Clinical relevance of neuropathological changes in Alzheimer’s disease
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Disclosure

In the last two years
Member of National/International Advisory Board: Actelion, Eli-Lilly, Lundbeck, Novartis, GE-Health, ROCHE, BIOGEN, NEURAXPHARMA
Investigator of Clinical Trial: ROCHE, UCB, Lundbeck, FORUM, AVID, GE-Health, Boehringer, BIOGEN
Topics

- The evolution of the concept of Alzheimer disease
- The neuropathological fingerprints of Alzheimer Disease across stages
- The relationship between neuropathology and clinical outcomes
- The impact of neuropathological changes on therapeutic strategies

What did go wrong? Where to go?
Sufficient exposure to high dose aducanumab reduced clinical decline across multiple clinical endpoints

- This reduction in clinical decline was statistically significant in EMERGE
- Biogen believes data from patients who achieved sufficient exposure to high dose aducanumab in ENGAGE support the findings of EMERGE
- After consultation with the FDA, we believe that the totality of these data support a regulatory filing
- Patients included in the futility analysis had enrolled early in the studies and had lower average exposure to aducanumab
- Two protocol amendments were put in place to enable more patients to reach high dose and for a longer duration
- Differences between EMERGE and ENGAGE can mostly be accounted for by greater exposure to high dose in EMERGE
Neuropathological Criteria

A diagnosis of AD is made when the criteria for intermediate or high likelihood of AD are met and the patient had a clinical history of dementia (NIA-RI Consensus 1997).

Current pathological criteria for AD were defined in 1997 by a workshop of the National Institute of Aging and the Reagan Institute.

The NIA-RI consensus recommendations combine the CERAD semiquantitative score of neuritic plaques and the Braak and Braak staging of NFTs to distinguish three probabilistic diagnostic categories:

(1) high likelihood, if there are frequent neuritic plaques (CERAD definite) and abundant isocortical NFTs (Braak stage V/VI);

(2) intermediate likelihood, if there are moderate neuritic plaques (CERAD probable) and NFTs are restricted to limbic regions (Braak III/IV), and

(3) low likelihood, if there are infrequent neuritic plaques (CERAD possible) and NFTs are restricted to the entorhinal cortex and/or hippocampus (Braak I/II).
What is Alzheimer disease?

- Biomarkers and neuropathological studies tell us that Alzheimer's starts many years prior the appearance of symptoms.
- Patients neuropathologically defined AD are genetically and clinically heterogeneous.
- The presence of pathology defines different baseline scores and trajectories for cognitive and functional decline in Ab+ and Ab- subjects.

- Alzheimer Disease is the major risk factor for cognitive decline in addition to age;
- Neuritic plaques and NFTs are the neuropathological hallmark of Alzheimer Disease;
- Amyloid deposition and fibrillogenesis is the main risk factor for the neuropathological hallmarks of Alzheimer Disease although TAU and TDP43 play also a major role in the development of the disease.

Age-specific population frequencies of cerebral β-amyloidosis and neurodegeneration among people with normal cognitive function aged 50–89 years: a cross-sectional study


Since 2004, the MCI investigators have enrolled individuals without dementia aged 70–89 years, and in 2012 started to enrol people without dementia aged 50 years and older.

To be eligible for inclusion in the present analysis, individuals must have been judged clinically to have no cognitive impairment on the basis of a battery of nine psychometric tests and assessments by a study coordinator and a physician (only results from the Auditory Verbal Learning Test are reported for simplicity). Participants also had to have undergone amyloid PET, [18F]FDG PET, and MRI within 7 months of their index clinical visit. Imaging results were obtained from March 28, 2006, to Dec 3, 2013. Amyloid PET, [18F]FDG PET, and MRI protocols were identical for all participants. APOE genotype was assessed by use of standard laboratory procedures with DNA extracted from blood.

