Challenges in Selecting Biomarker Outcomes in AD Clinical Trials

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# Stephen Salloway, M.D., M.S.
## Disclosure of Interest

**Research Support**

1. NIA-ADNI
2. NIA-DIAN
3. Alz Assoc-DIAN Clinical Trials
4. Fain Family Foundation, Champlin Foundation, White Family Foundation
5. Avid Radiopharmaceuticals

**Speakers Bureau**
- Athena

**Clinical Trials**
- Elan, Janssen Al, Baxter, BMS, Pfizer, Medivation, Genentech, Bayer, GE, Avid, Roche

**Consultant**
- Elan, Janssen Al, Astra-Zeneca, Avid-Lilly, Baxter, Pfizer, Athena, BMS, Merck, and Sanofi

I own no stocks or equity in any pharmaceutical company.
the best established brain imaging techniques in the detection & tracking of AD

From Reiman & Langbaum, in *Imaging in the Aging Brain*, 2009
Use of Imaging and CSF in Alzheimer’s Disease Clinical Trials

- Confirm the diagnosis of AD
- Determine eligibility for clinical trials
- Measure outcome or disease progression
- Demonstrate target engagement
- Monitor for safety
Volumetric MRI
Early Changes in Cortical Thickness Predict Cognitive Decline in ADNI Normal Controls
Examples of vMRI Outcomes in AD Clinical Trials
Will the brain become larger or smaller?

• MRI
  – AN1792-antibody responders had greater loss of brain volume and larger ventricles but no difference in Hc and no correlation with cognitive decline (Fox, 2005)
  – Bapineuzumab phase 2-no difference in brain volume for all Rx groups combined. Less volume loss in ApoE 4 non-carriers and increased ventricular size in ApoE4 carriers (Salloway, 2009)
  – Scyllo-inositol-No difference in cortical volume but increase in ventricular volume in the 250 mg group (Salloway, 2011)
  – Semagasestat phase 3-n=229, 4.3% decrease in hc volume and 1% decrease in WBV with treatment (Siemers, AAIC 2011)
  – Bapineuzumab phase 3-no difference in ApoE4 carriers and non-carriers on annual cortical rate of change-additional analyses pending (Salloway and Sperling, EFNS 2012)
Rate of Change in MRI Brain Volume (BBSI) by Treatment Group at Week 71 APOE ε4 Carriers in Bapineuzumab Phase 3

**BBSI:** Brain Boundary Shift Integral

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=238)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bapineuzumab 0.5 mg/kg (n=352)</td>
<td>1.175 (-0.340, 2.689)</td>
<td>0.128</td>
</tr>
</tbody>
</table>

**Sperling EFNS, 2012**
Rate of Change in MRI Brain Volume (BBSI) by Treatment Group at Week 71 APOE ε4 Non-Carriers in Bapineuzumab Phase 3

<table>
<thead>
<tr>
<th>Treatment Difference at Week 71</th>
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<tr>
<td>0.5 mg/kg</td>
<td>-0.336 (-2.216, 1.543)</td>
<td>0.725</td>
</tr>
<tr>
<td>1.0 mg/kg</td>
<td>1.514 (-0.459, 3.487)</td>
<td>0.132</td>
</tr>
</tbody>
</table>

Salloway EFNS, 2012
Possible Mechanisms for Decreased Brain Volume with anti-Amyloid Treatment

- Volume loss associated with amyloid lowering
- Decreased CSF clearance and ventricular expansion related to plugging of arachnoid villi with shifts in amyloid load
- Other

- No association between volume loss and clinical decline with AN1792, scyllo-inositol, bapineuzumab
Impact of Uncertainty in Volumetric MRI Cut-offs and Outcomes

• Not all AD patients have hippocampal volume loss at time of study screen (younger subjects) and hippocampal or cortical volume loss may not be related to AD pathology (elderly subjects)
• Effect on sample size calculations
• Risk in choosing vMRI as a key biomarker outcome
Amyloid PET
Change in C11 PIB in Bapineuzumab 202

- Gantenerumab -15.6% 60 mg and -35.7% 200 mg

Rinne Lancet Neurology 2010

Ostrowitzki, 2011
Change in Amyloid Burden as assessed by [11C] PiB-PET at Week 71 APOE ε4 Carriers in Bapineuzumab Phase 3

