What to tell patients and caregivers about the new AD therapies

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OU Medicine

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Relevant Disclosure and Resolution

Under Accreditation Council for Continuing Medical Education guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 24 months.

Linda A. Hershey, MD, PhD

I received a stipend from the AAN for being an Associate Editor for the journal, *Neurology*.

I received an honorarium from the ACP for editing a Neurology slide deck for the ACP board review course for internal medicine residents.

I received honoraria from *MedLink Neurology* (for writing several annual e-updates about memory loss, pre-MCI, sleep & dementia, vascular cognitive impairment, etc).

Learning Objectives

Upon completion of this session, participants will improve their competence and performance by being able to:

1. Review the biological causes of Alzheimer's disease.

2. Learn how to screen early dementia patients for lecanemab and other new monoclonal antibody therapies.

3. Discuss how to reduce the risk of amyloid-related imaging abnormalities (ARIA) with these new AD treatments.

Experimental or Off-Label Drug/Therapy/Device Disclosure

I will be discussing a few experimental or off-label drugs, and a few therapies that have not yet been approved by the FDA. I will be sure to clarify when these drugs are being mentioned.

What causes Alzheimer's ?

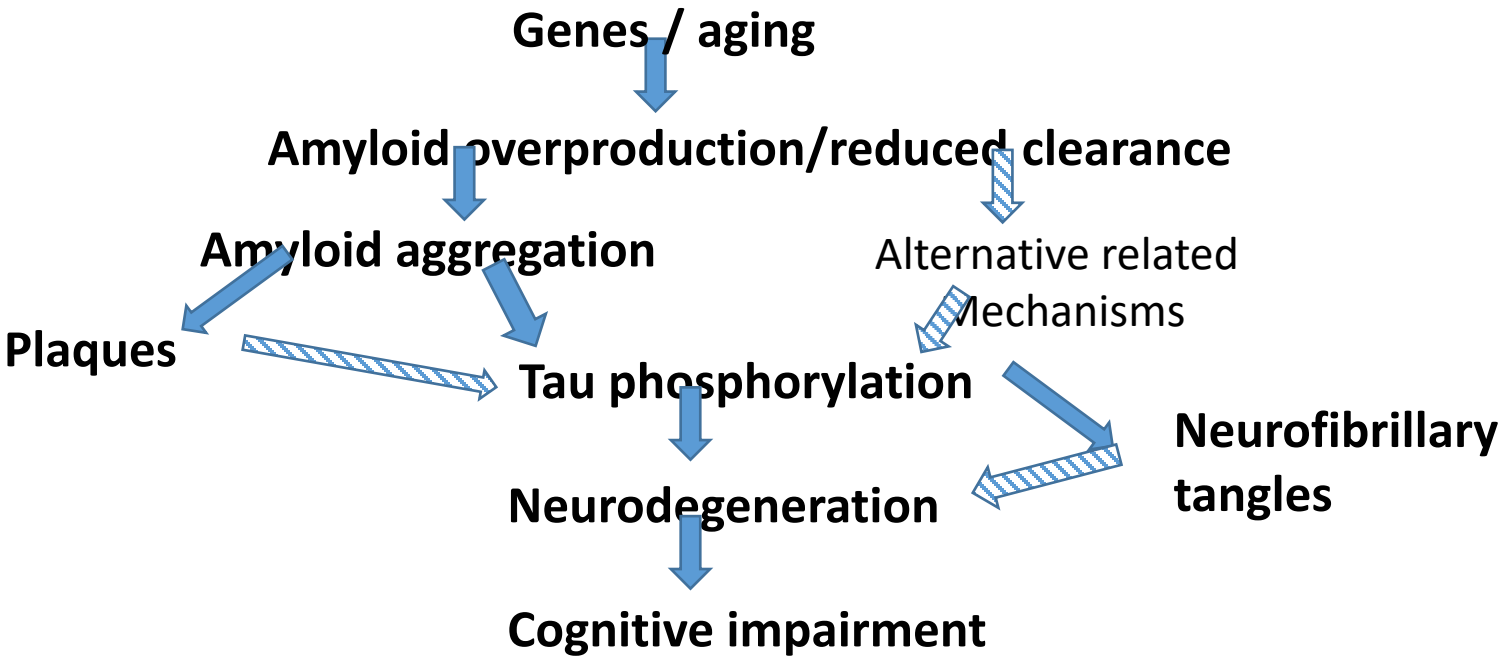
- **Dysregulation of amyloid metabolism** is thought to begin 10-20 years before patients develop symptoms of Alzheimer's disease (AD).

- A **"cascade"** of events begins with the appearance of extracellular **amyloid (A)** plaques, then intracellular neurofibrillary **tau (T)** tangles accumulate, followed by **neurodegeneration (N)**. Mild cognitive impairment (MCI), and eventual functional decline (dementia) follow months-years afterward.

