Aducanumab: Is There a New Treatment for Alzheimer’s Disease?

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Potential COIs:
NIH grant support for Alzheimer’s disease research; honoraria from the Institute for Clinical and Economic Review as an expert reviewer.

3 November 2021, 14:00 – 14:20

Current therapies

- 3 cholinesterase inhibitors
  - Donepezil (Aricept, 1996)
  - Galantamine (Razadyne, 2000)
  - Rivastigmine (Exelon, 2001)
- 1 partial N-methyl-D-aspartate (NMDA) receptor antagonist
  - Memantine (Namenda, 2003)
Alzheimer’s disease

- Characterized by microscopic changes of neuritic plaques and neurofibrillary tangles.

- Neuritic plaques
- Neurofibrillary tangles
- Beta amyloid (Aβ)
- Tau protein (hyperphosphorylated tau)

One way to prevent or treat Alzheimer’s disease might be to target amyloid or tau in the brain.

Amyloid changes come first

Amyloid precursor protein

BACE1

APP

Aβ42 monomers

Toxic Aβ oligomer

Amyloid plaque

Amyloid changes in the spinal fluid or brain may appear two decades before dementia symptoms first appear.

Tau changes come second

Becker RE et al., Nat Rev Drug Discov 2014;13(9):603

Becker RE et al., Nat Rev Drug Discov 2014;13(9):603

Nature Reviews Drug Discovery
Donepezil approved, 1996

First Alzheimer's drug approved (tacrine), 1993

Last Alzheimer's drug approved (memantine), 2003


Forest plot of anti-amyloidβ drugs on the Alzheimer's Disease Assessment Scale-cognitive subscale (RCTs)

A four point difference may be clinically meaningful.
**Small, phase-1b trial of aducanumab**

- **PRIME study**: Small trial with several different doses of aducanumab.
- Patients with prodromal or mild AD. About one year of monthly intravenous infusions of aducanumab or placebo.
- 197 were randomized; 152 completed treatment; 121 with baseline and one-year scans.
- High dropout rate.
- Analyses not based on intention-to-treat.

**It worked! Aducanumab removed β-amyloid plaques from the brain.**

**Amyloid-PET scans**

**Aducanumab Phase 3 Trial Design**

**ENGAGE (301)**: 46% from the U.S.

**EMERGE (302)**: 40% from the U.S.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Two 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies</th>
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<tbody>
<tr>
<td>Geography/Sample size</td>
<td>3285 patients at 348 sites in 20 countries</td>
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</tbody>
</table>
| Population | Early Alzheimer’s disease (MCI due to Alzheimer’s disease + mild Alzheimer’s disease dementia)  
\- MMSE 24-30, CDR-G 0.5, RBANS  
\- ≤ 85, with confirmed amyloid pathology |
| Doses | Two dosing regimens (low and high) and placebo; randomized 1:1:1 |
| Primary endpoint | CDR-SB at 18 months  
\- CDR-SB = Clinical Dementia Rating, sum of boxes |
| Other endpoints | Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI  
\- Sub-studies: amyloid PET, tau PET, CSF disease-related biomarkers |

Countries with active sites included:
- Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Poland, Portugal, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States
**CDR-SB (clinical dementia rating, sum of boxes)**

<table>
<thead>
<tr>
<th></th>
<th>NONE 0</th>
<th>QUESTIONABLE 0.5</th>
<th>MILD 1</th>
<th>MODERATE 2</th>
<th>SEVERE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
<td>No memory loss or slight inconsistent forgetfulness</td>
<td>Consistent slight forgetfulness; partial recollection of events; “benign” forgetfulness</td>
<td>Moderate memory loss; more marked for recent events; deficit interferes with everyday activities</td>
<td>Severe memory loss; only highly learned material retained; new material rapidly lost</td>
<td>Severe memory loss; only fragments remain</td>
</tr>
<tr>
<td><strong>Orientation</strong></td>
<td>Fully oriented</td>
<td>Fully oriented except for slight difficulty with time relationships</td>
<td>Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere</td>
<td>Severe difficulty with time relationships; usually disoriented to time, often to place</td>
<td>Oriented to person only</td>
</tr>
<tr>
<td><strong>Judgment &amp; Problem Solving</strong></td>
<td>Solves everyday problems &amp; handles business &amp; financial affairs well; judgment good in relation to past performance</td>
<td>Slight impairment in solving problems, similarities, and differences</td>
<td>Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained</td>
<td>Severely impaired in handling problems, similarities, and differences; social judgment usually impaired</td>
<td>Unable to make judgments or solve problems</td>
</tr>
<tr>
<td><strong>Community Affairs</strong></td>
<td>Independent function at usual level in job, shopping, volunteer and social groups</td>
<td>Slight impairment in these activities</td>
<td>Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection</td>
<td>No pretense of independent function outside home</td>
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</tr>
<tr>
<td><strong>Home and Hobbies</strong></td>
<td>Life at home, hobbies, and intellectual interests well maintained</td>
<td>Life at home, hobbies, and intellectual interests slightly impaired</td>
<td>Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned</td>
<td>Only simple chores preserved; very restricted interests, poorly maintained</td>
<td>No significant function in home</td>
</tr>
<tr>
<td><strong>Personal Care</strong></td>
<td>Fully capable of self-care</td>
<td>Needs prompting</td>
<td>Requires assistance in dressing, bathing, keeping of personal effects</td>
<td>Requires much help with personal care; frequent incontinence</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Dementia Rating (CDR): based on cognition and function**
Hughes et al, Brit J Psychiatry, 1982; Morris, Neurology, 1993

