The Future of Prevention and Treatment of Alzheimer’s Disease in Down Syndrome

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Alzheimer’s Disease Pathology
- tangles and plaques

www.nia.nih.gov

Preclinical
Moderate
Severe

www.nia.nih.gov

Neurofibrillary
**β-Amyloid in AD**

- Aβ plaques
- Oligomers
- Beta-amyloid Peptide
- APP
- Beta-secretase
- Cell Membrane
- Cell Surface
- Gamma-secretase

Images:
- [11C]PiB binding AD
- [11C]PiB binding HC

Source: [www.nia.nih.gov](http://www.nia.nih.gov)
- **Goal:** This longitudinal study will examine progression of AD related neuroimaging, biofluid, genetic and cognitive/functional biomarkers in **550 adults** with DS (>25 yrs of age) and 50 “biomarker-controls”

1. Examine existing and novel biomarkers of DS-AD and determine if they are similar to LOAD.

2. Study the direct and downstream effects of genetic variants from whole genome sequencing.


4. Provide data and specimen sharing for the broader scientific community.
Amyloid and Tau Imaging in Down Syndrome

Adapted from Braak, et al. J Neuropathol Exp Neurol. 2011
Estimating A+ duration time and age of A+ onset

- Mean A+ age:
  - APOE E4 carriers: 40.1(4.89) years
  - Non-carriers: 41.6(5.93) years
Alzheimer Disease Treatment Trials

Inclusion of People with Down Syndrome
Disease-Modifying Drugs for Alzheimer’s Disease

History of failure...

Possible reasons for failures of trials of disease-modifying drugs for Alzheimer's disease:

- inadequate understanding of the biology of Alzheimer's disease
- wrong treatment target
- starting the test of therapies too late in disease development
- incorrect drug doses
- the choice of the clinical endpoint for the trials and associated variability in measurement of endpoints within or between individuals
**ANTIBODIES AGAINST AMYLOID**

Several clinical trials are testing whether drugs called monoclonal antibodies can stem the symptoms of Alzheimer’s by preventing the toxic clumping of amyloid-β proteins. This process starts when enzymes cleave the amyloid precursor protein (APP). Amyloid-β proteins elongate into fibrils and then nucleate into plaques. All of the drugs bind to amyloid-β, but their primary targets in the process are different.

- **Donanemab**: Binds to plaques
- **Lecanemab**: Binds to protofibrils
- **Amyloid-β clumps into plaques**
- **Solanezumab**: Stops first phase of aggregation
- **Gantenerumab**: Blocks fibril elongation
- **Aducanumab**: Blocks second phase of aggregation

*Abbot et al., Nature 2022; slide provided by Carol Van Hulle, Ph.D.*
Aducanumab – Accelerated Approval – June 2021

22% slowing in cognitive decline

70% reduction in brain amyloid at 18 mos
A. CDR-SB Score

Worsening

27% reduction in rate of cognitive decline

No. of Participants

Lecanemab 859 824 798 779 765 738 714
Placebo 875 849 828 813 779 767 729

B. Amyloid Burden on PET

Less amyloid

77% reduction β-amyloid PET

No. of Participants

Lecanemab 354 296 275 276 210
Placebo 344 303 286 259 205
Major Progress towards AD Therapeutics

- Aducanumab: accelerated approval based on amyloid removal, but CMS non-coverage
  - Marketing of aducanumab has essentially ceased
  - Phase IV study moving forward
- Lecanemab: accelerated approval, expecting full approval
- In the next 3-6 months expect results for:
  - Phase 3 donanemab in Early AD
  - Phase 3 solanezumab in Preclinical AD

None of the clinical trials enrolled individuals with DS!
Aducanumab: Appropriate use recommendations

Jeffrey Cummings1  |  Steve Salloway2

1 Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas (UNLV), Las Vegas, Nevada, USA
2 Butler Hospital and Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA

Expert Panel recommends against treating amyloid positive patients with Down syndrome, dementia with Lewy bodies, or cerebral amyloid angiopathy with aducanumab. The Expert Panel recommends caution in treating patients with autosomal dominant AD and those with atypical AD syndromes until more data are available; the lack of information in these settings should be disclosed to potential treatment candidates. We are the beginning of the aducanumab era, and more data will inform the range of appropriate use of this agent.
The Down syndrome community hasn’t stayed silent. As the Centers for Medicare & Medicaid Services (CMS) considered whether to provide coverage for Eisai and Biogen’s controversial medicine Aduhelm back in 2022, the community wrote as many as 3,000 letters asking for coverage or at the very least, safety studies to see if the therapy could be used at all. The original proposal had exclusion criteria for “any neurological or other medical condition (other than AD) that may significantly contribute to cognitive decline.” CMS ultimately decided against this exclusion criteria, noting the overwhelming number of comments asking for a rethink of what one letter referred to as discrimination.
Down Syndrome – Alzheimer’s Disease: ideal candidates for anti-amyloid trials

