Latest Developments in Preclinical Alzheimer’s Disease

An Expert Interview with Martin R Farlow

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**Martin R Farlow**
Dr Farlow is Professor of Neurology and Vice-Chairman of Research in the Department of Neurology at the Indiana University School of Medicine in Indianapolis. He is also Associate Co-Director of the Indiana Alzheimer’s Disease Center in Indianapolis and leads a large Alzheimer and related dementias clinical trials site in the Department of Neurology. He has led and/or contributed to over 150 clinical trials over the last 25 years. Dr Farlow has lectured on the topics of aging, dementia, and Alzheimer’s disease at more than 300 meetings, conferences, and hospitals/medical schools throughout the world. A prolific author, Dr Farlow has presented more than 467 abstracts at professional meetings and has authored or co-authored more than 455 articles published in peer-reviewed journals such as The Lancet Neurology, Annals of Family Medicine, and Journal of the American Geriatrics Society. Dr Farlow’s research focuses on clinical trials of investigational drugs for the treatment of Alzheimer’s disease and related dementias being the lead investigator for several major studies including; tacrine, donepezil, rivastigmine, CAD106, and one of the leading investigators for solanezumab and has interests in trial design and safety. Dr Farlow also has clinically characterized and helped determine genetic linkage for several familial dementias including the second mutation associated with autosomal dominantly inherited Alzheimer’s disease, Gerstmann-Straussler-Scheinker disease and Multi Systems Tauopathy with Dementia.

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In the last decade, our understanding of Alzheimer’s disease has advanced considerably. Thanks to evolving biomarker research, it is now recognized that a preclinical stage occurs before the occurrence of symptoms. This preclinical phase has become the focus of considerable research efforts as early intervention is likely to offer the best chances of a cure. To date, very little clinical evidence is available in the effectiveness of drugs in this stage of the disease.

In an expert interview, Dr Farlow discusses the concept of preclinical Alzheimer’s disease and the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) trial, which is investigating drugs to slow or prevent disease progression in autosomal dominant Alzheimer’s disease families.

**Q. How is preclinical Alzheimer’s disease defined?**

Until recently, Alzheimer’s dementia was defined primarily by clinical criteria, characterized by deficits in memory and other cognitive functions that progressively impair activities of daily living. Clinical and laboratory studies demonstrate no other cause for these symptoms and there is no evidence of other neurodegenerative disease that could impair cognition. Over the last decades it has been recognized that, prior to developing dementia, people go through a phase called mild cognitive impairment, which is a pre-dementia but not preclinical phase. Symptoms include difficulties with short-term memory, recognizing items in the visual field, language, and executive functioning. When examined by objective cognitive tests, patients are found to have significant deficits but their deficits do not affect activities of everyday living. Recent clinical trials have found that, at the stage of mild cognitive impairment, despite absence of functional deficits in activities of daily living, the disease is biologically advanced and difficult to treat and therefore there is a clear need to define Alzheimer’s disease at an earlier stage.

A large number of genes have been recognized as being associated with an increased risk of Alzheimer’s disease, the most prominent being ApoE. People with this genotype are at increased risk of developing mild cognitive impairment and Alzheimer’s dementia in their 50s and 60s. In patients with this risk factor, the disease has been developing biologically at a preclinical level, before the appearance of any symptoms. Clinical trials are targeting individuals with this genetic risk factor with the aim of interrupting the disease process in the preclinical phase.
A large amount of research has found that there is a very early stage where no biomarkers are detectable but pathological changes in the brain are occurring due to biological processes that predispose to, or are the earliest steps on the road to, Alzheimer’s disease. It is believed that these changes then progress to a stage that involves deposition of beta-amyloid in the cortex of the brain. Beta amyloid is the chief component of plaques in Alzheimer’s disease. It can be detected by positron emission tomography (PET) scans using a ligand that attaches to the amyloid, and also by measuring levels of a peptide fragment known as Abeta 1-42 in the cerebrospinal fluid (CSF). Levels of this protein are decreased in patients with Alzheimer’s disease.

A further stage with no clinical symptoms is characterized by degeneration of neurons in the brain and this can be detected by PET scan using fludeoxyglucose to show abnormal glucose utilization. Another typical finding at this stage is high levels of a protein called Tau and its phosphorylated form, phospho tau. On a structural magnetic resonance imaging scan, the cortex can be seen to be thinner and it is possible to see shrinkage of the hippocampus, which is an area of the brain associated with short-term memory. These changes are initially not associated with dysfunction. The next stage involves early cognitive decline, detectable in groups of patients as poor performance on cognitive tests. Such changes are not diagnostic in the single patient. The disease progresses to objective clinical findings such as mild cognitive impairment.

Q: What advances have been made in neuroimaging for the diagnosis of preclinical Alzheimer’s disease?

Advances in neuroimaging methods such as amyloid-PET scans and MRI, as discussed above, have enabled us to detect early changes in the brain in patients with Alzheimer’s disease. These changes have been extremely helpful in research studies and have allowed us to begin clinical trials targeting patients at very early stages of the illness, prior to clinical symptoms. The hope is to catch the disease at an early stage, where minimal damage has been done, in order to have a better chance of delaying disease progression and ultimately preventing Alzheimer’s disease.

Q: Could you tell us a little about the DIAN-TU Next Generation Alzheimer’s prevention trial?

This trial is a second-generation trial. The initial DIAN-TU trial (ClinicalTrials.gov identifier: NCT01760005) targeted patients with dominantly inherited Alzheimer’s disease associated with either a presenilin or an amyloid gene mutation in a double-blind placebo-controlled trial with multiple arms. The first two arms investigated monoclonal antibodies (mAbs) against beta amyloid: gantenerumab and solanezumab. The third arm involved a BACE inhibitor. The trial is still ongoing but since the study initiation, evidence has become available from other trials investigating these drugs in sporadic Alzheimer’s disease, that has led to modifications of the original DIAN-TU trial. Firstly, BACE inhibitors have not been demonstrated to be effective in patients with established sporadic Alzheimer’s disease with mild cognitive impairment or mild dementia. As a result, the third arm of the study was discontinued. Another finding from trials suggests that the original mAbs chosen were probably administered at too low a dose to effectively engage the target, and therefore study protocols have been amended to give higher, hopefully more effective doses.

The second-generation trial will test two interventions against placebo. One will be a drug targeting Tau, which is associated with the formation of neurofibrillary tangles, one of the characteristic findings of Alzheimer’s disease; the other has not yet been chosen. The population will be primarily younger, very early preclinical Alzheimer’s disease patients who are carrying the dominantly inherited genes for Alzheimer’s disease. The trial uses evidence that has accumulated from the DIAN-TU trial and is applying a model of disease progression using biomarkers. A composite outcome measure has been developed that is very sensitive, even in preclinical patients. It is recognized that, in these trials, initial dosage assignments, and how a different drug is administered, may need to change over time, and an algorithm is being built into the trial that allows adjustment. The trial is designed to last 4 years but will maintain a blinded collection of data until the last patient is treated. This aim is to maximize the probability of determining whether a given drug is beneficial in these patients in particular and in Alzheimer’s disease in general.