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<th>Treatment Difference at Week 71</th>
<th>Bapineuzumab Mean (95% CI)</th>
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<tr>
<td>Placebo (n=40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bapineuzumab 0.5 mg/kg (n=75)</td>
<td>-0.101 (-0.168, -0.034)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Reduction

Global Cortical Average SUVr Mean (+/-SE)

Weeks

(PiB PET analysis population: baseline global cortical average > 1.35; 6.5% did not meet threshold)
Change in Amyloid Burden as assessed by $[^{11}C]$ PiB-PET at Week 71
APOE $\varepsilon$4 Non-Carriers in Bapineuzumab Phase 3

Treatment Difference at Week 71

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<th>Treatment</th>
<th>Mean (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled 0.5/1.0 mg/kg</td>
<td>0.021 (-0.099, 0.140)</td>
<td>0.724</td>
</tr>
</tbody>
</table>

Reduction

Global Cortical Average SUVr Mean (+/-SE)

(PiB PET analysis population: baseline global cortical average > 1.35; 36.1% did not meet threshold)

Salloway EFNS, 2012
Change in Amyloid Burden as assessed by [\^{11}\text{C}] PiB-PET at Week 71 APOE ε4 Non-Carriers in Bapineuzumab Phase 3

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<tr>
<td>0.5 mg/kg</td>
<td>0.085 (-0.046, 0.215)</td>
<td>0.193</td>
</tr>
<tr>
<td>1.0 mg/kg</td>
<td>-0.048 (-0.182, 0.086)</td>
<td>0.466</td>
</tr>
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No significant treatment differences between groups; post hoc exploratory analysis suggested a within cohort signal for reduction in PiB PET at 1.0 mg/kg dose (nominal p = 0.057)

(PiB PET analysis population: baseline global cortical average > 1.35; 36.1% did not meet threshold)
Possible Reasons for the Sizeable Number of ApoE Non-Carriers with Low SUVr

- Measurement error
- Presence of additional pathologies
- Subjects did not have AD
- Plan to compare CSF and PIB in subjects who participated in both sub-studies
- Future studies should ensure that subjects receiving anti-amyloid treatments have significant amyloid pathology
CSF
Examples of CSF Outcomes in AD Clinical Trials

• CSF
  – AN1792-decreased CSF tau but no change in $A\beta_{42}$ in antibody responders (Gilman, 2005)
  – Scyllo-inositol-decreased $A\beta_{42}$ but no difference in tau or p-tau (Salloway, 2011)
  – Avagasestat phase 2-decrease in CSF $A\beta_{1-42}$ at highest dose only (Coric, 2012)
  – Solanezumab phase 2-12 weekly doses, dose-dependent increase in plasma and CSF total $A\beta_{1-40}$ and $A\beta_{1-42}$ (bound and unbound) and increase in unbound CSF $A\beta_{1-42}$ (Farlow, 2012)
  – Bapineuzumab phase 2-decreased p-tau and trend for decreased tau but no difference in $A\beta_{42}$ (Blennow 2012)
  – Bapineuzumab phase 3-decreased p-tau in ApoE carriers and in the 1 mg/kg dose in non-carriers, no significant effect on $A\beta_{42}$ (Sperling and Salloway, EFNS, 2012)
Change in CSF Phospho-tau by Treatment Group at Week 71
APOE ε4 Carriers in Bapineuzumab Phase 3

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<tr>
<th>Treatment</th>
<th>Mean (95% CI)</th>
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<tr>
<td>Placebo</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>0.5 mg/kg</td>
<td>-6.75 (-11.45, -2.06)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Reduction

CSF P-tau 181P

Mean (+/-SE) Change From Baseline (pg/mL)

Weeks

Sperling EFNS, 2012
Change in CSF phospho-tau by Treatment Group at Week 71
APOE ε4 Non-Carriers in Bapineuzumab Phase 3

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<tbody>
<tr>
<td>Placebo (n=77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled Bapineuzumab (n=101)</td>
<td>-3.30 (-7.30, 0.71)</td>
<td>0.106</td>
</tr>
<tr>
<td>0.5 mg/kg (n=47)/1.0 mg/kg (n=54)</td>
<td></td>
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Salloway EFNS, 2012
Change in CSF phospho-tau by Treatment Group at Week 71
APOE ε4 Non-Carriers in Bapineuzumab Phase 3

