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General Information

Key Personnel (in addition to PI):

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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/coi_seong.pdf
https://yoda.yale.edu/system/files/coi_form wl.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT00575055 - ELN115727-302 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Trial of Bapineuzumab (AAB-001, ELN115727) In Patients With Mild to Moderate Alzheimer's Disease Who Are Apolipoprotein E4 Carriers
2. NCT00574132 - ELN115727-301 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Trial of Bapineuzumab (AAB-001, ELN115727) In Patients With Mild to Moderate Alzheimer's Disease Who Are Apolipoprotein E4 Non-Carriers
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Proof-of-Concept study of a patient selection algorithm for disease modifying treatments in Alzheimer’s disease

Narrative Summary:

Alzheimer’s disease (AD) is viewed as a beta-amyloid (A?)-triggered tauopathy, but the modest and inconsistent clinical benefits of A?-lowering therapies have cast doubt on the amyloid cascade hypothesis. In this project, we plan to reanalyze the datasets of Alzheimer’s disease clinical trials to investigate effects of patient selection to the modest clinical benefit. We propose to identify a subgroup of patients who is most likely to benefit from A?-lowering drugs applying our brain connectivity-based A?-tau interaction model.

Scientific Abstract:

Background: The pharmaceutical industry has made an extraordinary investment in AD clinical trials, but to date we have only one disease-modifying therapy. Many trials have targeted A?, but even some trials demonstrating A?-lowering effects have failed to show clinical benefit. A clear cause for their failure has not been identified, but it appears to be successful in subgroups of patients. The remaining question is how to identify who is most likely to benefit from A?-lowering drugs.

Objective: To apply our pre-developed connectivity-based A?-tau interaction mapping algorithm to improve the clinical efficacy of A?-lowering drugs at the individual level in the treatment arm.

Study Design: We seek to apply our novel molecular interaction mapping algorithm to investigate whether our A?-tau interaction model could explain why A?-lowering drugs have shown only modest clinical benefit, even when A?-lowering is achieved. Compare results of clinical benefits between subgroups of our therapeutic classification algorithm.

Participants: We will analyze participant-level original data elements and variables.

Primary and Secondary Outcome Measure(s): individual participant-level probability of clinical benefit from A?-lowering drugs.

Statistical Analysis: A?-tau interaction-based subgroup analysis

Brief Project Background and Statement of Project Significance:

For decades, Alzheimer’s disease (AD) researchers have proposed that brain amyloid-beta (A?) deposition is the primary pathophysiological event that somehow triggers tau neurofibrillary tangles to spread beyond the medial temporal lobe and out into the heteromodal neocortex [1-5]. This hypothesis remains in doubt, however, because: (1) A? and tau deposition begin within spatially disparate brain regions [2] and (2) A?-lowering agents have shown modest and inconsistent benefits, at best, in AD clinical trials. In our recent research work, we identified two pivotal, region-specific A?-tau interactions that explain the topographical dissimilarity between A? and tau and provided a road map for enhanced patient selection in AD clinical trials [6]. The research work has been published from Neuron: “Regional A?-tau interactions promote onset and acceleration of Alzheimer’s disease tau spreading”. Here in this paper, we used large publicly available datasets from two continents to construct a connectivity-based A?-tau interaction model that addresses long-standing questions about the early A?-tau interaction and the accelerated tau propagation that occurs when patients transition from mild memory impairment to dementia [7,8].

Although this work focuses on the fundamental molecular anatomy of AD, it also has major potential clinical implications. As you know, the United States Food and Drug Administration recently approved the A?-lowering...
antibody, aducanumab, for treatment of mild cognitive impairment and mild dementia due to AD. This landmark approval has intensified the need to stratify patients based on the likelihood that they will benefit from any amyloid-lowering treatments currently in the pipeline [9]. Our model predicts that many patients being considered for most of the clinical trials may be too advanced, whereas many cognitively normal persons may fall within the ideal amyloid-lowering treatment window, providing important potential guidance for AD prevention trials.

