Editorial

One Step Forward Toward a Surrogate Endpoint for Clinical Trials of Alzheimer's Disease Drugs: The Results of PharmaCog WP5 (European ADNI)

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Alzheimer's disease (AD) consists of a cascade of molecular neurobiological events leading to profound disability. Despite not always coherent, a significant amount of preclinical, genetic, and epidemiologic evidence indicates that brain amyloidosis in the form of fibrillary extracellular plaques is an early event in the disease course, that amyloid is often followed by aggregation of intracellular hyperphosphorylated tau, and that this is followed by synaptic dysfunction, neuronal loss, memory loss, and finally progression to profound dementia. Importantly, at the time when even mild memory symptoms are present, biological events (brain amyloidosis and tauopathy, and functional and structural brain changes) are detectable via analyses of the cerebrospinal fluid and imaging techniques (MRI and PET).

Research is very active on developing a curative strategy. In 2018, 26 drugs for AD were in phase III, 17 of which were disease modifiers targeting amyloid, tau, neuroprotection, and metabolic mechanisms [1]. Unfortunately, despite different mechanisms of actions, all the disease modifying drugs tested so far have invariably failed to achieve clinical endpoints. Drug development in AD is so expensive and risky that a number of major pharma companies are leaving the field. Ameliorating the predictability and efficiency of clinical trials is one of the major unmet needs of AD research.

A common strategy to decrease the group size required to detect a signal of efficacy of an experimental drug and contract the observation time of clinical trials (and consequently decrease costs and increase drug testing throughput) is the use of surrogate endpoints. In HIV research, instead of following hundreds of infected patients for years to detect a decreased incidence of opportunistic infections and mortality, the anti-retroviral drug zidovudine was developed on a few dozens of patients who were tested for the number of CD4 lymphocytes as an endpoint of clinical trials [2]. In the neurological field, the use of white matter changes on FLAIR MRI as a surrogate for disease progression in multiple sclerosis has been used to demonstrate the efficacy of interferon beta-1b in phase III registration trials [3].

In AD, an accepted surrogate of disease progression is not yet available. The most credited surrogate, hippocampal atrophy rates, was ditched by trials showing greater atrophy rates in patients responding

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to anti-amyloid treatment than placebo and non-responders [4]. In the neuropsychological field, the pitfalls of individual tests of disease progression such as ADAS-Cog are being overcome through the use of composite measures [5]. These compound the normalized signal coming from tests tapping different cognitive functions (e.g., word list recall for verbal memory, trail making test for executive function, digit-symbol for attention, etc.) into one single measure. This strategy allows to reduce the impact of test-specific correlates unrelated to the effect of interest (e.g. concomitant use of psychotropic medications on attention, concomitant cerebrovascular disease on executive function, etc.).

With this logic in mind, the PharmaCog project was built to develop a matrix of biomarkers which can be used to select patients to be enrolled in clinical trials and detect the effect of a drug candidate. The matrix is developed in parallel in animal models and humans in order to fill the frequent gap between preclinical results of drug development and human studies, and has the potential to more accurately predict the success of future drugs in early stages of drug development (https://www.imi.europa.eu/projects-results/project-factsheets/pharma-cog). PharmaCog was funded by the European Commission's Innovative Medicine Initiative (IMI) and EFPIA – European Federation of Pharma Industry Association and involved a consortium of 12 corporate and 18 academic partners, 5 small and medium enterprises, the European Medicines Agency, and a patient advocate organization. One of the four major modules of PharmaCog was a longitudinal study of 150 mild cognitive impairment memory clinic patients followed longitudinally with clinical, imaging, and cerebrospinal fluid markers of progression with an ADNI-like design and ADNI-compatible data collection procedures [6].

This Mini-Forum of the *Journal of Alzheimer's Disease* summarizes the major findings of this initiative, sometimes referred to as European ADNI [7]. Structural changes (regional atrophy on MRI),

functional changes (rest fMRI connectivity and EEG rhythms power density), and peripheral biomarker changes ($A\beta_{42}$, $A\beta_{40}$, and clusterin) were studied over time. The results went to inform a statistical exercise where all of the above biomarkers were tested for sensitivity to change into a multivariable multimodal matrix of disease progression. While clearly not the final word on the issue, we believe that these results represent a significant step forward toward the holy grail of a surrogate endpoint for clinical trials of AD drugs.

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