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Editorial

Introduction to the Special Issue on the A4 Study

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The A4 (Anti-Amyloid treatment in Asymptomatic Alzheimer's) Study (1) arose from the recognition that amyloid accumulation in brain, which occurs in about 30% of clinically unimpaired individuals aged 65 and older, is accompanied by evidence of neurodegeneration and cognitive decline that defines the preclinical stage of Alzheimer's disease (2). A composite cognitive function scale was developed to serve as a primary outcome measure (3), as well as other novel outcome measures appropriate for this very early stage of AD. The A4 trial was launched in 2014 testing an antibody against monomeric amyloid, solanezumab. Solanezumab has only modest effects on fibrillar amyloid deposits but showed promise in initial studies with mild AD dementia participants (though a subsequent Phase 3 trial was negative (4)).

The results from the A4 Study were negative; solanezumab did not slow cognitive decline over the 4.5-year treatment period (5). But the trial confirmed the high prevalence of amyloid in cognitively normal older individuals and demonstrated clear evidence of cognitive, clinical and functional decline in preclinical AD. A companion study, LEARN (Longitudinal Evaluation of Amyloid Risk and Neurodegeneration) (6), with individuals interested in joining A4 but who screen-failed on the basis of normal amyloid PET scan results, followed participants with a similar schedule of assessments to provide a valuable comparator group. Together, A4 and LEARN comprise a rich longitudinal dataset to elucidate the earliest changes related to preclinical AD and the aging brain. In this special issue of JPAD, a series of papers explore this dataset.

In accordance with the Collaboration on Alzheimer's Prevention guidelines (7), the A4 (and LEARN) pre-randomization datasets were released for public sharing one year after the completion of screening activities (8) [ida.loni.usc.edu]. The data has been downloaded about 1500 times to date by students, trainees and scientists around the world. By the end of June 2024, the full longitudinal A4 and LEARN datasets will be shared. Additional trials in the preclinical AD population have now been launched (9). Preliminary evidence from successful trials of lecanemab (10) and donanemab (11) in symptomatic AD suggest that that aggressive amyloid removal (and perhaps other interventions against AD) will yield the greatest clinical benefits at the earliest stage of disease. It is our hope that continuing scrutiny of the A4 and LEARN data will facilitate further advances in therapy that will reduce the devastating burden of this disease.

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