The Importance of Early Identification of Alzheimer’s Disease

Alessandro Padovani
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University of Brescia
<table>
<thead>
<tr>
<th>Company Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/Patent</th>
<th>Stock Options</th>
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Disclaimer

- Aducanumab is an investigational medicine and the benefit/risk profile has not been fully established. It has not received any marketing authorization and there is no guarantee that it will obtain such authorization in the future.

- The information and any data presented is early interim data from ongoing clinical trials and it is made available for scientific discussion only, in consideration of the general interest of the scientific community with respect to any progress in the research and development of possible treatments for Alzheimer disease.

- The information and any data presented are developed from scientist research and are not intended to predict the availability of any particular drug or therapy.
Why we are here today

“The first person to be cured of Alzheimer's is a person in a Clinical Trial”

AfricanAmericansAgainstAlzheimer's

Alois Alzheimer
An assumption

- We believe that treatment earlier in the disease course may have greater benefit for the patient

- With no treatment yet slowing or stopping the course of disease – why do we believe that? Why have we gone in that direction?
What’s important in inventing and developing new therapies?

- Deep understanding of disease biology
- Strong linkage of targets to disease
- Improved translational measures
- Patients most likely to respond
- Improved trial design
- Promising investigational compounds
Key factors important to project progression in clinical phase

- Human genetic data is more common in projects that succeed vs fail in PhII.
- Successful projects are more likely to have biomarkers (82 vs 30%)\(^1\)
- Proof of Mechanism – quantifiable target engagement has a positive impact on progression to PhII (38%), PhIII (21%) or launch (10%)\(^2\)

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How do we rate the strength of connection to disease?

- Generate evidence that builds confidence in or invalidates the scientific hypothesis
- A target is only truly validated when a drug for that target is successfully approved
What are the current hypotheses being tested?

- Genetic linkage of target to disease
- Presence & role of target: In disease pathways / tissue
- Modulation of target: Impact on disease pathways in vitro & in vivo
- Approved drug / effect on a clinical endpoint

Investigational Compounds – Aducanumab
Aducanumab is a human IgG1 anti-Aβ monoclonal antibody developed by Biogen and Neurimmune.

Reverse Translational Medicine™ Technology

Selected donor cohorts

Clinical trial

CMC TOX

B-cell screening

Immune response

Antibody cloning

In vitro validation

Recombinant production

In vivo validation

Multiple Aβ antibodies target the N-terminus

Aβ binding Specificity
- All forms of Aβ
- Aggregated Aβ
- Soluble Aβ

Aducanumab is highly selective for aggregated Aβ

Aducanumab binds to:
- Soluble oligomers
- Insoluble fibrils

Selectivity of aducanumab for $\alpha$-syn aggregates is driven by valency, low affinity for soluble monomer, and rapid kinetics.

**Binding studies using SPR**

<table>
<thead>
<tr>
<th>Fragment</th>
<th>Dissociation rate</th>
<th>Equilibrium affinity</th>
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<tbody>
<tr>
<td>Fab Fragment</td>
<td>$K_d(s^{-1})$</td>
<td>$K_D(nM)$</td>
</tr>
<tr>
<td>Aducanumab (mlgG chimer)</td>
<td>&gt;1</td>
<td>~9,000</td>
</tr>
<tr>
<td>Gantenerumab (mlgG chimer)</td>
<td>$1.5 \times 10^{-2}$</td>
<td>23</td>
</tr>
<tr>
<td>Bapineuzumab (mouse 3D6)</td>
<td>$7.9 \times 10^{-4}$</td>
<td>1.1</td>
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</table>

What structural features drive the selectivity of antibodies for Aβ aggregates?

Crystal structure (2.1 Å) of aducanumab Fab with Aβ 1-11

Aducanumab binds to Aβ peptide with a “light touch”
A shallow and compact epitope may contribute to the selectivity for high molecular weight Aβ forms, without targeting Aβ monomers

<table>
<thead>
<tr>
<th></th>
<th>BSA (Å²)</th>
<th>CDR contacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aducanumab</td>
<td>530</td>
<td>12</td>
</tr>
<tr>
<td>Bapineuzumab</td>
<td>537</td>
<td>23</td>
</tr>
<tr>
<td>Gantenerumab</td>
<td>903</td>
<td>24</td>
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</table>


BSA, buried surface area; CDRs, complementary-determining regions
Interaction between aducanumab and Aβ is shallow, with a subtle interface in comparison with those of other anti-Aβ antibodies.
Dose-dependent reduction of amyloid burden upon chronic treatment in Tg2576 mice

Brain exposure proportional to dose and plasma
Range of brain-to-plasma ratio 0.1–1%

In vivo binding to amyloid deposits (anti-hu IHC)

Dose-dependent reduction of amyloid (chronic treatment in Tg2576 mice)

Patients Most Likely to Respond / Improved Translational Measures from Preclinical to the Clinic
What have we learnt about disease progression?

