Detection of Preclinical Alzheimer’s disease: Implications for Prevention Trials

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The continuum of Alzheimer’s disease

Preclinical

“Normal” Aging

MCI

Dementia

Cognition

Years

NIA-AA Preclinical Workgroup
Sperling R et al 2011
The pathophysiological process of AD begins well more than a decade before dementia.

Age is the greatest risk factor for AD.

One third of clinically normal older individuals harbor evidence of amyloid-β accumulation.

These “Aβ+ Normals” demonstrate “AD-like” structural and functional imaging abnormalities, subtle memory deficits, and faster rates of cognitive decline – an population at high risk for progression to AD dementia.
PET Amyloid Imaging in Clinically Normal Older Individuals

Harvard Aging Brain Study

Sperling, Mormino, Johnson *Neuron* 2014
Preclinical Alzheimer’s Disease

Prevalence of plaques in CN

(Davies, 1988, n=110)
(Braak, 1996, n=551)
(Sugihara, 1995, n=123)

Prevalence of Aβ+ PET in CN

~15 yrs

Prevalence of AD Dementia
(Tobias, 2008)

Adapted from Rowe C et al Neurobiology of Aging 2010
Stage 0
No biomarker abnormalities

Stage 1
Asymptomatic amyloidosis
- High PET amyloid retention
- Low CSF Aβ_{1-42}

Stage 2
Amyloidosis + Neurodegeneration
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

SNAP
Suspected non-Alzheimer pathology
- Neurodegeneration markers without evident amyloidosis

MCI ➔ Dementia due to AD

Sperling, Mormino, Johnson Neuron 2014
Adapted from Sperling 2011, Jack 2012
Relationship between markers of Amyloid β deposition and markers of neurodegeneration

Harvard Aging Brain Study

Mormino E et al. JAMA Neurology 2014
Subjective cognitive concerns associated with advancing stages of preclinical AD

Amariglio et al. *Neurology* 2015
Amyloid and Tau PET Imaging

Sperling, Mormino, Johnson  *Neuron* 2014
Higher Amyloid Burden Associated with Higher Tau Burden

Adjusted model for age, gender, education $r=0.34; p=0.00013$
Relationship of Tau and Memory by Amyloid Status

- PiB- Slope = -1.07
  \( r = -0.09 \)
  \( p = 0.35 \)

- PiB+ Slope = -3.42
  \( r = -0.52 \)
  \( p = 0.0014 \)

Interaction term (PiB x T807)
  \( p = 0.089 \)
Hypothetical Interaction of Amyloid and Tau in Preclinical AD

Sperling, Mormino, Johnson Neuron 2014
Symptomatic Therapy

Natural History of Alzheimer’s Disease

Disease-Modifying Therapy

Symptomatic Therapy

Cognitive Function

Years

Treatment of Alzheimer’s Disease
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?
Testing the Right Target and the Right Drug at the Right Stage of Alzheimer's Disease

Primary Prevention
Delay onset of AD pathology
• Decrease Aβ₄₂ production
• Prevent tangle formation

Secondary prevention
Delay onset of cognitive impairment in individuals with evidence of pathology
• Decrease accumulated Aβ 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 screening PET imaging

• Randomized, double-blind, placebo-controlled Phase 3 trial solanezumab vs. placebo for 168 weeks

• Trial N=1000+ (N=500+ per treatment arm)

• Observational cohort of Aβ negative “screen fails” – LEARN study (N=500)

• Ethics component – Disclosure of amyloid status
The continuum of Alzheimer’s disease

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The A4 Study

Anti-Amyloid Treatment

Cognition

Amyloid -

Amyloid + Treated

Amyloid + Placebo

A4
A4 Screening and Randomization

Randomization (with stratification on APOE and education)

Randomization
Double-blind treatment period 168 weeks

Active treatment
N = 500

Treatment completers
N = 350

Placebo
N = 500

Placebo completers
N = 350

LEARN study
N = 500

LEARN study completers
N = 350

Telephone screen
N > 10,000

In clinic screen
N = 5,000

PET amyloid imaging
N = 3,300

Obtain MRI on Aβ+
N = 1,100

LEARN study natural history arm of Aβ-
(age and education matched)
N = 500

Sperling R et al Sci Trans Med 2014
A4 Status as of Dec 1, 2015

- 63 sites enrolling in US, Canada and Australia
- Over 2700 participants screened/currently in screening process
- Current PET eligibility = 33%
- 378 participants randomized
- LEARN companion protocol launched
- 71 Tau PET images acquired
Amyloid-β accumulation (CSF/PET)
Synaptic dysfunction (FDG-PET/fMRI)
Neocortical Tau-mediated neuronal injury
Brain structure (volumetric MRI)
Cognition
Clinical function

Clinical Disease Stage
Normal
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A4 Study - Anti-Amyloid Treatment in Asymptomatic AD

Figure adapted from Jack et al. 2010, Sperling et al. 2011
EARLY Study ("A5") – BACE inhibitor

- Amyloid-β accumulation (CSF/PET)
- Synaptic dysfunction (FDG-PET/fMRI)
- Neocortical Tau-mediated neuronal injury
- Brain structure (volumetric MRI)
- Cognition
- Clinical function

Clinical Disease Stage

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EARLY (A5)
EARLY (A5) Trial

- Janssen sponsored trial of an oral BACE inhibitor with academic collaboration
- EARLY will be a global study - launching first in Europe, Australia, Asia, then US
- Amyloid eligibility by CSF or PET – same “amyloid positive” normals criteria as in A4
- Broader age range – 60-85 years old
  - Participants age 60-65 must have APOE risk factor
- Broader cognitive range than A4
- Longer trial – up to 4.5 years
Longitudinal Amyloid-β Accumulation in Clinically Normal Elders

Harvard Aging Brain Study

Aaron Schultz and Keith Johnson HAI 2015
A3 Study = Ante-Amyloid prevention of AD
Getting closer to Primary Prevention!

Abnormal

- Amyloid-β accumulation (CSF/PET)
- Synaptic dysfunction (FDG-PET/fMRI)
- Neocortical Tau-mediated neuronal injury
- Brain structure (volumetric MRI)
- Cognition
- Clinical function

Clinical Disease Stage

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Clinical Function

A3

Graphic: Clinical disease progression stages with A3 study points.
A3 Study!

- A3 will leverage the A4 /A5 screening to identify people with “subthreshold” Aβ levels who are at high risk for continued amyloid accumulation
- Four year Phase IIb/IIIa 4 trial - BACE inhibitor
- Primary outcomes are biomarkers – rate of Aβ accumulation, tau spreading, MR atrophy
- Exploratory sensitive cognitive outcomes (iPAD)
- Public-private-philanthropic partnership (P4)
  - Currently have 5 interested industry partners
  - NIH grant will be submitted Dec 11th!
Encouraging history from other fields

- Cholesterol Wars in Cardiology
  - Good vs. bad cholesterol
  - Secondary prevention trials in familial hypercholesterolemia and in post-MI
  - Reduction of cholesterol estimated to have reduced cardiac morbidity and mortality by 28%
  - As in “A3” rationale, recommendations for treating cholesterol have steadily evolved to lower LDL
- Amyloid does not have to be “the” cause of AD, merely “a” critical factor that can impact the disease at the optimal time!
Thank you!

• Paul Aisen, ATRI at USC and ADCS at UCSD
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