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EDITORIAL

PREVENTIVE TRIALS FOR ALZHEIMER'S DISEASES: THE MULTI-DOMAIN AND THE TARGETED THERAPIES APPROACHES WILL HAVE TO BE ASSOCIATED

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Many initiatives are presently on going around the world to prevent dementia. In the US most of the preventive trials are based on biomarkers and targeted drug approach (1-4), in the EU most of the large European funded trials focuses on multi-domain intervention (5, 6). These different approaches will have probably to joint together in the future. A consensus about the need to treat AD in the pre-symptomatic phase has emerged following the disappointing results of several trials that enrolled subjects with mild to moderate disease, as well as accumulating research demonstrating that AD pathologic process begins decades before the appearance of symptoms. Several lessons can be learned from past prevention trials (7, 8). The targeted populations were too diverse, the interventions probably not strong enough, and the time of exposure was too short. We have learned from these trials that future prevention trials must be targeted, use strong interventions with known biological activity, and must be sustained with a long-term intervention (9-14). In this editorial, we propose that these prevention trial approaches have to be associated:

The targeted therapy preventive approaches based on biomarker: Preventing AD by targeting a specific population with a specific drug, mostly anti-amyloid. Such preventive approaches and trials are based on biomarkers and imaging to select a study population in accordance with the mechanism of the specific drug. Among these initiatives the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4 trial) is the first prevention trial in subjects determined to be at risk based on brain amyloid demonstrated with PET imaging (1). This placebo-controlled trial use solanezumab as the treatment and a composite of well-validate neuropsychological tests known to be sensitive in the early stages of cognitive decline as the primary outcome. The A4 trial aims to exclude older persons without cognitive impairment who, based on the absence of brain amyloid, are much less likely to develop AD. Other trials are targeting a similar population using beta secretase inhibitors. Many current trials are also targeting Pro-dromal Alzheimer's patients with already late MCI and amyloid signature in the brain. Many drugs are presently on trials in this domain mostly monoclonal anti-body and beta secretase inhibitors (8,15). In our point of view a population is missing : those who have early MCI. These individual are not eligible for really preventive trial like A 4 trial because they have some impairment but also not eligible for Pro-dromal Alzheimer because they are not enough impaired (16). All these cut off are arbitrary and variable, by age , educational level, time of the days, sleepiness…. In our point of view those with early MCI are probably a good target population for preventive trial . Finally this approaches underlined the Suspected non-Alzheimer disease pathophysiology (SNAP). SNAP is a biomarker-based concept that applies to individuals with normal levels of amyloid-β biomarkers in the brain, but in whom biomarkers of neurodegeneration are abnormal. The term SNAP has been applied to clinically normal and to mild cognitive impairment subjects. For Jack et al (17) SNAP is present in ~23% of clinically normal individuals aged >65 years and in ~25% of mildly cognitively impaired individuals. APOE*ε4 is underrepresented in individuals with SNAP compared with amyloid-positive individuals. Clinically normal and mildly impaired individuals with SNAP have worse clinical and/or cognitive outcomes than individuals with normal levels of neurodegeneration and amyloid-β biomarkers (17)

The multi-domain intervention trial approaches (5, 6). The idea here is to have a strong intervention adding the effects of several interventions for eg: physical exercise, cognitive exercise, nutrition, optimal treatment of vascular and metabolic risk factors. The rationale for this approach stems from studies showing that several environmental factors are associated with the risk of developing dementia (18-29). These factors may include educational level, vascular and metabolic risk factors, physical activity, cognitive stimulation, and nutritional status (18-29). It may also be possible to identify healthy adults at high risk of AD and likely to benefit from intervention based on subjective memory complaint, ApoEε4 carriage, family history of AD, or the presence of frailty; and use multi-domain interventions to compensate for low specificity; Due ot the safety of these intervention long –term trial is feasible.

These both approaches will have to join in the future. What will be probably the future of clinical practice: A preventive approach, integrated into primary care settings that begins with longitudinal monitoring of memory function in a general population with memory complaints or other risk factors to identify decliners, followed by a specific intervention based on biomarkers and imaging discussed case by case. A prevention approach could start by making general recommendations to a large, diverse population (e.g., those age 50 years or older with normal cognition) on diet, physical and cognitive exercise, and risk factor control.

Among those with memory complaints and/or a family

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history of dementia, a tailored multi-domain intervention might be proposed, including nutrition, physical and cognitive exercise, and risk factor control, such as was used in the MAPT or FINGER trials (5, 6). Ideally, these interventions could be delivered by PCPs who, at the same time, could begin longitudinal monitoring of cognition as a way to identify decliners for the next level of prevention trials.

If subjects with early MCI, biomarkers (e.g., CSF amyloid, tau, as well as PET scans) may be considered. Plasma biomarkers would greatly enhance the ability to conduct large, longitudinal progression studies. At that point, it should be possible to offer multi-domain interventions to those who are biomarker-negative and oral drugs such as anti-amyloid drugs to those who are biomarker positive or those who transition to biomarker positivity during follow-up.

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