proteins, in most cases PET scans are limited to a single molecular target, such as amyloid plaque. Usually only one or two PET scans are administered to minimize radiation exposure.”

Imaging can provide information that is significantly more detailed when used in conjunction with genetic information and nonimaging biomarkers.

“Different biomarkers are likely to be more useful at particular stages of disease or in screening different at-risk groups,” Dr. Saykin says. “Once AD is detected during the early preclinical or prodromal phases, prior to extensive neurodegenerative changes, imaging can serve as a longitudinal biomarker to monitor response to therapy. Imaging and other approaches such as CSF analysis and genetics provide complementary information when used in combination. Our group and others have reported, for example, that PET, MRI, CSF, and plasma biomarker results are all significantly influenced by variation in APOE and other genes.”

Progress in the development of blood-based biomarkers, which is occurring at a very rapid pace, is tempered somewhat by the need for validation.

“There is a critical need for inexpensive and noninvasive biological markers to improve early detection and diagnosis of AD,” says Maria Carrillo, PhD, Vice President of Medical and Scientific Relations at the Alzheimer’s Association. “Blood-based biomarkers with the potential for widespread clinical use will need to be validated in large groups of subjects who are represen-
tative of a diverse aging population, and the gathering, storage, and processing of such biomarkers must be standardized for dependability of use and consistent interpretation of results.”

An International Society to Advance Alzheimer’s Research and Treatment (ISTAART) professional interest area (PIA) is creating standards and guidelines for the development of novel blood biomarkers and intends to validate them for use in research settings, clinical trials, diagnostics, and clinical practice. This ISTAART PIA also is developing a central data repository and sample bank network.

“A blood test for determining cholesterol levels is now available almost anywhere in the world,” Dr. Carrillo says, “and there are recognized standards for how and when to take the blood, how to process it, and how to interpret the results. The ISTAART PIA will help develop similar standards for AD biomarkers, so that eventually simple predictive and diagnostic tests can be effectively implemented.”

CURRENT CLINICAL TRIALS

Current clinical trials, characterized by a new focus on secondary prevention, involve the testing of populations comprising asymptomatic individuals at risk of developing AD, presymptomatic individuals with AD-related mutations, and/or individuals with prodromal AD. The Collaboration for Alzheimer’s Prevention (CAP) consortium facilitates collaborative interactions among the first four of the following trials to maximize translatable findings. The Food and Drug Administration and European Medicines Agency, with input from CAP, issued guidance to assist these trials in pursuing an innovative regulatory pathway.17

The A4 Study

The Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease (A4) study® is a three-year, placebo-controlled, randomized clinical trial that will screen 5,000 clinically normal older individuals to identify and enroll 1,000 with increased amyloid accumulation on PET imaging, who are thus at increased risk for cognitive decline. Individuals enrolled in the first trial will be randomized to receive solanezumab or placebo; screened individuals who do not show evidence of elevated amyloid accumulation may be eligible to participate in the LEARN study, a companion observational arm that will run parallel to the A4 treatment arm with identical cognitive assessments. A4 and LEARN study participants will be followed for 168-week treatment and observation periods. Investigators anticipate that the A4 trial design will serve as a platform for secondary prevention trials with other anti-amyloid agents, such as beta-secretase inhibitors, and for combinations of agents.

The DIAN-TU Study

In 2012, the Dominantly Inherited Alzheimer’s Network Trials Unit (DIAN-TU)® launched a phase 2/3, randomized, double-blind, placebo-controlled, multicenter study of solanezumab or gantenerumab (Hoffman-LaRoche) in individuals at risk for dominantly inherited AD. A total of 210 participants with presenilin 1, presenilin 2, or amyloid precursor protein (APP) mutations have been assigned to receive solanezumab or gantenerumab in a phase 2 trial that may last up to two years. If biomarker endpoints are successfully met in the phase 2 trial, participants will make a seamless transition to a phase 3 trial (the DIAN-TU Adaptive Prevention Trial) with a cognitive endpoint and an expected total enrollment of 400 participants. Presenilin 1, presenilin 2, and APP mutations are rare, and individuals with these mutations together account for less than 1 percent of all individuals who develop AD. The goal of the DIAN-TU trials is to use biomarkers of target engagement, such as amyloid PET and CSF amyloid-beta measures, in addition to downstream biomarkers, including CSF tau, phospho-tau, MRI structural atrophy, functional MRI, PET with [18F]-fluorodeoxyglucose, and tau PET imaging, to track changes in the brains of individuals with these gene mutations who have not yet developed AD. The trial will also seek to test drugs that may slow or halt disease-related changes and possibly prevent the emergence of symptoms such as memory loss. The DIAN-TU trial platform is evaluating additional drugs to test in registration trials with built-in seamless transitions from biomarker to cognitive endpoints.

