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EDITORIAL

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USE OF BIOMARKERS IN ALZHEIMER'S TRIALS

B. VELLAS

Gérontopôle, U 558, Alzheimer's Disease Clinical Research Center, CHU Toulouse, France, E-mail: vellas.b@chu-toulouse.fr

The concept of disease-modifying treatment is difficult to define and is subject to much debate. It's aims are to reduce the progression rate, with an effect on the physiopathological mechanism of the disease and to have a long-lasting (i.e. at least 18 months) effect on disability (1). For regulatory purposes a disease-modifying effect will be considered when the pharmacologic treatment delays the underlying pathological or pathophysiological disease process and when this is accompanied by an improvement of clinical signs and symptoms of the dementing condition. A true disease-modifying effect cannot be established conclusively based on clinical outcome data alone. Such a clinical effect must be accompanied by strong supportive evidence from a biomarker programme (Siemers)." The guidance goes on to say that if the clinical data is supported by a "convincing package of biological and/or neuroimaging data," a claim of disease modification could be considered. Cognitive assessment and clinical assessment have been sufficient for the development of symptomatic treatments that directly improve cognition in the short-term (Aisen). Disease-modifying treatments, requiring trials with many subjects and long observation periods, are complicated by variance in cognitive and clinical assessments. Biomarkers may more clearly: reflect AD neurobiology and select the good target population, provide indications of AD neurobiology prior to any symptoms (identification of optimal subjects for disease-modifying interventions), increase the power to detect disease-modifying therapeutic effects substantially compared to standard outcomes. In late onset AD all the evidence suggests that dementia results from a combination of pathological processes, the most common of which are the plaques and tangles of AD and a variety of vascular lesions. Searching for a different biomarker diagnosis, that could differentiate AD from vascular dementia for example, may not only be a difficult task but may be conceptually incorrect for S Lovestone (1). Predicting later onset dementia is of questionable value and ethical complexity in clinical practice. For disease-modifying trials, a predictive marker or a marker of severity, rather than an early-disease diagnostic marker, would be of great value. We are happy to present, in this JNHA special issue, a series of papers presented at the Oxford Task Force on Use of Biomarkers in Alzheimer's Therapeutic Trials (1-17). Use of surrogate instead of clinical endpoints in AD clinical trials would significantly decrease their duration and efficiency. The aims of the Gispen study (17) were to evaluate the validity of biomarkers that are currently being proposed as potential surrogate endpoints. We really think that this journal's special issue can contribute in this field.

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