CTAD Highlights November 15, 2013

San Diego, California. One of the central themes of the sixth annual Clinical Trials in Alzheimer's Disease (CTAD) conference, which opened yesterday in San Diego, California, is the idea of testing potential new therapies not in older people with dementia, but in younger, asymptomatic, genetically determined populations where the risk of developing the disease is high and with a predictable course. This shift in focus has given rise to three large prevention trials to be conducted by the Alzheimer's Prevention Initiative (API), the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), and a partnership of Takeda and Zinfandel Pharmaceuticals (the TOMMorrow trial). All of these studies, as well as a fourth study called the Anti-amyloid therapy in Asymptomatic AD (A4) trial aim to slow the progression of disease in people at high risk of developing AD prior to the onset of symptoms.

Individuals with Down syndrome represent an even larger group of people with an elevated risk of developing AD. "Every single person with Down syndrome will develop Alzheimer's pathology by age 40, and more than half will have dementia by age 60," said William Mobley, M.D., Ph.D., Chair of Neurosciences at the University of California, San Diego. Since Down syndrome affects some 6 million people worldwide. this population represents the largest group of individuals with early onset AD, far more than the number with AD-inducing genetic mutations.

Dr. Mobley maintained that this population can help accelerate the development of treatments for AD for a number of reasons beyond the high prevalence: the diagnosis can be made long before the onset of dementia and followed longitudinally; AD patients with Down syndrome are younger and relatively healthier than older AD patients who frequently have other medical problems; and Down syndrome patients frequently have supportive and motivated caregivers. To this end, UCSD has launched the Down Syndrome Biomarker Initiative (DSBI) to do for the Down syndrome community what the Alzheimer's Disease Neuroimaging Initiative (ADNI) has done for the larger AD community: discover, develop, and standardize biomarkers to accelerate the understanding of AD pathological and clinical progression.

There are other reasons to study AD in the Down syndrome population, according to Dr. Mobley. "Evidence shows that the neuropathology is nearly identical to what is seen in sporadic AD," increasing the likelihood that treatment effects in Down syndrome would be recapitulated in sporadic AD. Indeed, research in Dr. Mobley's lab using mouse models of Down syndrome to explore the mechanisms of neurodegeneration support the idea that parallels can be drawn between AD and Down syndrome.

New recruitment strategies

Even as trials with selected high risk populations are being planned or getting underway, drug developers are exploring strategies for recruiting the large numbers of people that will be needed for studies in the wider population. One possible approach that has attracted interest from pharmaceutical companies and others involved in conducting clinical trials is the use of internet-based screening of cognition as a recruitment tool.

According to Bruce Albala, Ph.D. of Eisai, Inc., brief internet screening approaches enable the efficient collection of data while placing a low burden on potential subjects, caregivers, and staff. In a pilot test of such a system, Eisai set up a web portal to collect demographic information, evaluate depression and memory complaints, and assess cognition using the CogState Brief Battery, a four-task, 15 minute test of various aspects of cognition. In this pilot study, about half of those screened were found to be ineligible for the trial. In addition to saving time and resources by screening out these people without requiring them to come to a clinical trial center with an informant, the system allows subjects to learn quickly whether they are likely to be eligible for a trial.

Larry Ereshefsky,PharmD of PAREXEL International cited another reason why internet based screening approaches may improve recruitment rates for clinical trials. "Stigma prevents people from taking part in trials," he said. "Home screening may increase the number of people who will take part."

Another possible recruitment approach, said Dr. Ereshefsky, might be to mine deidentified data in electronic health records to identify people with a high probability of having MCI. "What I'm suggesting is that web-based screening is a tool that can be used to harness other tools such as electronic health records," he said.

Treating neuropsychiatric symptoms

Another prominent theme at CTAD this year has been the importance of treating neuropsychiatric symptoms such as agitation, aggression, psychosis, and apathy in people with AD. "These are common symptoms, they are very clinically meaningful, disabling to patients and families, increase costs, drive institutionalization, and they measurably decreased the quality of life of our patients," said Jeffrey Cummings, M.D., Sc.D., Director of the Cleveland Clinic Lou Ruvo Center for Brain Health. Despite the high burden of these symptoms, no drugs have been approved to treat them in patients with AD. Moreover, AD patients are typically excluded from trials of psychotropic medications, which means little is known about their effects in people with dementia. One reason that so few trials have been conducted in patients with neuropsychiatric symptoms, according to Dr. Cummings, is that the presence these symptoms makes trial participation difficult for both the patients and their caregivers. As a result, the average neuropsychiatric test score for patients in clinical trials is about 9 or 10, while the scores for clinic populations averages about 15-20 (higher scores indicate more severe symptoms).

Despite the challenges of testing drugs for these symptoms, there are currently 4 drugs in late stage (phase 3) trials and another 6 in earlier stages of testing. This represents a substantial increase over previous years, not only in terms of the number of drugs but in the diversity of mechanisms being explored, said Dr. Cummings.