Very early treatment of Alzheimer's disease: experiences in J-ADNI and A4 study

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Deposition of amyloid β peptides ($A\beta$) as senile plaques and tau as neurofibrillary changes is the hallmark neuropathological lesions of Alzheimer's disease (AD); these fibrous protein deposits are implicated in AD pathogenesis and regarded as the prime target for the disease-modifying therapies (DMT). $A\beta$ is produced by sequential proteolytic cleavages by β - and γ -secretases. γ -Secretase, harboring presenilins (PS) as the catalytic center, forms the C terminus of $A\beta$ that determines its propensity to aggregate: missense mutations in PS genes cause familial AD by altering the preferred γ -secretase cleavage sites to increase production of pathogenic $A\beta$ 42 species. Protease inhibitors to suppress $A\beta$ production or anti- $A\beta$ antibodies to promote $A\beta$ clearance were tested in recent clinical trials for DMTs at the dementia stage of AD, which altogether failed to meet the clinical endpoints, underscoring the needs for early intervention and biomarkers. To establish imaging and fluid biomarkers that surrogate the AD pathology, longitudinal observational clinical studies including AD Neuroimaging Initiative (ADNI) and Japanese ADNI have contributed greatly towards the goal of very early treatment hopefully at the mild cognitive impairment (MCI) and preclinical AD stages, by delineating the early natural course of AD. It is being demonstrated that the clinical and biomarker profiles of MCI due to AD, i.e., prodromal stage of AD, in J-ADNI were remarkably similar to those in North American ADNI, supporting the harmonization of global clinical trials in Western and Asian countries. Furthermore, secondary prevention trials in preclinical AD, i.e., anti- $A\beta$ therapies in asymptomatic, amyloid positive elderly individuals, e.g., the A4 study, are successfully being initiated worldwide, paving the way toward the very early treatment of AD.