CAMD AD Hippocampal Volume Team

Derek Hill of IXICO plc on behalf of the team

Annual Meeting, October 15 2015

Slides from:
Adam Schwarz
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AD HV Imaging Project Team

- **AbbVie**—David Ryman
- **Alzheimer’s Association**—Maria Carrillo, Jim Hendrix
- **BioClinica**—Joyce Suhy, Joel Schaerer, Luc Bracoud
- **Biohaven Medical Services**—Robert Berman
- **Boehringer Ingelheim**—Mark Gordon
- **Critical Path Institute**—Diane Stephenson, Klaus Romano, Volker Kern, Steve Arnerić
- **Eli Lilly**—Peng Yu, Brian Willis
- **Fatebenefratelli**—Giovani Frisoni, Alberto Redolfi, Marina Boccardi
- **FDA**—Jim Kaiser
- **Icon**—David Raunig
- **Ixico**—Derek Hill, Robin Wolz, Katherine Gray
- **Janssen**—Mahesh Samtani, Jerry Novak
- **Novartis**—Richard Meibach, Paul Maguire
- **Pentara**—Suzanne Hendrix
- **Pfizer**—Kaori Ito, Rachel Schindler, Sean Xie
- **Roche**—Tracie Carey
- **Takeda**—Pat Cole
- **USDavis**—Laurel Beckett
- **University of Trento, Italy**—Jorge Jovicich
- Chahin Pachai
Overview

• Context: Recent clinical trial results have important implications subject selection in future trials
• The need for enrichment/stratification strategies is increasingly apparent
• Update on the maturity and value of hippocampal volume (HCV) as an enrichment biomarker
• Looking to the future: combining biomarkers and incorporating disease models
Recent Scientific Data

• Increasing evidence that amyloid-targeted treatment is effective in some people:
  - Early in disease,
  - Amyloid positive,
  - Rapidly progressing,
  - Sufficient dose.

**Challenge is finding these people:**

• In clinical trials
• Even more so in the clinic
Emerging case for careful patient selection
Bapineuzumab & Solanazumab Mild to Moderate Phase III Results

- 6.5% of APOEɛ4 carriers and 36.1% of noncarriers amyloid-ve on PET

- Aβ- subjects did not demonstrate the same rate of cognitive decline typically observed in AD dementia

- Should amyloid targeted therapies only be given to amyloid +ve subjects?
Emerging case for careful patient selection:
Amyloid enrichment in Avagacestat trial

Original Investigation | CLINICAL TRIAL

Targeting Prodromal Alzheimer Disease With Avagacestat
A Randomized Clinical Trial

Amyloid enrichment can exclude slow progressors, but screen failure rate very high
Emerging case for careful patient selection
Gantenerumab MCI post hoc analysis (SCarlet RoAD)

- Prodromal AD study with amyloid biomarker terminated early due to futility analysis
- Post hoc analysis stratifying patient groups into slow and fast progressors using CDR-SOB, FAQ and HCV as covariates.
  - In fast progressors, Roche detected a “concentration-dependent treatment effect on ADASCog and MMSE”.

Is an amyloid biomarker alone insufficient?

Emerging case for careful patient selection
Aducanumab Results and Solanezumab Delayed Start Analysis

• Aducanumab phase Ib data
  - Evidence of efficacy with dose effect
    • Suggestion the placebo group more rapidly progressing than in other studies.

• Solanezumab delayed start trial design analysis
  - Potential case for disease modification from EXPEDITION EXT
  - modest therapeutic benefit.

• Will amyloid +ve enrichment in EXPECTION 3 increase clinical effect?
  - Or are there lessons from SCarlet RoAD?
Where does hippocampal volume (HCV) fit in?

- Low hippocampal volume is a biomarker of a neurodegenerative phenotype
- Face validity and > 20 years of clinical data
- It is later in the disease development than amyloid accumulation therefore provides “proximity marker” to clinical disease
- Potential value either alone or with other biomarkers
Hippocampal atrophy in Alzheimer’s Disease

AD = Alzheimer’s Disease.  MCI = Mild Cognitive Impairment.
Biomarker development adapted from the framework of Pepe et al. 2001

Phase 1: Rationale for the use of BM
- PA Potential leads
  - PA1 Identify discrimination accuracy AD/HC
- PA1 Assess capacity of earliest (MCI) detection
- PA2 Criteria for positivity
- PA3 Impact of covariates
- PA4 Compare markers
- PA5 Detect predictive features
- PA6 Cost/benefit quantification
- PA7 Practical feasibility
- PA8 Compliance in ≠ settings
- PA9 Compare ≠ protocols
- PA10 Estimate impact & costs
- PA11 Monitor false negatives

Phase 2: Discrimination ability of the BM
- PA1 Identify discrimination accuracy AD/HC
- PA2 Criteria for positivity
- PA3 Impact of covariates
- PA4 Compare markers