We therefore seek to identify who is most likely to benefit from A? -lowering drugs by applying our connectivity-based A? -tau interaction mapping algorithm, and to improve the clinical efficacy of A? -lowering drugs at the individual level in the treatment arm. This will increase the probability of success in future AD clinical trials.

**Specific Aims of the Project:**

Aim 1: Validate & fine-tune the connectivity-based A? -tau interaction mapping algorithm for patient stratification in amyloid-lowering treatments.
Aim 2: Analyze the dataset from YODA Project of Alzheimer’s disease clinical trials to investigate the efficacy of our patient stratification method in maximizing clinical benefits of the experimental clinical trials.
Aim 3: Propose a new patient selection algorithm for future Alzheimer’s disease clinical trials targeting either amyloid or tau molecules.

**What is the purpose of the analysis being proposed? Please select all that apply.**

- New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
- Confirm or validate previously conducted research on treatment effectiveness
- Participant-level data meta-analysis
- Summary-level data meta-analysis using only data from YODA Project
- Develop or refine statistical methods
- Research on clinical trial methods
- Research on clinical prediction or risk prediction

**Research Methods**

**Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:**

In the treatment arm, selected participants must have baseline and longitudinal Alzheimer’s Disease Assessment Scale-cognitive Subscale (ADAS-Cog) and mini-mental state examination (MMSE) measurements, baseline MRI scan and amyloid-PET or CSF biomarker data, demographic information, and date of diagnosis.

**Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:**

The main outcome measure will be individual participant-level probability of clinical benefit from A? -lowering drugs.

**Main Predictor/Independent Variable and how it will be categorized/defined for your study:**

The main predictor variable is the individual characteristics used to determine clinical benefit from A? -lowering drugs. These characteristics could include demographic information such as age, sex, years of education, and ApoE status, baseline and longitudinal cognitive functions, concomitant medications, diagnosis at baseline, and regional retention of amyloid and tau proteins. Tau-PET imaging may not be available from all datasets, therefore tau retention will be predicted using MRI scans. We will apply our pre-trained machine learning models to predict regional tau information from MRI-extracted features.

**Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:**

Other demographic information, labs, vitals, time since symptom onset, time since diagnosis.

**Statistical Analysis Plan:**

Our stratification algorithm suggested two important transitions during the natural history of AD, based on: remote
A? tau interaction within the lateral entorhinal cortex (EC) and local A? tau interaction within the inferior temporal gyrus (ITG). To examine subjects’ status with respect to these transitions, we computed quantitative thresholds for each metric. The first threshold was computed by multiplying the regional cutoff of the EC remote A? influence metric by the tau W-score cutoff. Similarly, for the second threshold, the regional cutoff for the ITG local amyloid SUVR was multiplied by the tau W-score cutoff. Using this approach, we classified each subject into one of four groups: (1) least affected by the tau pathology (“tau-negative” group) in EC [10], (2) subthreshold EC remote A? tau interaction despite the presence of EC tau (“latent tau”), (3) suprathreshold EC remote A? tau interaction but subthreshold ITG A? tau local interaction (“spreading tau”), and (4) suprathreshold ITG A? tau local interaction (“propagating tau”). Values for each metric were calculated in each hemisphere separately. We finally analyze the clinical outcome after treatments for those subgroups.

Software Used:
Python

Project Timeline:

- Project start date: August 16, 2022.
- Analysis completion date: June 30, 2023.
- Results reported back to the YODA project: July 31, 2023

Dissemination Plan:

We expect that the applications we develop will be useful for Alzheimer’s disease drug development. We plan to publish the results in journals related to Alzheimer’s disease (e.g., Alzheimer’s & Dementia, Neurology).

Bibliography:


Supplementary Material:

https://yoda.yale.edu/sites/default/files/6th_bibliography_0.pdf