A biomarker-driven trial of angiotensin receptor blockers for prodromal Alzheimer

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Country

USA

Title of project or programme

A biomarker-driven trial of angiotensin receptor blockers for prodromal Alzheimer

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 3,545,933.94

Start date of award

01/01/2016

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Clinical Research... Clinical Research - Extramural... Clinical Trials and Supportive Activities... Dementia... Neurodegenerative... Neurosciences... Translational Research

Research Abstract

? DESCRIPTION (provided by applicant): The renin angiotensin aldosterone system (RAAS) is an ideal system to target for safe and effective pharmacological modulation of vascular factors centrally involved in Alzheimer's disease (AD) pathogenesis. Specifically, angiotensin receptor blockers (ARBs) may positively alter neuropathological markers of AD including Amyloid beta and Tau. ARBs also alter vascular function and inflammation, cerebral perfusion, and endothelial dysfunction. Patients with mild cognitive impairment may harbor AD-signature biomarkers (MCI- AD) in their cerebrospinal fluid (CSF) which offers a golden window of opportunity for drug testing in the earliest clinical stages of AD. The use of a CSF biomarker-driven clinical trial is an important approach in AD research and may address prior failures in AD drug development. It improves diagnostic accuracy and identifies patients at the verge of conversion to clinical AD. Both factors improve efficiency of phase II trials and decrease the risk of failed Phase III transition. Further, exploring the potential benefit of promising existing drug (i.e. ""repurposing"") such as ARBs shortens the time to provide urgently needed management options for this devastating illness. Biomarkers of peripheral and central vascular function may be important surrogate markers to test the effectiveness of candesartan as a novel treatment for AD, specifically to evaluate hypothesized mechanisms of action and to validate target engagement. We plan to incorporate a set of neuro- vascular biomarkers (Tau, Amyloid ? imaging, perfusion, hippocampal volume, and vascular function) in this phase II study to identify the ideal surrogate endpoint for a larger trial of candesartan in MCI-AD. Therefore, we are proposing to conduct a 1-year PHASE II double-blind randomized clinical trial using candesartan in 40 non-hypertensive individuals with MCI-AD who have CSF AD signature profiles. Our over-arching hypothesis is that in individuals with MCI-AD, treatment with candesartan is safe and is associated with improved neuronal and vascular AD-related biomarkers This pilot study will (i) test the feasibility of conducting a biomarker-driven clinical trial in MCI-AD, (ii) assess the safety of candesartan in non-hypertensive individuals with MCI-AD, and (iii) aid us in the selection of the surrogate endpoint (s) from the included set of neuro- and vascular biomarkers for an ARB trial. Participants will be recruited from the greater Atlanta area and evaluated at the clinical site of the Emory Alzheimer's disease research center (ADRC). Evaluations will include lumbar puncture, neuroimaging, non-invasive vascular assessments, and circulating cellular and protein inflammatory measures. These data will guide a future PHASE III trial.

Lay Summary

PUBLIC HEALTH RELEVANCE: Although great advances have been made in understanding Alzheimer's disease (AD) underlying mechanisms, few therapeutic agents are available. This study investigates the effect and mechanism of action of an angiotensin receptor blocker (Candesartan) on AD biomarkers in individuals with mild cognitive impairments due to AD. If proven effective, this medication will provide additional treatments for this devastating illness.

Further information available at:

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Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

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