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<th>p-value</th>
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<tr>
<td>0.5 mg/kg</td>
<td>0.05 (-4.78, 4.88)</td>
<td>0.984</td>
</tr>
<tr>
<td>1.0 mg/kg</td>
<td>-6.19 (-10.82, -1.56)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Reduction

CSF p-tau 181P

Mean (+/-SE) Change From Baseline (pg/mL)

Weeks

Salloway EFNS, 2012
Targets for Amyloid-Lowering and CSF Markers of Neurodegeneration

- Smaller PIB and p-tau effect sizes in bapineuzumab phase 3
  - Phase 2 combined carriers and non-carriers and included higher doses
- Does the magnitude of amyloid-lowering matter
  - Is the target maximizing the decrease from baseline, stabilization, or slowing rate of increase?
  - How will the outcomes vary across the stages of AD?
- Tolerability may limit dose and optimal anti-amyloid effects
  - Different Abeta targets
  - Compound modifications
  - Alternative dosing strategies
  - Combining anti-amyloid therapies-e.g., BACE inhibitor and monoclonal antibody or anti-amyloid and tau compounds
Dissociation between biomarker and clinical results in bapineuzumab phase 3

- No evidence of clinical benefit in mild-moderate AD dementia but PiB PET provides evidence of target engagement and p-tau lowering suggests effects on downstream neurodegeneration

Potential explanations
- AD dementia stage of disease may be too far advanced (with widespread irreversible neuronal loss) to demonstrate clinical benefit
- Anti-amyloid monoclonal antibodies may not be the most effective way to target amyloid
- Anti-amyloid therapies may require intervention at earlier stage of AD
- May need greater amyloid reduction
Utilizing Amyloid Cut-offs as Selection Criteria in AD Clinical Trials

- Cut-offs may vary at different stages of the disease and by genetic status
- Issues with assay variability
- CSF cut-off-\(\text{A}\beta 42\), tau/\(\text{A}\beta 42\), or both
- High screen failure rate
- Include only amyloid + in symptomatic trials
- Include amyloid + in secondary prevention/preclinical trials and possibly amyloid negative in high risk populations
MRI Safety Monitoring for ARIA
First seen on routine MRI at week 6 (2 weeks after the 2\textsuperscript{nd} dose) in ApoE4,4 subject and resolved by week 17

Ostrowitzki 2011, Salloway 2009
• Low incidence of ARIA-E at baseline in mild-mod AD trials
  – 2/2,700 in the Lilly phase 3 semagacestat and solanezumab trials
  – 3/223 in the bapineuzumab phase 2 mild-mod AD trials
  – 1/209 n the phase 2 BMS gamma secretase study

• Two additional cases with Rx in BMS gamma secretase mild-mod


Case of subtle VE from the BMS Phase 2 gamma secretase trial
Incidence Proportion: Treatment Emergent Adverse Events of Special Circumstance (APOE ε4 Carriers) Bapineuzumab phase 3

<table>
<thead>
<tr>
<th>AEs of Special Circumstance</th>
<th>Placebo N=448 (%)</th>
<th>Bapineuzumab 0.5 mg/kg N=673 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIA-E (vasogenic edema)</td>
<td>1 (0.2)</td>
<td>103 (15.3)</td>
</tr>
<tr>
<td>Symptomatic ARIA-E*</td>
<td>0 (0.0)</td>
<td>16 (2.4)</td>
</tr>
<tr>
<td>Intracranial hemorrhage**</td>
<td>7 (1.6)</td>
<td>7 (1.0)</td>
</tr>
<tr>
<td>Seizure/Convulsion</td>
<td>1 (0.2)</td>
<td>7 (1.0)</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>4 (0.9)</td>
<td>5 (0.7)</td>
</tr>
</tbody>
</table>

ARIA-E: amyloid-related imaging abnormalities with edema or effusion

*Symptoms reported in ARIA-E (VE) subjects, with an incidence ≥2% included: headache and confusional state. Among the VE cases, % symptomatic in 0.5 mg/kg group=15.5%

**Excludes hemosiderin deposits, such as microhemorrhage
### Incidence Proportion: Treatment Emergent Adverse Events of Special Circumstance (APOE ε4 Non-Carriers) Bapineuzumab phase 3