**CDR sum of boxes ranges from 0 (best) to 18 (worst).**
Minimal clinically important difference estimated at 1-2 points.

Results from ENGAGE and EMERGE

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<th>ENGAGE</th>
<th>EMERGE</th>
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<tr>
<td><strong>Baseline CDR-SB, Mean</strong></td>
<td>Placebo (n=545)</td>
<td>ADU Low Dose (n=547)</td>
</tr>
<tr>
<td><strong>Adjusted Mean Change From Baseline at Week 78 (95% CI)</strong></td>
<td>1.56 (1.23, 1.77)</td>
<td>1.38 (1.16, 1.59)</td>
</tr>
<tr>
<td><strong>Difference vs. Placebo (95% CI)</strong></td>
<td>--</td>
<td>-0.18 (-0.47, 0.11)</td>
</tr>
<tr>
<td><strong>% Difference vs. Placebo</strong></td>
<td>--</td>
<td>-12%</td>
</tr>
<tr>
<td><strong>p-value vs. Placebo</strong></td>
<td>--</td>
<td>0.2250</td>
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ADU: aducanumab, CDR-SB: Clinical Dementia Rating-Sum of Boxes, CI: confidence interval, ITT: intention-to-treat *p<0.05.

FDA Statistical review

“In summary, the totality of the data does not seem to support the efficacy of the high dose [aducanumab].

....

For these reasons, substantial evidence has not been met in this application.”

ARIA (amyloid related imaging abnormality) edema and hemorrhage

41% of people receiving high-dose aducanumab

10% of people receiving placebo
"In 2012, Congress passed the Food and Drug Administration Safety Innovations Act (FDASIA). Section 901 of FDASIA amends the Federal Food, Drug, and Cosmetic Act (FD&C Act) to allow the FDA to base accelerated approval for drugs for serious conditions that fill an unmet medical need on whether the drug has an effect on a surrogate or an intermediate clinical endpoint.

A surrogate endpoint used for accelerated approval is a marker—a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. Likewise, an intermediate clinical endpoint is a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug."

"Accelerated approval" based on amyloid

Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need. Fast Track

Amyloid-PET scan

Time line

First Alzheimer’s drug approved (tacrine), 1993
Last Alzheimer’s drug approved (memantine), 2003
ENGAGE enrollment begins, Aug. 2015
Both trials stopped for futility, Mar. 21, 2019
Biogen presentation to the FDA, Oct. 22, 2020
Aducanumab approved, June 7, 2021
Phase-4 confirmatory trial required by Aug. 2029

IND filed, 2011
IND filed, 1996
Data cutoff, Dec. 26, 2018
Data cutoff, July 20, 2020
Advisory Committee meeting, Nov. 6, 2020

PRIME 1b results published, 2016
"Approved under the accelerated approval pathway"

10 votes no
0 votes yes
1 abstention

DONEpezil approved, 1996

Aducanumab approved, June 7, 2021

PRIME 1b results published, 2016

IND filed, 1996
✓ Older FDA approved medications for Alzheimer’s disease (like donepezil or memantine) improve cognitive skills compared to no treatment, but only to a modest degree.

✓ Aducanumab removes amyloid from the brain, but results from two very large Phase-3 trials did not show meaningful improvement in cognition or function after 18 months of drug infusion.

✓ Aducanumab has side effects (ARIA) that are common and sometimes serious.

✓ Aducanumab was approved by the FDA on the basis of its effects on brain amyloid, not because it is safe and effective ("accelerated approval").

✓ Some neurologists (and some hospital networks) will not prescribe aducanumab. Others will consider prescriptions for some patients.

✓ We need treatments that make patients visibly better and prevent the disease from developing in the first place, and that requires research.
Clinical Core – ADRC & Udall Center –
neuropsychologist, Memory Support Program manager, nurse coordinator, clinical research manager, and research associate coordinators

Dr. Maya Yutsis
Jennie Clark
Isabelle Yi
Veronica Ramirez
Nicole Caceres
Maria-Lucia Campos
Nicole Corso
James Kelbert
T’Lesa Meadowcroft

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Thank You
To our patients, research volunteers, family members, caregivers