<table>
<thead>
<tr>
<th>Overall (n=985)</th>
<th>Amyloid negative, neurodegeneration negative (A N: n=503)</th>
<th>Amyloid positive, neurodegeneration negative (A N: n=213)</th>
<th>Amyloid negative, neurodegeneration positive (A N: n=130)</th>
<th>Amyloid positive, neurodegeneration positive (A N: n=139)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>70–89 years</td>
<td>74 (62–80)</td>
<td>70 (63–76)</td>
<td>74 (70–80)</td>
<td>77 (74–83)</td>
</tr>
<tr>
<td>50–74 years</td>
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<tr>
<td>50–54 years</td>
<td>54 (52–64)</td>
<td>26 (23–29)</td>
<td>100 (72–100)</td>
<td>81 (62–91)</td>
</tr>
<tr>
<td>55–59 years</td>
<td>26 (23–29)</td>
<td>100 (72–100)</td>
<td>81 (62–91)</td>
<td>91 (62–67)</td>
</tr>
<tr>
<td>60–64 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–64 years</td>
<td>93 (85–100)</td>
<td>13 (12–16)</td>
<td>13 (12–16)</td>
<td>14 (12–16)</td>
</tr>
<tr>
<td>65–69 years</td>
<td>80 (63–98)</td>
<td>37 (28–46)</td>
<td>10 (8–12)</td>
<td>5 (4–6)</td>
</tr>
<tr>
<td>70–74 years</td>
<td>110 (52–154)</td>
<td>58 (25–89)</td>
<td>28 (13–51)</td>
<td>45 (18–75)</td>
</tr>
<tr>
<td>75–79 years</td>
<td>91 (43–142)</td>
<td>44 (21–59)</td>
<td>36 (17–56)</td>
<td>40 (19–67)</td>
</tr>
<tr>
<td>80–84 years</td>
<td>40 (24–61)</td>
<td>45 (27–62)</td>
<td>33 (20–50)</td>
<td>50 (30–73)</td>
</tr>
<tr>
<td>85–89 years</td>
<td>17 (11–36)</td>
<td>16 (10–24)</td>
<td>20 (13–30)</td>
<td>27 (14–51)</td>
</tr>
</tbody>
</table>

Data are median (IQR) or number (%). AVLT=Auditory Verbal Learning Test. *Sum of trials 1–5 plus the immediate and delayed recall trials (possible total score of 205).

Table 1: Participant characteristics

Table 2: Numbers of participants in each biomarker group by 5-year age stratum

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Figure 1: Estimated frequency (percentage) of participants in each biomarker group, by age
The unsolved question: what comes first, the egg or the chicken?
The pattern and the distribution of amyloid plaques correlates very poorly with which brain regions appear to be sick and to clinical severity. In contrast, the amount and distribution of neurofibrillary tangles tracks fairly well with how the disease moves cognitively in a particular patient.
WHAT HAVE WE LEARNT IN THE LAST YEARS ABOUT ALZHEIMER DISEASE?
CONVERGENT EVIDENCES ARGUE STRONGLY FOR AMYLOID AS THE MAIN FACTOR DRIVING THE PATHOLOGICAL PROCESS

Elevated amyloid at baseline was defined by florbetapir SUVR greater than 1.1 (a threshold derived from discrimination of probable Alzheimer cases from younger healthy control participants in an independent data set) or CSF Aβ42 less than 192 pg/mL (a threshold derived from discrimination of autopsy-confirmed Alzheimer cases in an independent data set).

Participants were classified as having elevated amyloid if they met either threshold. Otherwise, they were classified as having normal amyloid.
Our results indicate a sequence of observable phenomena in preclinical AD:

1. **Amyloid-β increase was the initial event observed**, including in those with low-Aβ levels. In the first observation period, Aβ increased but cognition did not decline until the second period. Tau measures were not available in the first period, but Aβ measures were associated with subsequent tau changes (model 1) and final tau levels (models 3-5).

2. Tau increase in inferior temporal neocortex, while measurable in low-Aβ individuals, was faster in those who were increasing Aβ. Our data indicate that tau changes are more closely associated with the rate of Aβ change than by Aβ levels (model 1). A short delay between Aβ and tau increases is likely to occur in some individuals.

