Topic #1

The latest advances in the understanding of the pathophysiology of Alzheimer’s Disease and the development of disease-modifying therapies

Gary Romano
On behalf of the EFPIA Working Group

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Disclosure

- Gary Romano is the Head of AD clinical development for Janssen R&D.
Historically AD diagnosis was based on clinical symptoms alone and trials were necessarily focused on the dementia stages.
Biomarker and neuropathological studies have since shown that the pathophysiological processes of AD begin more than a decade before clinical symptomatology.
IWG-2 and National Institute of Aging – Alzheimer’s Association establish research criteria for early, asymptomatic stage of AD based on presence of pathological biomarkers.

**Preclinical AD ~**
Asymptomatic at risk for Alzheimer’s Dementia

May begin 10+ years before prodromal AD
“despite differences in methodology...the findings converge convincingly.”

Table 3: Proportion of participants who progressed to MCI/AD within 15 months by stage

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Proportion progressed to MCI/dementia within 15 mo, n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trend test stage 0-3</td>
<td>6 (5), 5 (11), 8 (21), 3 (43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage 0 vs 1-3</td>
<td>6 (5) vs 16 (18)</td>
<td>0.002</td>
</tr>
<tr>
<td>Stage 1 vs 2</td>
<td>5 (11) vs 8 (21)</td>
<td>0.26</td>
</tr>
<tr>
<td>Stage 2 vs 3</td>
<td>8 (21) vs 3 (43)</td>
<td>0.21</td>
</tr>
<tr>
<td>Stage 1-3 vs SNAP group</td>
<td>16 (18) vs 7 (10)</td>
<td>0.18</td>
</tr>
<tr>
<td>Stage 2 + 3 vs SNAP group</td>
<td>11 (24) vs 7 (10)</td>
<td>0.05</td>
</tr>
<tr>
<td>Stage 0 vs SNAP</td>
<td>6 (5) vs 7 (10)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Vos et al
Lancet Neurology 2013

Knopman et al
Neurology 2012
“Despite the use of CSF analysis rather than neuroimaging to assess biomarkers and use of a convenience rather than a population-based sample, the frequencies coincide reasonably well (figure). As such, these two studies, although not definitive, provide strong support for the validity of the construct of preclinical AD.”
Amyloid detection using PET imaging in ‘Normal Controls’ MCI* and Demented AD patients**

*Mild Cognitive Impairment  
**clinically diagnosed, likely contains cases of non-AD pathology  
***high levels of amyloid burden (above normal threshold)
Emerging evidence suggests that Tau aggregation pathology is also a very early event in pathogenesis.

Regulatory framework needs to be open to alternative theories of molecular pathogenesis.


May begin 10+ years before prodromal AD.
Rationale for Targeting Preclinical AD (Asymptomatic At Risk for Alzheimer’s Dementia)

• Pathophysiological process of AD begins before onset of symptoms and dementia
  - New evidence indicates about 1/3 of asymptomatic older individuals harbor evidence of amyloid accumulation*
  - Developing work with tau markers (CSF, imaging) suggests tau pathology also begins in asymptomatic stage.

• Amyloid positive asymptomatic individuals*
  - Have AD-like structural and functional imaging abnormalities
  - Have subtle memory deficits, and faster rates of cognitive decline
  - Represent an older population at high risk for progression to AD dementia
  - Now amenable for a disease interception study

Reisa Sperling
*Harvard Ageing Study Group, others
AAIC, 2014
Clinical Trials in Preclinical AD are now feasible

• Reliable biomarker assays for diagnosis are available
  • CSF measures of Abeta and Tau/p-Tau
  • Amyloid PET ligands

• Asymptomatic subjects at risk can be accurately identified & recruited
  • Early disease stage registries/cohorts are being assembled

• Subtle cognitive decline can be measured with fit-for-purpose cognitive assessments in individuals who are asymptomatic at risk
  • E.g., PACC cognitive composite (Donohue et al, Neurology 2014)
The continuum of AD and normal aging
Summary

• AD pathophysiology begins decades before manifest clinical impairment

• Research criteria established for early, asymptomatic stage of AD by IWG-2 and NIA-AA
  – Based on presence of pathological biomarkers
  – Independent cohort studies provide strong support for the validity of the construct of preclinical AD.

• Clinical trials in preclinical AD are now feasible

• AD presents unique challenges to the development and registration of therapeutics for early disease interception

• Regulatory guidance can help to overcome these barriers to investment
Key Issues: Disease Intervention in Preclinical Alzheimer’s presents unique challenges for drug development

- Trials in preclinical AD will require treatment of asymptomatic at-risk subjects who may not develop cognitive impairment for many years.

- Demonstration that disease interception in preclinical AD delays time to later stages of disease will take many years of observation.

- Clinical trials of long duration are likely to result in a large percentage of missing data, making it infeasible to assess long-term outcomes.

Regulatory guidance can help to lower these barriers to investment...
Key Issue: Trials in preclinical AD will require treatment of asymptomatic at-risk subjects who may not develop cognitive impairment for many years.

• From the Discussion Paper:
  - “Preclinical AD refers to the pathophysiological stage when in vivo molecular biomarkers of AD are present, but clinical symptoms are absent”

• Question:
  - Does the Agency agree that for the purposes of a risk-benefit assessment preclinical AD should be considered a disease population?
Key Issue: Demonstration that disease interception in preclinical AD delays time to later stages of disease will take many years of observation.

Questions:

• Does the Agency agree that stage specific endpoints based on clinically relevant phenotypic manifestations at that stage of disease might be sufficient for approval?
  - E.g. In preclinical AD, in which cognitive decline is the only manifestation of disease, would slowing of cognitive decline be sufficient for full approval?

• Does the Agency agree that demonstration of the clinical meaningfulness of such a cognitive treatment effect could be established through disease modeling based on data external to the drug trial?
  - E.g. data from observational studies linking cognitive decline to functional decline and/or time to dementia
Key Issue: Assessment of Efficacy in Preclinical AD

From Discussion Paper:

*In section 4.5 (Assessment of Therapeutic Efficacy) specific recommendations for prodromal AD and dementia are provided. However, no specific recommendations are provided for assessment of efficacy in secondary prevention trials in Preclinical AD (asymptomatic at risk of AD or presymptomatic AD)*

Question:

Does the Agency agree that the draft guidance should also include specific recommendations for the assessment of efficacy in secondary prevention trials in subjects with Preclinical AD?