Latest Discoveries in Alzheimer’s Disease

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Alzheimer Disease: A Global Epidemic

The Alzheimer’s Association 2018 Report
Alzheimer Disease: Major Cause of Mortality

Amyloid and Tau Cascades in Alzheimer Disease

Xiao et al., Front. Aging Neurosci., 06 November 2020 with permission (Open Access)
Other Disease Mechanisms and Pathways

The pathological evolution of Alzheimer’s disease

Stages of Neurodegeneration

**Stages I-II**
Transentorhinal Clinically Silent

**Stages III-IV**
Limbic Incipient AD

**Stages V-VI**
Neocortical Fully developed AD

Braak and Braak 1991


AD Biomarker Profile: High CSF tau and p-tau181 and low CSF Aβ42

Leuzy et al. *Brain*. 2016 Sep; 139(9): 2540–2553 (with permission-Open Access)
I. UPDATED RESEARCH FRAMEWORK FOR AD

TOWARDS BIOMARKER-BASED DEFINITIONS OF AD
Theoretical Model of Disease Progression


Biomarkers: Central Concept in the Updated Research Framework of AD: AT(N)

The ATN Framework for Alzheimer Disease Diagnosis and Characterization

Amyloid “A”

Volumetric MRI

FDG-PET

Imaging Biomarkers of Neurodegeneration “N”
Advances in AD Diagnosis:

Blood Biomarkers and Emerging Markers of Other Pathologies

CSF p-tau217 outperforms CSF p-tau181

Plasma p-tau181: New AD-Specific Blood Marker


Plasma p-tau217: Great Promise as Most Sensitive and Specific Blood Test for AD

Plasma Markers Can Detect Brain Amyloid

Schinder SE, et al. Neurology. 2019;93(17):e1647-e1659 (with permission)

P-tau231 May Precede Amyloid in AD Brains

Understanding the Clinicopathological and Molecular Heterogeneity of AD

Biomarkers of AD Pathologies: Beyond Amyloid and Tau

Tarawneh, R. Biomarker Insights, 2020 (with permission)
**New Biomarkers And Big Data Analytics: Data-Driven Disease Models**

Iturria-Medina et al. Nat Commun 7, 11934 (2016) with permission (Open Access)

**AI Algorithms Identify 4 AD Subtypes**

Young et al. Nat Commun 9, 4273 (2018) with permission (Open Access)

Vogel et al. Nat Med. 2021 May;27(5):871-881 with permission
Update on Investigational AD Therapies

Anti-amyloid immunotherapies: Effectively Remove Amyloid And May Slow Down Disease Progression

**Results**

Amyloid Plaque Reduction with Aducanumab

Amyloid PET images at Baseline and at Week 54

- Actually shown to penetrate the brain and decrease AB in patients with AD in a time- and dose-dependent manner
- Mean PET SUVR composite score at baseline was 1.44
- After 54 wks of treatment, this decreased significantly (P < 0.001) in the 3, 6, and 10 mg/kg dose groups
- Change in placebo group was minimal

NEWS: Aducanumab FDA-Approved June 7, 2021
As First Disease-Modifying Treatments for AD

- Aducanumab is an amyloid beta-directed antibody indicated for the treatment of early symptomatic Alzheimer’s disease.
- This targets soluble and insoluble (aggregated) Aβ peptides
- This indication was just recently approved under accelerated approval based on reduction in amyloid beta plaques observed in treated patients.
- Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.
- Both Phase 3 clinical trials includes patients with:
  - Clinical Dementia Rating (CDR) score of 0.5 (equivalent to MCI)
  - MMSE 24-30
  - RBANS (Repeatable Battery for Assessment of Neuropsychological Status) delayed memory index of ≤ 85

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf

Aducanumab reduces amyloid burden

Figure 1: Reduction in Brain Amyloid Beta Plaque (Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 1

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf
Clinical Endpoints

Figure 2: Line Plot of Primary Efficacy Endpoint (Change From Baseline in CDR Sum of Boxes) in Study 1

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Placebo (N=548)</th>
<th>ADUHELM High dose (N=547)</th>
<th>Placebo (N=548)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Change from baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference from placebo (%)</td>
<td>1.35</td>
<td>-0.39 (-2.2%)</td>
<td>1.74</td>
</tr>
<tr>
<td>p</td>
<td>0.0120</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>26.3</td>
<td>26.4</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-2.7</td>
<td>-2.7 (-12%)</td>
<td>-3.3</td>
</tr>
<tr>
<td>Difference from placebo (%)</td>
<td>0.6</td>
<td>-0.18%</td>
<td>p=0.0493</td>
</tr>
<tr>
<td><strong>ADAS-Cog 13</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>22.246</td>
<td>21.867</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>3.763</td>
<td>-1.400 (-27%)</td>
<td>5.162</td>
</tr>
<tr>
<td>Difference from placebo (%)</td>
<td>-1.400 (-27%)</td>
<td>5.162</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.0097</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ADCS-ADL-MCI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>42.5</td>
<td>42.6</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-2.5</td>
<td>-2.5 (-40%)</td>
<td>-4.3</td>
</tr>
<tr>
<td>Difference from placebo (%)</td>
<td>1.7</td>
<td>-0.40%</td>
<td>p=0.0006</td>
</tr>
<tr>
<td><strong>NPI-10</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Mean baseline</td>
<td>4.5</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.2</td>
<td>-1.3 (-87%)</td>
<td>1.5</td>
</tr>
<tr>
<td>Difference from placebo (%)</td>
<td>0.2</td>
<td>-1.3 (-87%)</td>
<td>p=0.0215</td>
</tr>
</tbody>
</table>

*P-value was not statistically controlled for multiple comparisons.

