PRESS RELEASE

Highlights from the 5th International Conference on Clinical Trials in Alzheimer's Disease, October 30 in Monte Carlo, Monaco.

At the 5th International Conference on Clinical Trials for Alzheimer's Disease (CTAD) on Tuesday, October 30th, researchers continue to discuss strategies for tackling the disease in its earliest stages.

Selecting subjects for presymptomatic trials

As the focus of AD drug development moves increasingly to the presymptomatic stages of the disease, it has become essential to identify people who are on track to develop AD so that trials can be enriched with subjects likely to show benefits from treatment within a relatively short period of time. Measures of brain shrinkage and cognitive decline are commonly used to differentiate individuals on the AD trajectory from those with normal brain aging. However, a study presented at CTAD by Dominic Holland, Ph.D. from the University of California, San Diego, showed that it may be difficult to distinguish AD from normal aging in the oldest old, since clinical decline and brain atrophy tend to slow with advanced age in individuals with MCI and AD, but speed up in healthy controls. "If you are interested only in having power to detect change, the younger the cohort the better, but if you develop a therapy you want to know how well it is tolerated by various age groups, so you would want to enroll older people," said Dr. Holland.

Dr. Holland also presented data showing that while rates of change in measures of regional brain atrophy and cognitive performance are high enough in the MCI phase of the disease to detect a statistically significant effect with a reasonably sized trial over a reasonable time period, there can be significant gains (i.e., smaller numbers of subjects needed) by selecting those likely to be at elevated risk for AD based on cerebrospinal fluid (CSF) levels of the AD-relevant proteins beta-amyloid and tau, or baseline measures of regional brain atrophy. However, in cognitively normal individuals, even those showing biomarker signs of being at elevated risk for presymptomatic AD, structural and cognitive rates of change are too low to adequately power a trial of standard duration. These findings mean that long natural history studies of AD are needed to understand the biomarker changes that precede dementia, said Dr. Holland.

Trial Shows Benefits from Multi-Domain Intervention

Professors Bruno Vellas, Thierry Voisin, and Pierre Payroux from Toulouse University Hospital, and Carole Dufouil from Bordeaux University Hospital, presented data from three imaging sub-studies of the MultiDomain Alzheimer's Preventive Trial (MAPT). MAPT was set up to test systematically whether a multi-domain intervention that provides nutritional counseling, physical exercise, cognitive stimulation, and social activities, in combination with omega-3 fatty acid supplementation, is effective in slowing cognitive decline in elderly, frail individuals. Results from the imaging studies suggest that the intervention reduced markers of neurodegeneration, although it is too early to tell whether those changes lower the risk of developing AD.

Epidemiologic studies have suggested a role for nutrition, physical exercise, cognitive activities, and social stimulation in maintaining cognitive function. The MAPT intervention trial randomized 1680 subjects to one of four groups: multi-domain treatment plus omega-3 fatty acids, multi-domain plus placebo, omega-3 alone, or placebo alone. Cognitive and functional assessments are conducted at baseline, 6, 12, 24, and 36 months by research staff blind to the intervention received. In addition, subgroups of subjects agreed to undergo imaging studies intended to determine whether the treatment produced a biological effect that could be detected either by a change in brain metabolism, decreased brain shrinkage, or a change in the deposition of amyloid plaques in the brain.

Brain metabolism was assessed using FDG-PET scans performed at baseline and 6 and 12 months in 34 subjects receiving the multi-domain intervention plus omega-3 fatty acids and another 34 subjects in the non multi domain intervention group, placebo or omega 3 but without physical and cognitive exercise. Hypometabolism in certain areas of the brain has been linked to AD and, when used as a longitudinal measure, is thought to be a marker of neurodegeneration. The results from the MAPT FDG-PET ancillary study support this idea: Those in the treatment group showed significantly higher brain metabolism compared to the placebo group in the pre-frontal region of the brain at both 6 months and 12 months. These results, while preliminary, suggest not only that the multidomain intervention may help protect frail elderly individuals from neurodegeneration, but also support using FDG-PET to monitor treatment effectiveness.

Another subgroup of MAPT subjects participated in a study of florbetapir (Amyvid), an imaging agent that enables the visualization of amyloid plaques in the brain of living individuals. The florbetapir ancillary study of MAPT was designed to examine the association between amyloid deposition and frailty in a subset of 184 non-demented elderly individuals. This analysis revealed that at baseline, nearly 37% of the volunteers had florbetapir uptake levels in the cortex that were considered positive for amyloid pathology. Amyloid positivity was associated with lower cognitive function but not frailty.

The final subgroup included 444 subjects who underwent MRI scans to assess mean intracranial volume, brain parenchymal fraction, and total hippocampal volume. All three measures have been linked to neurodegeneration in AD patients. The goal of the study was to define the relationship between frailty and markers of brain atrophy and whether they might represent a common pathway in AD. Hippocampal volume was significantly correlated with walking speed and repeated chair stands, but there was no such association with global atrophy. Further analyses are planned using additional frailty markers and MRI measures such as voxel-based analysis, cortical morphology, diffusion tensor imaging and functional MRI.

Pr. Vellas said that these studies highlight the importance of considering both frailty and cognitive function in prevention trials. “In clinical practice when an older adult has some kind of physical impairment they are also more likely to become demented. This must be taken into consideration when we do larger studies.”