Phase 3: Detection ability in early phase
- PA1 Assess capacity of earliest (MCI) detection
- PA2 Criteria for positivity
- PA3 Impact of covariates
- PA4 Compare markers

Phase 4: BM accuracy in real world patients
- PA Assess true/false referral rate in BM-diagnosed patients
- PA Estimate impact on morbidity & disability

Phase 5: Quantify the impact of BM-based diagnosis on relevant outcomes
- PA Assess true/false referral rate in BM-diagnosed patients
- PA Estimate impact on morbidity & disability

Context of use (clinical trial enrichment – MCI)

Slide courtesy of Marina Boccardi & Giovanni Frisoni
Biomarkers of neurodegeneration are embedded in the 2011 NIA-AA research criteria for MCI due to AD

The diagnosis of mild cognitive impairment due to Alzheimer’s disease: Recommendations from the National Institute on Aging and Alzheimer’s Association workgroup

Marilyn S. Albert, Steven T. DeKosky, Dennis Dickson, Bruno Dubois, Howard H. Feldman, Nick C. Fox, Anthony Gamst, David M. Holtzman, William J. Jagust, Ronald C. Petersen, Peter J. Snyder, Maria C. Carrillo, Bill Thies, Creighton H. Phelps

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (tau, FDG, sMRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI—core clinical criteria</td>
<td>Uninformative</td>
<td>Conflicting/indeterminant/untested</td>
<td>Conflicting/indeterminant/untested</td>
</tr>
<tr>
<td>MCI due to AD—intermediate likelihood</td>
<td>Intermediate</td>
<td>Positive</td>
<td>Untested</td>
</tr>
<tr>
<td>MCI due to AD—high likelihood</td>
<td>Highest</td>
<td>Untested</td>
<td>Positive</td>
</tr>
<tr>
<td>MCI—unlikely due to AD</td>
<td>Lowest</td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; sMRI, structural magnetic resonance imaging.
A systematic survey of the published literature indicated strong evidence for low hippocampal volume as an enrichment biomarker in MCI.
De novo calculations confirmed literature findings and robustness to HCV measurement algorithm

Table 1
Results of Coalition Against Major Diseases’ de novo analysis. The AUC for four different hippocampal volume quantification algorithms applied to ADNI-I data indicate the prediction by MRI hippocampal volume of clinical conversion to Alzheimer’s dementia within two years.

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Training, n</th>
<th>Testing, n</th>
<th>AUC based on clinical conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEAP</td>
<td>149</td>
<td>173</td>
<td>0.7565</td>
</tr>
<tr>
<td>NeuroQuant</td>
<td>149</td>
<td>173</td>
<td>0.7516</td>
</tr>
<tr>
<td>FreeSurfer</td>
<td>148</td>
<td>171</td>
<td>0.7536</td>
</tr>
<tr>
<td>HMAPS</td>
<td>128</td>
<td>161</td>
<td>0.7290</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the receiver–operating characteristic curves; LEAP, Learning Embeddings for Atlas Propagation; HMAPS, Hippocampus Multi-Atlas Propagation and Segmentation.

Table 2
AUC values reported in the Coalition Against Major Diseases literature review

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>AUC based on clinical conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakkour et al. [e9]</td>
<td>49</td>
<td>0.65</td>
</tr>
<tr>
<td>Devanand et al. [38]</td>
<td>139</td>
<td>0.77</td>
</tr>
<tr>
<td>Fleisher et al. [e10]</td>
<td>129</td>
<td>0.60</td>
</tr>
<tr>
<td>Galluzzi et al. [42]</td>
<td>90</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Abbreviation: AUC, area under the receiver–operating characteristic curves.
Robustness of automated hippocampal volumetry across magnetic resonance field strengths and repeat images

Robin Wolz\textsuperscript{a,b}, Adam J. Schwarz\textsuperscript{c}, Peng Yu\textsuperscript{c}, Patricia E. Cole\textsuperscript{c}, Daniel Rueckert\textsuperscript{b}, Clifford R. Jack, Jr.,\textsuperscript{d}, David Raunig\textsuperscript{e}, Derek Hill\textsuperscript{a,*}, for The Alzheimer’s Disease Neuroimaging Initiative
Hippocampal volume measurements are highly reliable (test-retest)

Wolz R et al. (2014) Alzheimers & Dementia 10 430
Operationalizing hippocampal volume as an enrichment biomarker for amnestic mild cognitive impairment trials: effect of algorithm, test-retest variability, and cut point on trial cost, duration, and sample size