3. **Cognitive decline was most closely associated with tau change, beyond baseline Aβ and tau.**

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**The evolution of Alzheimer Disease**

- **Synaptic/neuronal function and density**
- **Aβ deposition** (neuritic plaques)
- **Microglia and astrocyte activation**
- **Tau pathology** (NFT)

![Graph showing the evolution of Alzheimer Disease](Cell 2019 179, 312-339DOI: (10.1016/j.cell.2019.09.001))
THE CLINICAL CONSEQUENCES

1) Different therapies and strategies across stages of 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 replacement

Clinical disease stage:
- Normal
- Preclinical
- MCI
- Dementia
2) The development of diagnostic criteria

**AD BMs GROUPs – AT(N) classification**

<table>
<thead>
<tr>
<th>AT(N) biomarker grouping</th>
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<tbody>
<tr>
<td><strong>A</strong>: Aggregated Aβ or associated pathologic state</td>
</tr>
<tr>
<td>CSF Aβ_{42}, or Aβ_{42}/Aβ_{40} ratio</td>
</tr>
<tr>
<td>Amyloid PET</td>
</tr>
<tr>
<td><strong>T</strong>: Aggregated tau (neurofibrillary tangles) or associated pathologic state</td>
</tr>
<tr>
<td>CSF phosphorylated tau</td>
</tr>
<tr>
<td>Tau PET</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>N</strong>: Neurodegeneration or neuronal injury</td>
</tr>
<tr>
<td>Anatomic MRI</td>
</tr>
<tr>
<td>FDG PET</td>
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<tr>
<td>CSF total tau</td>
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</tbody>
</table>

Abbreviations: Aβ, β amyloid; CSF, cerebrospinal fluid. NOTE. See section 9.4 for explanation of (N) notation.


Aβ, amyloid-beta; AD, Alzheimer's Disease; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; IWG, International Working Group; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NIA-AA, National Institute on Aging-Alzheimer's Association; PET, positron emission tomography; p-Tau, phosphorylated-Tau; t-Tau, total-Tau

Slide adapted from AADC 2017 Biogen symposium
3) A useful framework for therapeutic testing

Fig. 2: Frameworks defining the stages of Alzheimer’s disease

A → T → (N) → (C)

T → A → (N) → (C)

A → (N) → (C)

W → A → (N) → (C)

X → A → (N) → (C)

Y → T → (N) → (C)

Z → T → (N) → (C)
Clinical trial of Aβ clearance strategy resulting in decreased amyloid plaque burden

THE CASE OF ANTIAMYLOIDS
DO THEY IMPACT ON AMYLOID?
**Predicted Plaque Removal in E/E and GRADUATE**

- **Inadequate amyloid reduction**
- **~19% threshold based on PRIME 10 mg/kg @ 52 wk**
- **Adequate amyloid reduction**

* Final analysis will include confidence interval around predictions

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**Gantenerumab reduced amyloid below threshold toward floor**

- Continued reduction between Month 24 and Month 36

- Consistent amyloid reduction between Months 24 and 36 in nearly all patients
- Amyloid levels appeared to be driven to the absolute amyloid floor value in many patients
  - 26% of patients had centiloid values < 0 at Month 24
  - 43% of patients had centiloid values < 0 at Month 36

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**Patient-level amyloid reductions (N = 23)**

- Centiloids vs. Month
- Amyloid positivity threshold 24
Amyloid PET trajectories in analysis population subgroups

33% more amyloid PET reduction at 24 months in the higher PET group

DO THEY IMPACT ON TAU?
Those treated with aducanumab had statistically significant reductions in CSF phospho-Tau levels compared with those treated with placebo, although sample sizes for these measures were small.

This suggests that clearing amyloid with aducanumab, a monoclonal antibody to β-amyloid aggregates, removes amyloid as shown in earlier trials and may also have a downstream effect of lowering tau levels.