- Predictable age range for AD onset
- A genetic form of AD with near full penetrance
- Emergence of AD biomarkers are similar to those in sporadic AD

Things to consider for AD therapeutics for people with DS:

- Safety!!!
- Amount of target engagement
- Timing of therapies
- Types of administration
# Lecanemab in Early Alzheimer’s Disease

van Dyck CH et al. DOI: 10.1056/NEJMoa2211294

## Table 3. Adverse Events:*

<table>
<thead>
<tr>
<th>Event</th>
<th>Lecanemab (N=898)</th>
<th>Placebo (N=897)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>798 (88.9)</td>
<td>735 (81.9)</td>
</tr>
<tr>
<td>Adverse event related to lecanemab or placebo†</td>
<td>401 (44.7)</td>
<td>197 (22.0)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>126 (14.0)</td>
<td>101 (11.3)</td>
</tr>
<tr>
<td>Death</td>
<td>6 (0.7)</td>
<td>7 (0.8)</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation of the trial agent</td>
<td>62 (6.9)</td>
<td>26 (2.9)</td>
</tr>
<tr>
<td>Adverse event that occurred in ≥5% of participants in either group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>237 (26.4)</td>
<td>66 (7.4)</td>
</tr>
<tr>
<td>ARIA with microhemorrhages or hemosiderin deposits</td>
<td>126 (14.0)</td>
<td>69 (7.7)</td>
</tr>
<tr>
<td>ARIA-E</td>
<td>113 (12.6)</td>
<td>15 (1.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>100 (11.1)</td>
<td>73 (8.1)</td>
</tr>
<tr>
<td>Fall</td>
<td>93 (10.4)</td>
<td>86 (9.6)</td>
</tr>
</tbody>
</table>

* Amyloid Related Imaging Abnormalities
# ARIA and Anti-Amyloid mAbs

<table>
<thead>
<tr>
<th></th>
<th>Aducanumab</th>
<th>Lecanemab</th>
<th>Donanemab</th>
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<tbody>
<tr>
<td>Amyloid Clearance</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>ARIA-E Incidence%</td>
<td>42.0</td>
<td>12.6</td>
<td>27.5</td>
</tr>
<tr>
<td>ARIA-H Incidence%</td>
<td>19.0</td>
<td>14.0</td>
<td>30.5</td>
</tr>
</tbody>
</table>

84% of ARIA-E cases were asymptomatic and self-limiting

Adapted from Withington et al, 2022

Keck School of Medicine of USC
Alzheimer’s Therapeutic Research Institute

ACTC-DS
Alzheimer’s Clinical Trials Consortium
Down Syndrome

*Slide Courtesy of Mike Rafii, M.D., Ph.D.*
A phase 1b/2, multicenter, randomized, placebo-controlled study to assess the safety, tolerability, immunogenicity, and pharmacodynamic effects of ACI-24.060 in prodromal Alzheimer’s disease and in adults with Down syndrome

Placebo-controlled Phase 1b/2 Study Overview

- Multicenter, adaptive, placebo-controlled, dose-escalation, double-blind, randomized Phase 1b/2 study in people with:
  - Abeta pathology confirmed by PET\(^3\) scan
- Prodromal AD (CDR\(^1\)-Global Score 0.5; age 50-75 years)
- Non-demented people living with DS (age 35–50 years)

Study design

- IA\(^3\) of safety/tolerability and immunogenicity
- Biomarker analyses including Abeta PET and others
- Up to 4 different doses and/or dose regimens
- Expansion of one cohort to assess effect on Abeta PET
- Initiation using selected dose identified in AD (based on safety/tolerability and immunogenicity)

Outcome measures

- Safety/tolerability
- Pharmacodynamics: Serum anti-Abeta antibody titers
- Exploratory biomarkers and clinical endpoints

Trial Schematic

- Treatment in AD (up to 4 dose/regimen cohorts) (12 months)
- Dose selection (safety / immunogenicity)
- Expansion in AD (12 months)
- Treatment in DS (18 months)
- Follow up (6 months)
- Follow up / expansion phase in AD

Interim analyses

- Safety/tolerability
- Immunogenicity – antibody titers
- Biomarkers – Abeta-PET, pharmacodynamics, target engagement

ACTC-DS
Alzheimer’s Clinical Trials Consortium
Down Syndrome

Slide Courtesy of Mike Rafii, M.D., Ph.D.
Future Directions

• Alzheimer’s Clinical Trial Consortium (ACTC) launched in 2017

  • Initiated ACTC – Down Syndrome (DS) in 2019 (PI – Rafii)
  • TRC-DS, a trial-ready cohort for AD treatment trials across 15 ACTC-DS sites using R61 / R33 funding

• TRC-DS Goals
  • Establish a network of infrastructure to conduct AD clinical trials in adults with DS
  • Develop a well-characterized, trial-ready cohort to facilitate enrollment into AD trials for adults with DS
  • Conduct a randomized trial of an anti-amyloid therapeutic utilizing TRC-DS as a run-in cohort.
Thank you!

All the participants & families