- Biomarkers tell us that Alzheimer’s starts many years prior to the appearance of symptoms.
- In previous Phase 3 studies, patients were enrolled without evidence of amyloid pathology (Alzheimer’s pathogenesis).
- The presence of pathology defines different baseline scores and trajectories for cognitive and functional decline in Ab+ and Ab-subjects.
Identifying patients most likely to respond to an anti-amyloid mechanism of action – amyloid PET screening

<table>
<thead>
<tr>
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<th>Prodromal (n=139)</th>
<th>Mild (n=133)</th>
<th>Overall (n=278)(^a)</th>
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<tbody>
<tr>
<td><strong>Amyloid PET findings by binary visual readings, n (%)</strong></td>
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<tr>
<td>Amyloid-positive</td>
<td>69 (50)</td>
<td>100 (75)</td>
<td>170 (61)</td>
</tr>
<tr>
<td>Amyloid-negative</td>
<td>70 (50)</td>
<td>33 (25)</td>
<td>108 (39)</td>
</tr>
<tr>
<td><strong>Amyloid PET findings via quantitative analysis, n (%)</strong></td>
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<tr>
<td>Amyloid-positive</td>
<td>79 (57)</td>
<td>104 (78)</td>
<td>185 (67)</td>
</tr>
<tr>
<td>Amyloid-negative</td>
<td>60 (43)</td>
<td>29 (22)</td>
<td>93 (33)</td>
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</table>

\(^a\)Includes 6 patients with unknown AD stage.
Clinical proof of mechanism for aducanumab – dose and time-dependent reduction in amyloid plaque as measured by PET

Dose and time dependent reduction in composite SUVR (PET)\(^1\)

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Analysis visit (weeks)</th>
<th>Placebo</th>
<th>3 mg/kg</th>
<th>6 mg/kg</th>
<th>10 mg/kg</th>
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<tbody>
<tr>
<td></td>
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<td>54</td>
<td>21</td>
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</table>

Amyloid-β (Aβ) plaque reduction: example amyloid PET images\(^2\)

Nominal p values: * P<0.05; **P<0.01; ***P<0.001 vs placebo.


ANCOVA, analysis of covariance; SE, standard error; SUVR, Standardized uptake value ratio
**Amyloid plaque reduction with aducanumab regional analysis SUVR at Week 54**

Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline composite SUVR. PD analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter; Sevigny et al. Randomized, Placebo-Controlled, Phase 1b Study of the Anti–Amyloid Beta Antibody Aducanumab (BIIB037) in Patients with Prodromal or Mild Alzheimer’s Disease: Interim Results. Platform Presentation at CTAD 2015.

*P<0.05; **P<0.01; ***P<0.001 vs placebo
Dose- and time-dependent reductions in SUVR observed with aducanumab regardless of reference/target regions

Centiloid conversion

Centiloid: a 0 to 100 scale, anchored by young controls (45 years) and typical AD patients

Objective: to standardize quantitative amyloid imaging measures by converting the outcome of each particular analysis method or tracer to the centiloid scale

Methods:
• A centiloid conversion equation established using a public database from Global Alzheimer’s Association Information Network (GAAIN; http://www.gaain.org) and an amyloid PET data set from Avid Radiopharmaceuticals (46 subjects, each underwent a PiB and a florbetapir scan)
• PRIME amyloid PET SUVR measures converted to centiloid units using the centiloid conversion equation
• Percent change in amyloid PET measures calculated using the following:
  \[
  \frac{\text{Follow up Centiloid} - \text{Baseline Centiloid}}{\text{Baseline Centiloid}} \times 100
  \]

Aducanumab Ph1b amyloid results in SUVR and centiloid: 69% reduction in amyloid plaque load

Viglietta et al. Aducanumab titration dosing regimen: 12-month interim analysis from PRIME, a randomized, double-blind, placebo-controlled Phase 1b study in patients with prodromal or mild Alzheimer’s disease. Platform Presentation at CTAD 2016. Data on file. Nominal p values: * P<0.05; **P<0.01; ***P<0.001 vs placebo. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline composite SUVR. PD analysis population is defined as all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter. ANCOVA, analysis of covariance; SE, standard error

Date of preparation: March 2018
Clinical proof of concept: effect of aducanumab on clinical decline as measured by CDR-SB & MMSE (exploratory endpoints)

**Change in CDR-SB**

CDR-SB is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-SB. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment.

**Change in MMSE**

MMSE is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline MMSE. Efficacy analysis population is defined as all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment.

Ph1b Aducanumab CDR-SB by patient subgroup

Vigilietta et al. 12-Month Interim Analysis of APOE4 Carriers for Fixed and Titration Dosing Regimens in PRIME, a Phase 1b study of Aducanumab. Platform presentation at ADPD 2017, Vienna, Austria. CDR-SB was an exploratory endpoint. Analyses based on observed data. Difference from placebo and 95% CI based on ANCOVA model. ANCOVA for change from baseline with factors of treatment, laboratory Apo ε4 status (carrier and non-carrier) [for clinical stage subgroup analysis only], and baseline CDR-SB. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.

ApoE ε4 Carriers

<table>
<thead>
<tr>
<th>Aducanumab dose</th>
<th>1 mg/kg (n=13)</th>
<th>3 mg/kg (n=18)</th>
<th>6 mg/kg (n=19)</th>
<th>10 mg/kg (n=16)</th>
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<tbody>
<tr>
<td>CDR-SB Difference vs Placebo (95% CI for difference)</td>
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Prodromal AD

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<tr>
<td>CDR-SB Difference vs Placebo (95% CI for difference)</td>
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Mild AD

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<th>Aducanumab dose</th>
<th>1 mg/kg (n=15)</th>
<th>3 mg/kg (n=15)</th>
<th>6 mg/kg (n=16)</th>
<th>10 mg/kg (n=13)</th>
</tr>
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<tbody>
<tr>
<td>CDR-SB Difference vs Placebo (95% CI for difference)</td>
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</table>
What’s important in inventing and developing new therapies?

- Deep understanding of disease biology
- Strong linkage of targets to disease
- Patients Most Likely to Respond
- Improved Investigational Compounds
- Improved Translational Measures
- Improved trial design