<table>
<thead>
<tr>
<th>AEs of Special Interest</th>
<th>Placebo N=524 (%)</th>
<th>Bapineuzumab 0.5 mg/kg N=337 (%)</th>
<th>Bapineuzumab 1.0 mg/kg N=329 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIA-E (vasogenic edema)</td>
<td>1 (0.2)</td>
<td>14 (4.2)</td>
<td>31 (9.4)</td>
</tr>
<tr>
<td>ARIA-E (symptomatic)*</td>
<td>0 (0.0)</td>
<td>5 (1.5)***</td>
<td>5 (1.5)***</td>
</tr>
<tr>
<td>Intracranial hemorrhage**</td>
<td>7 (1.3)</td>
<td>1 (0.3)</td>
<td>6 (1.8)</td>
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<tr>
<td>Seizure/Convulsion</td>
<td>5 (1.0)</td>
<td>1 (0.3)</td>
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<td>6 (1.1)</td>
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<td>3 (0.9)</td>
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ARIA-E: amyloid-related imaging abnormalities with edema or effusion

*Symptoms reported in ARIA-E (VE) subjects, with an incidence ≥2% included: headache, confusional state, cognitive disorder, dizziness, memory impairment, hemiparesis, agitation, abnormal behavior, fatigue, and gait disturbance. Among the VE cases, % symptomatic in 0.5 mg/kg group=35.7%; in 1.0 mg/kg group=16.1%*  

**Excludes hemosiderin deposits, such as microhemorrhage

Salloway EFNS, 2012
Bapineuzumab Phase 2 MRI Re-read Project and Open-Label Extension (251)

- Mean # of infusions prior to identification of ARIA-E was 2.4
- In 251 the cumulative risk of developing ARIA-E dropped from 6.7% for infusions 1-3, compared to 2.7% for infusions 4-10
- ARIA-E not observed beyond 2 years of exposure
- Median duration for resolution was 113 days
- 8 patients re-dosed after resolution with asymptomatic recurrence in 1
- Incident microhemorrhage (ARIA-H) observed in 17/36 (47%) ARIA-E subjects compared to 7/177 (4%) subjects without ARIA-E

Sperling and Salloway, Lancet Neurology, 2012
12 cases of ARIA-E initially detected in Phase II 201 Bapineuzumab: Relationship to Dose and ApoE Genotype
• ARIA-type changes also occur in cases of cerebral amyloid angiopathy

A case of biopsy proven CAA

Oh 2004; Kinnecom 2007; Lim 2008; Greenberg 2009
Early immunization

Extravasation

Disrupted smooth muscle associated with Aβ

Aβ clearance

Courtesy Gene Kinney
Possible Role of Aquaporin 4 in ARIA E


Decreased perivascular AQP4 and redistribution to astrocytic soma and processes in capillary with Aβ deposit.
The Vascular Clearance Model of ARIA

NORMAL

Aβ
AQP4
Capillary
Artery

Potential risk factors
- Age
- ApoE
- Inflammatory components
- Others

AD-Like Pathology

fluid

Disrupted smooth muscle associated with Aβ

Deposition of Aβ

Recovery of smooth muscle

Repeated Immunization

fluid

Likelihood of ARIA and timing may depend on multiple factors
- Severity of CAA and underlying vascular integrity
- Efficiency of vascular Aβ removal
- Others

Courtesy Gene Kinney, Ph. D.
Recommendations from the Alz Assoc ARIA Workgroup and SS

- Monitor for ARIA frequently (every 3 months) in early development (Phase II), adjust dose based on ApoE carrier status
- May be able to decrease frequency of monitoring in longer pivotal trials, also guided by clinical symptoms
- Sensitive, standardized acquisition protocols for ARIA detection
- Allow patients with <5 microhemorrhages at baseline
- Hold Rx until ARIA-E clears for patients with significant ARIA, it may be possible to safely continue Rx for subtler forms, ? incident mH, stop Rx for macrohemorrhage

Sperling, Alz and Dementia, 2011
Summary

• Biomarkers are an important tool in AD clinical trials

• Challenges:
  – Standardize techniques and establish reliability
  – Determine the direction and magnitude of change for each biomarker based on compound targets for different stages of the disease
  – Better understand the mechanisms underlying biomarker effects and their relationship to clinical outcomes
The Butler Hospital Memory and Aging Program