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Biomarker End-points

<table>
<thead>
<tr>
<th>Biomarker Endpoint at Week 78</th>
<th>ADUHELM High dose</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amyloid Beta PET Composite SUVR</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mean baseline</td>
<td>1.383</td>
<td>1.375</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.264</td>
<td>0.014</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-0.278, p&lt;0.0001</td>
<td></td>
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<tr>
<td><strong>Amyloid Beta PET Centiloid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>85.3</td>
<td>83.5</td>
</tr>
<tr>
<td>Change from baseline (%)</td>
<td>-60.8 (-71%)</td>
<td>3.4</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-64.2, p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td><strong>CSF p-Tau (pg/mL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>100.11</td>
<td>72.55</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-22.93</td>
<td>-0.49</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-22.44, p=0.0005</td>
<td></td>
</tr>
<tr>
<td><strong>CSF t-Tau (pg/mL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>686.65</td>
<td>484.00</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-112.44</td>
<td>-0.39</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-112.05, p=0.0088</td>
<td></td>
</tr>
</tbody>
</table>

\(P\)-values were not statistically controlled for multiple comparisons.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf

Aducanumab—in the clinic

- Is administered as an intravenous (IV) infusion over approximately one hour every four weeks and at least 21 days apart.
- Patients with mild cognitive impairment due to Alzheimer disease
- Evidence of Amyloid on Amyloid-PET scans
- Brain MRI within a year prior to starting the infusion as a baseline
- Safety has not been assessed in patients who have pre-treatment localized superficial siderosis, 10 or more brain microhemorrhages, and/or with a brain hemorrhage greater than 1 cm within one year of treatment initiation

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf
ARIA-E and ARIA-H

- ARIA-E or ARIA-H were observed in 41% of treatment compared to 10% of placebo groups
- ARIA-E was observed in 35% of treated patients compared to 3% of placebo
- ARIA-E was more common in APOE4 carriers (42%) vs APOE4 noncarriers (20%)
- Most ARIAs occurred within the first 8 doses but can occur any time
- ARIAs were mild in 30%, moderate in 58% and severe in 13%
- Resolution occurred in 68% of ARIA-E patients by 12 weeks, 91% by 20 weeks, and 98% overall after detection
- 10% of patients on the full dose had more than one episode of ARIA
- Besides ARIA, angioedema and hypersensitivity have been reported

Amyloid Related Imaging Abnormalities (ARIA)

<table>
<thead>
<tr>
<th>ARIA Type</th>
<th>Radiographic Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>ARIA-E</td>
<td>FLAIR hyperintensity confined to sulcus and or cortex/subcortical white matter in one location &lt; 5 cm</td>
</tr>
<tr>
<td></td>
<td>FLAIR hyperintensity 5 to 10 cm, or more than 1 site of involvement, each measuring &lt; 10 cm</td>
</tr>
<tr>
<td></td>
<td>FLAIR hyperintensity measuring &gt; 10 cm, often with significant subcortical white matter and/or sulcal involvement. One or more separate sites of involvement may be noted.</td>
</tr>
<tr>
<td>ARIA-H microhemorrhage</td>
<td>≤ 4 new incident microhemorrhages</td>
</tr>
<tr>
<td>ARIA-H superficial siderosis</td>
<td>1 focal area of superficial siderosis</td>
</tr>
<tr>
<td></td>
<td>5 to 9 new incident microhemorrhages</td>
</tr>
<tr>
<td></td>
<td>10 or more new incident microhemorrhages</td>
</tr>
<tr>
<td></td>
<td>2 focal areas of superficial siderosis</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 focal areas of superficial siderosis</td>
</tr>
</tbody>
</table>

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf
**ARIA Follow-up**

- Enhanced clinical vigilance for ARIA is recommended during the first 8 doses
- Clinical evaluation of symptomatic patients with suspected ARIA should include a brain MRI
- Brain MRIs should be obtained routinely prior to the 7th infusion (first dose of 10 mg/kg) and 12th infusion (sixth dose of 10 mg/kg) to evaluate for the presence of asymptomatic ARIA.
- For patients with radiographic ARIA, enhanced clinical vigilance is recommended including possible need for additional MRIs
- For ARIA-E or mild/moderate ARIA-H, treatment may continue with caution. If dosing is temporarily suspended, dosing may resume at that same dose and titration schedule.
- In Studies 1 and 2, temporary dose suspension was required for radiographically moderate or severe ARIA-E and radiographically moderate ARIA-H.
- In Studies 1 and 2, permanent discontinuation of dosing was required for radiographically severe ARIA-H.

**ARIA-Case Report Outlining Suggested Treatment**

Anti-Tau Trials

Current clinical trials targeting tau (Adapted from Congdon and Sirgudsson, 2018)

MIR-NATs: Noncoding RNAs That Regulate Tau Translation In Vivo

Unraveling New Disease Mechanisms

Beyond Protein Aggregation:
Immune Mechanisms and Vascular Disturbances are Key Players

Immune Dysregulation as a Central Mechanism in AD

Targeting Inflammation in AD; Anti-TREM2 Antibodies

RNA-seq identifies different microglial subtypes in AD
Novel Therapeutic Targets
Big Data Analytics at Forefront of AD Drug Discovery

VGF Gene As A Key Regulator of AD

Beckman et al. Nat Commun 11, 3942 (2020) with permission
AD and the Gut Microbiome