CTAD 2016 – Highlights December 9, 2016

San Diego, California, USA, December 9, 2016. The second day of the 9th international conference on Clinical Trials in Alzheimer’s Disease (CTAD) featured continued exploration of new treatments being developed for AD including interventions in in early as well as late stages of development.

One therapeutic option that has been greeted enthusiastically is aducanumab, a human monoclonal antibody that binds aggregated but not monomeric forms of beta amyloid; and that has been shown in AD mouse models to remove amyloid plaques from the brain. In his keynote address on Thursday, Paul Aisen, MD said he thinks aducanumab could halt amyloid pathology entirely by removing brain amyloid during the preclinical stage of disease.

Biogen Idec has initiated two phase 3 trials of aducanumab, even as it continues analyzing the Phase 1b study called PRIME. Biogen had previously reported data showing that the main safety concern was a dose-dependent increased incidence of amyloid-related imaging abnormalities-vasogenic edema (ARIA-E) in carriers of the apolipoprotein E4 allele, a genetic marker that increases the risk of developing AD. They also had reported a dose-dependent reduction in amyloid (assessed using PET imaging) after 12 months of treatment compared to no reduction in amyloid among participants receiving placebo. Additional data presented at CTAD by Vissia Viglietta, MD, PhD, showed that by gradually increasing the dose from 1 mg/kg to 10 mg/kg they could reduce the incidence of ARIA-E.

Samantha Budd Haeberlein, PhD, also presented new information from PRIME, including data from a 12-month long-term extension in which participants originally randomized to the placebo or lowest dose groups were switched to receive higher doses, while those in the higher dose groups continued to receive the same dose. Exploratory endpoints, including decreased amyloid plaque burden and changes from baseline on clinical endpoints, showed statistically significant benefits and no new safety signals, supporting the decision to start Phase 3 trials.

Promising new treatments targeting tau, the protein found in neurofibrillary tangles in the AD brain, were also featured at the Conference. AXON Neuroscience, for example, earlier this year reported Phase 1 data demonstrating safety and tolerability of AADvac1, a vaccine that stimulates an immune response against tau. At CTAD, Matej Ondrus, MD, presented data from a follow-up study confirming the favorable safety profile and showing that booster doses of vaccine following the initial 6-dose regimen induced a sustained immune reaction to pathological tau. A Phase 2 study is now underway to test different dosing options and look for signals of clinical efficacy.

In another approach targeting tau, an early clinical trial of AbbVie’s ABBV-8E12, an anti-tau monoclonal antibody, showed an acceptable safety and pharmacokinetic
profile in participants with progressive supranuclear palsy (PSP), a rare disease caused by the accumulation of pathological tau in nerve cells.

Stem cells offer yet another therapeutic strategy that has shown promise in the treatment of AD. Aimee Pierce, MD, a neurologist at University of California, Irvine, called stem cells a “hugely exciting topic for patients,” noting that two early Phase clinical trials of stem cell therapeutics for AD are currently underway. In these studies, the goal is not to replace neurons killed off by the disease but to alter other cellular processes such as neuroinflammation. For example, preclinical data presented by Tristan Bolmont, PhD, from Stemedica International in Lausanne, Switzerland demonstrated that multiple injections of human mesenchymal stem cells reduced plaques and neuroinflammation in mouse models of AD.

Drugs and biologics were not the only therapeutic approaches being pursued for the treatment of AD that were discussed at CTAD. Marwan Sabbagh, MD, a neurologist at the Barrow Neurological Institute in Phoenix, Arizona, presented data suggesting that a treatment approach in development by Neuronix, which combines transcranial magnetic stimulation (TMS) with cognitive training may safely provide a statistically significant cognitive benefit for patients with mild to moderate AD.

Given that the challenges in drug development extend beyond scientific and clinical questions, CTAD participants also grappled with policy and infrastructure issues. A workgroup of the NIA and Alzheimer’s Association presented their latest efforts to re-evaluate and revise the 2011 guidelines defining and staging AD across the entire continuum of the disease for research purposes. The need for this revision reflects an evolution in our understanding of the disease and increased data on biomarkers, said Cliff Jack of the Mayo Clinic in Rochester, Minnesota.

As drug development for AD moves to earlier stages of disease, conducting clinical trials has become more challenging than ever, said Dr. Budd-Haeberlein. Inaccuracy of diagnosis and inadequate tools for detecting change in the early stages of disease lead to larger and longer trials and a higher rate of screen failures, making recruitment of study subjects especially challenging. Budd-Haeberlien said there are currently more than 50 ongoing Phase 3 AD trials with an average of nearly 1000 patients per study. “We simply need to put more patients into the funnel,” she said at a ‘Town-Hall’ discussion on a proposed national campaign to raise public awareness. The goals of the campaign will be to encourage public participation, engage clinicians to direct patients to trial sites, and build a network of sites with the capacity and ability to enroll participants. Representatives of industry, the NIA, and non-profits such as the Alzheimer’s Association have begun this process, and the NIA plans to host a meeting in the spring of 2017 to craft a blueprint for moving this effort forward, said Laurie Ryan, PhD, of the NIA.