DO THEY IMPACT ON CLINICAL MEASURES?
Directional trend of association between higher amyloid PET reduction and slower cognitive decline on ADAS-Cog11

<table>
<thead>
<tr>
<th>Linear regression</th>
<th>MMRM higher vs lower PET reduction</th>
<th>Joint linear mixed model</th>
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<tbody>
<tr>
<td>ADAS-Cog11 progression</td>
<td>ADAS-Cog11 progression</td>
<td>ADAS-Cog11 progression</td>
</tr>
<tr>
<td><strong>Worsening</strong></td>
<td><strong>47% less progression in the higher PET group</strong></td>
<td><strong>47% less progression in the higher PET group</strong></td>
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<tr>
<td>y = 0.064x + 18.66</td>
<td>p = 0.07</td>
<td>p = 0.31</td>
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<tr>
<td><strong>Higher</strong></td>
<td><strong>Higher PET reduction group</strong></td>
<td><strong>Higher PET reduction group</strong></td>
</tr>
<tr>
<td><strong>Lower</strong></td>
<td><strong>Lower PET reduction group</strong></td>
<td><strong>Lower PET reduction group</strong></td>
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<table>
<thead>
<tr>
<th>Regression parameter</th>
<th>Estimated Effect Size</th>
<th>p value</th>
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<tbody>
<tr>
<td>Change in ADAS-Cog predicted by PET slope*</td>
<td>0.15</td>
<td>0.21</td>
</tr>
<tr>
<td>Change in ADAS-Cog predicted by PET baseline**</td>
<td>0.11</td>
<td>0.36</td>
</tr>
</tbody>
</table>

*Estimate > 0: faster PET reduction predicts slower ADAS-Cog decline.
**Estimate > 0: higher PET baseline predicts faster ADAS-Cog decline.
ADUCANUMAB BIOLOGICAL AND CLINICAL EFFECTS

Amyloid PET

EMERGE

ENGAGE

CDR-SB

EMERGE

ENGAGE

<table>
<thead>
<tr>
<th></th>
<th>WK 0</th>
<th>WK 26</th>
<th>WK 78</th>
<th>WK 0</th>
<th>WK 26</th>
<th>WK 78</th>
<th>WK 0</th>
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<th>WK 78</th>
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<td>157</td>
<td>128</td>
<td>90</td>
<td>157</td>
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<td>437</td>
<td>297</td>
<td>540</td>
<td>400</td>
<td>336</td>
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<tr>
<td>ADU</td>
<td>55</td>
<td>48</td>
<td>43</td>
<td>55</td>
<td>48</td>
<td>43</td>
<td>147</td>
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<td>127</td>
<td>116</td>
<td>114</td>
<td>97</td>
<td>114</td>
<td>97</td>
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FUTURE SCENARIOS
Antiamyloids are not a Magic Bullet

THE RIGHT TARGET FOR THE RIGHT DRUGS AT THE RIGHT STAGE FOR THE RIGHT TIME INTERVAL
Cumulative events over the 20-year follow-up period. Cumulative incidence functions are provided for the outcomes of death resulting from (A) all causes, (B) cardiovascular disease, (C) coronary heart disease, and (D) noncardiovascular disease. *P* values were determined by Cox proportional hazards model.


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**Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease**

Given the complex nature of the Alzheimer process, it is unlikely that the most effective disease modifying therapy could be achieved by a single compound with a single target.

COMBINATION THERAPIES
Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer’s disease progression

Emerging evidence from both animal and human studies supports the association between dysbiosis of the gut microbiota and the microglia activation during AD development. This study aims to investigate the mechanistic linkage between gut microbiota and AD progression, and to explore the potential intervention strategies.

“GV-971 is a novel, marine-derived oligosaccharide, which has multi targeting mechanisms including inhibition of amyloid-β fibril formation, neuroinflammation, and recondition of dysbiosis of gut microbiota”

Conclusions

Experimental and preliminary clinical studies indicate that targeting amyloid and tau are the KEY STRATEGY to prevent and treat AD since the earliest stages.

The mechanisms by which the accumulation of amyloid develops are still little known, as are the mechanisms by which amyloid has a variable influence on the metabolism of tau but IMMUNITY and INFLAMMATION seem to play an important role in Alzheimer’s disease.

Data derived from different studies support the need to stratify subjects based on disease stage and neuropathological characteristics.

STRATEGIES BY COMBINING DIFFERENT DRUGS IN DIFFERENT PHASES acting on distinct neuropathological targets should be part of a effective therapeutic approach aimed at treating AD progression.