The A4 Study
Anti-Amyloid Treatment in Asymptomatic Alzheimer’s disease

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Need for Earlier Intervention

• Ten (maybe 9½) Phase III trial failures at stage of AD dementia over the past decade!
• Intervention prior to dementia (widespread irreversible brain cell loss) may have better chance of changing clinical course of the disease
• Delaying dementia by 5 years would reduce projected Medicare costs by nearly 50%
• Think about what happens in cancer, stroke, HIV, diabetes, osteoporosis …. if we wait to treat until after symptoms appear?
The Continuum of Alzheimer’s Disease

Normal Aging

Cognitive function

Preclinical

MCI (Prodromal AD)

Dementia

Years
PET Amyloid Imaging

Harvard Aging Brain Study

Sperling, Johnson NeuroMolecular Med 2010
Preclinical Alzheimer’s Disease?

Prevalence of plaques in HC
(Davies, 1988, n=110)
(Braak, 1996, n=551)
(Sugihara, 1995, n=123)

~15 yrs

Prevalence of PiB+ PET in HC

Prevalence of AD
(Tobias, 2008)

Rowe C et al Neurobiology of Aging 2010
Evidence of Amyloid-Related Alterations in Neural Function and Structure

Cognition in Amyloid Pos vs. Neg in HC > 70 years old

WMS Immediate      WMS Delayed                     Digit -Symbol

Sperling R et al Neurobiology of Aging 2013
Subjective memory concerns associated with amyloid burden among “normal” elderly

Amariglio R et al *Neuropsychologia* 2012

Perrotin A et al *Arch Neurology* 2012
Effect of amyloid on memory and non-memory decline from preclinical to clinical Alzheimer’s disease

AIBL data  Lim Y et al *Brain*  2014
Testing the Right Target and the Right Drug at the Right Stage of Alzheimer’s Disease

Primary Prevention
Delay onset of AD pathology
- Decrease $\text{A}_\beta_{42}$ production
- Prevent tangle formation

Secondary prevention
Delay onset of cognitive impairment in individuals with evidence of pathology
- Decrease accumulated $\text{A}_\beta$ burden
- Decrease neurodegeneration with anti-tau or neuroprotective agents

Tertiary prevention and treatment
Delay onset or progression of dementia
- Neuroprotection-prevent neuronal loss
- Enhance function of remaining neurons
- Neurotransmitter repletion

A4 Study Synopsis

• Secondary prevention trial in clinically normal older individuals (age 65-85) who have evidence of amyloid-β pathology on PET imaging
• Randomized, double-blind, placebo-controlled trial of solanezumab vs. placebo for 168 weeks
• Trial N=1000+ (N=500+ per treatment arm)
• Observational cohort of amyloid negative “screen fails” – LEARN study
• Ethics component – Disclosure of amyloid status
The continuum of Alzheimer’s disease
The A4 Study

- Amyloid -
- Amyloid + Treated
- Amyloid + Placebo

Cognition

Anti-Amyloid Treatment
A4 Eligible Participants

- Age 65 – 85 years; general good health
- One out of five from under-represented minority
- MMSE 27-30 (Education adjustment)
- CDR 0 – Will allow subtle subjective memory complaint if no evidence of impaired function
- Logical Memory II score of 15 – 8 for high education; 13 – 6 for low education
- Evidence of elevated amyloid accumulation on screening PET amyloid imaging
LEARN Observational Cohort
Longitudinal Evaluation of Amyloid Risk and Neurodegeneration

- Funded by the Alzheimer’s Association and philanthropic foundations
- Selected from “screen fails” at Screening Visit 2
- 400 “Amyloid Negative” +100 “Amyloid Intermediate” or “Indeterminate”
- Matched on demographics to A4 treatment arms
- Will undergo same clinical and Imaging assessments - Tau imaging in a subset
A4 Primary Outcome - Cognitive

- Primary outcome – Rate of decline on ADCS Preclinical AD Cognitive Composite (PACC)
  - Free and Cued Selective Reminding Test
  - LMIIa paragraph – Delayed recall
  - Digit Symbol
  - Global cognition
  - MMSE

- Based on power calculations from ADNI, AIBL, ADCS-PI - A4 is powered to detect 30% slowing
A4 Novel Outcome Measures

• “Patient” or Participant reported outcomes
  – Cognitive Function Index
  – C-PATH questionnaire and MAC-Q on iPad
  – Updated Instrumental ADL (Galasko)

• Impact of amyloid disclosure
  – Perception of time
  – Concern about developing AD dementia

• Computerized Cognitive Composite (C3)
  – CogState Card Playing tasks on iPad
  – Face-name and Pattern Separation
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A4 Biomarker Outcomes

- **PET amyloid imaging**
  - Decrease in mean cortical SUVr
- **CSF phospho-tau and tau (in subset)**
- **Volumetric MRI**
  - Cortical thinning
  - Hippocampal atrophy
- **Functional MRI**
  - Task-free default network connectivity
- **PET tau imaging**
Tau PET

70 y/o MMSE = 27

Keith Johnson CTAD 2013
T807 Tau vs. PiB Amyloid-β
Harvard Aging Brain Study

$r=0.45, p<0.0001$
A4 Sites in US, Canada, and Australia
A4 Recruitment

A4Study.org

1-844-A4-STUDY
A4 is Enrolling!

- 46 sites with IRB approval
- 6 sites fully qualified to enroll
  - UCSD – Star site!!!
  - Brown
  - Mayo Clinic
  - UC Irvine
  - Brown
  - Yale
  - Iowa

- Hope to have most sites up by this summer
A4 Partnership

• A4 is funded through a public-private-philanthropic partnership (P4)
  – NIA, Eli Lilly, Avid, CogState, Alzheimer’s Association, several philanthropic organizations

• All data from A4 study will be made available to the field
  – Screening data made available when enrollment complete, treatment data after regulatory submission

• Collaboration for Alzheimer Prevention
  – A4, DIAN, API, Fidelity, Alz Assoc, NIA
A4 (and beyond…)

• A4 study intended as a platform to test the hypothesis that treatment during the preclinical stages of AD can slow cognitive decline and to determine if there is a “critical window” for successful anti-amyloidoid therapy

• A5 – Likely a beta-secretase inhibitor

• COMBAT – Combination Alzheimer Therapy
  – BACE inhibitor + Anti-A\(\beta\) antibody
  – Anti-A\(\beta\) + Anti-Tau
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