Peng Yu\textsuperscript{a}, Jia Sun\textsuperscript{a},\textsuperscript{b}, Robin Wolz\textsuperscript{c},\textsuperscript{d}, Diane Stephenson\textsuperscript{e}, James Brewer\textsuperscript{f}, Nick C. Fox\textsuperscript{g}, Patricia E. Cole\textsuperscript{h}, Clifford R. Jack Jr\textsuperscript{i}, Derek L.G. Hill\textsuperscript{c},\textsuperscript{g}, Adam J. Schwarz\textsuperscript{h},\textsuperscript{*}, for the Coalition Against Major Diseases and the Alzheimer’s Disease Neuroimaging Initiative
Cut-point defined with respect to normative reference range

Specify aHCV cut-point based on normative reference population

Enroll only aMCI subjects with aHCV < cut-point
MCI subjects with smaller hippocampi progress more rapidly

- Enriched population (HV < 25% of normal)
- All MCI subjects
- Subjects excluded (HV >= 25% of normal)

Subjects with smaller HV at baseline progress more rapidly

Slower progressing subjects are excluded
Prospective application of HCV biomarker to clinical trial cohort

- Re-use of (negative) clinical trial data remains a significant challenge for biomarker qualification
- Access to raw data (MRI scans etc) is especially difficult to secure
- CAMD is delighted to have access to the Novartis IndeXX study data
- IndeXX had a very slow rate of conversion from MCI to AD in the placebo group, making it an especially interesting, if challenging, dataset for enrichment biomarkers
- CAMD is proposing an analysis plan to the FDA for this dataset.
Combining Amyloid +ve & Hippocampal Volume
ADNI MCI cohort

Stepwise enrichment with HCV and Am+

Austin et al. Combination of biomarkers for amyloid positivity and structural neurodegeneration for enrichment of amnestic MCI clinical trials
CTAD 2014
Combining HCV and Amyloid biomarkers
Clinical trial data (Avagacestat)

<table>
<thead>
<tr>
<th></th>
<th>HCV+ Whole cohort</th>
<th>HCV- Whole cohort</th>
<th>HCV+ PET cohort</th>
<th>HCV- PET cohort</th>
<th>HCV+/PET+</th>
<th>Non-(HCV+/PET+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects (%)</td>
<td>152 (80%)</td>
<td>37 (20%)</td>
<td>29 (67%)</td>
<td>14 (33%)</td>
<td>25 (58%)</td>
<td>18 (41%)</td>
</tr>
<tr>
<td>Annualized Brain volume loss (mL/y) - SE</td>
<td>11.6 (0.4)</td>
<td>7.1 (0.6)</td>
<td>11.2 (0.9)</td>
<td>5.8 (1.0)</td>
<td>11.6 (0.9)</td>
<td>5.8 (0.9)</td>
</tr>
<tr>
<td>Annualized Ventricular volume increase (mL/y) - SE</td>
<td>2.89 (0.09)</td>
<td>1.62 (0.10)</td>
<td>2.81 (0.22)</td>
<td>1.32 (0.22)</td>
<td>2.88 (0.21)</td>
<td>1.37 (0.22)</td>
</tr>
<tr>
<td>Annualized Hippocampal volume loss (mm³/y) - SE</td>
<td>241 (7)</td>
<td>133 (12)</td>
<td>235 (18)</td>
<td>96 (24)</td>
<td>246 (18)</td>
<td>95 (22)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ADNI NC</th>
<th>ADNI MCI Non-Converters</th>
<th>ADNI MCI Converters</th>
<th>ADNI AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>160</td>
<td>237</td>
<td>109</td>
<td>123</td>
</tr>
<tr>
<td>Annualized Brain volume loss (mL/y) - SE</td>
<td>5.9 (0.5)</td>
<td>7.0 (0.7)</td>
<td>10.0 (0.9)</td>
<td>13.7 (0.9)</td>
</tr>
<tr>
<td>Annualized Ventricular volume increase (mL/y) - SE</td>
<td>1.42 (0.11)</td>
<td>1.88 (0.17)</td>
<td>3.08 (0.25)</td>
<td>4.22 (0.28)</td>
</tr>
<tr>
<td>Annualized Hippocampal volume loss (mm³/y) - SE</td>
<td>105 (5)</td>
<td>174 (7)</td>
<td>266 (9)</td>
<td>344 (9)</td>
</tr>
</tbody>
</table>

BMS and Bioclinica
Conclusions and next steps

• Recent scientific data supports need for improved clinical trial enrichment methodology
• While amyloid biomarkers (CSF, Amyloid PET) have clear benefit, the HCV biomarker provides complementary information about progression
• Literature review and prospective application to ADNI 1 and 2 cohorts demonstrates enrichment performance of HCV
• Plan to apply HCV to assess enrichment performance on IndeXX study being submitted to FDA
• Increasing data illustrating potential for HCV to be used in combination with other biomarkers (eg: Amyloid) and clinical data (eg: cognitive/function tests) to provide better enrichment performance
• Computer modelling appear to lead to better enrichment performance compared to sequential application of biomarkers
• CAMD is exploring opportunities for qualification or combination biomarkers for AD