The API ADAD Study

The Alzheimer’s Prevention Initiative (AP) Autosomal Dominant Alzheimer’s Disease (ADAD) trial is one of the first prevention trials conducted in cognitively healthy individuals who are certain to develop AD because of their genetic background. This study will include approximately 300 people from a large extended family in Colombia who share risk for a rare genetic mutation that typically triggers AD symptoms around age 45.20,21

Participants in the double-blind, placebo-controlled trial will receive an injection of either crenezumab (Genentech/AC Immune) or a placebo at set intervals for up to five years. The study will test whether crenezumab can protect participants in the short or long term from developing signs of AD. Using targeted biomarkers, state-of-the-art imaging, and sophisticated cognitive measures—which allow researchers to detect and track the disease presymptomatically—researchers will be able to see whether the amount of amyloid in the brain decreases, whether brain size is maintained, and, most importantly, whether cognitive function is preserved.

In addition, to better understand the natural process of early-onset autosomal-dominant AD, researchers will compare changes in clinical symptoms and signs over time in people with and without the mutation who are treated with a placebo. Following the completion of the trial, efficacy and biomarker data and findings will be shared with the entire research community.

The TOMMORROW Trial

The TOMMORROW trial is designed to test the effectiveness of pioglitazone (AD-4833; Takeda), a drug already FDA-approved to treat type-2 diabetes, in the prevention of AD in individuals at risk for the disease. It also will examine the degree to which the TOMM40 risk allele confers a greater
Vol. 39  No. 5 • May 2014 • P&T

After Disappointments, Alzheimer’s Researchers Seek Out New Paths

In this five-year, phase 3, double-blind, placebo-controlled study, researchers will examine whether pioglitazone’s ability to regulate glucose metabolism and insulin sensitivity and reduce inflammation will have a protective effect that is sufficient to prevent high-risk patients from developing mild cognitive impairment and AD. Pioglitazone’s efficacy in delaying the onset of AD in cognitively normal individuals will be compared with placebo, based on comparisons of cognitive decline, functional decline, and changes in activities of daily living.

Approximately 5,800 asymptomatic individuals between the ages of 65 and 83 years will be screened with the goal of enrolling about 120 participants at each of approximately 50 sites. All participants will undergo a blood test to establish APOE and TOMM40 genotypes. Cognitively normal individuals determined to be at high risk for developing AD will be randomized to receive either AD-4833 or placebo, and those in the treatment group will receive AD-4833 orally once per day.

The SNIFF Study

The Study of Nasal Insulin in the Fight Against Forgetfulness (SNIFF) is a multicenter, double-blind, placebo-controlled phase 2/3 trial sponsored by the Alzheimer’s Disease Cooperative Study to evaluate the impact of inhaled insulin in participants with mild memory impairment and early AD. In this 18-month study, approximately 240 people ages 55 to 83 years will be given either intranasal insulin (INI) or placebo for 12 months, followed by an open-label six-month period during which all participants will receive INI.

Some evidence indicates that insulin performs multiple functions in the brain and that insulin dysregulation may contribute to AD pathogenesis. INI has shown promise in short-term clinical trials. Conducted at 29 locations, SNIFF will examine INI’s effects on cognition, entorhinal cortex and hippocampal atrophy, and CSF biomarkers. The study aims to examine whether baseline AD biomarker profile, gender, or the presence of the APOE4 allele predict treatment response.

CONCLUSION

During the past decade, clinical trials that have focused on strategies for reducing the production and accumulation of Aβ in the brains of individuals with AD have offered valuable information. They have launched a new era of AD prevention trials, in which the pursuit of methods for modulating Aβ levels will be accompanied by the use of novel biomarkers that should offer greater insights into the role that Aβ plays in the disease process. Knowledge gleaned from these trials also has begun to inform the development of drugs that address non-amyloid targets, including at least one that involves a creative method for crossing the blood–brain barrier, and most likely will continue to inform research that ultimately moves in the direction of combination therapy.

REFERENCES

Alzheimer’s Researchers Seek New Paths

continued from page 369


27. Aricept, prescribing information. St. Louis, Missouri; Forest Laboratories; 2013.