- Several large-scale clinical trials have been conducted in the last few years to evaluate the safety and benefit of investigational drugs that modulate the production and clearance of brain amyloid. The ultimate goal of these trials is to **slow the process of neurodegeneration**.

Hardy & Higgins, "AD: The amyloid cascade hypothesis." Science, 1992.
Jack et al, "NIA-AA Research Framework." Alzheimers & Dementia, 2018.
Aschenbrenner et al, "Influence of tau-PET, amyloid…" Neurology, 2018.
Knopman & Hershey, "Implications of the approval…" Neurology, 2023.

The amyloid cascade hypothesis



Knopman & Hershey, "Implications of ….lecanemab…", Neurology, 2023

How is MCI different from dementia?

- **MCI** = Pts with mild cognitive impairment (MCI) have minimal problems with instrumental daily activities (IADLs), but they complain of memory loss, language problems, and/or other cognitive problems (executive, visuospatial, etc).

- **Dementia** = Pts with Alzheimer's disease with dementia (AD-dementia) have 2 or more signs of cognitive impairment in addition to functional problems with instrumental activities (shopping, doing laundry, preparing meals, doing chores, driving, etc).

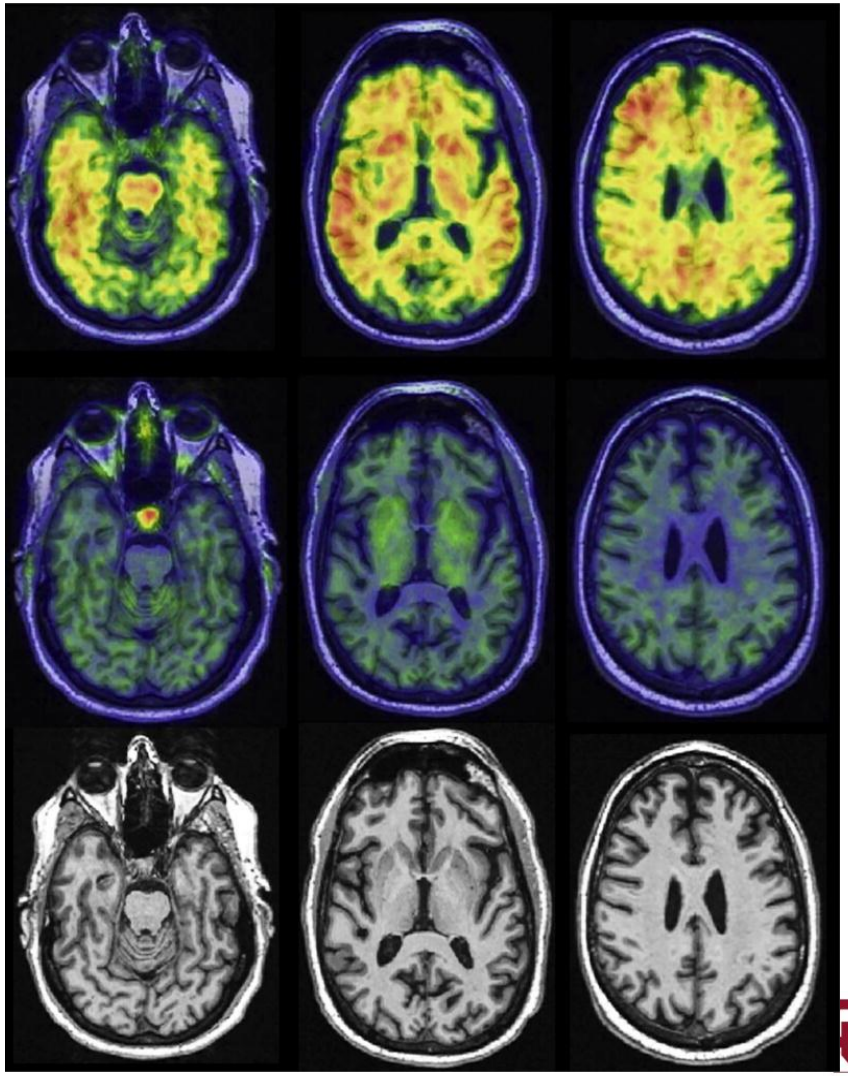
How is AD diff from “dementia”?

- Alzheimer’s disease is thought to be caused by the abnormal accumulation of certain proteins in and around brain cells.
- **Amyloid (A)**…starts to accumulate around neurons 10-20 years before patients develop symptoms.
- **Tau (T)**…begins to accumulate within brain cells around the same time that symptoms develop (in the MCI stage).
- Both of these proteins are thought to have toxic effects on brain cells, resulting in **Neurodegeneration (N)** (dementia stage).

- “Dementia” can develop in a large group of diseases that can cause cognitive and functional problems in older adults. The most common dementias are AD, vascular cognitive impairment, dementia with Lewy bodies, Parkinson disease dementia and the fronto-temporal dementias.

MCI pt with A+T-N-changes

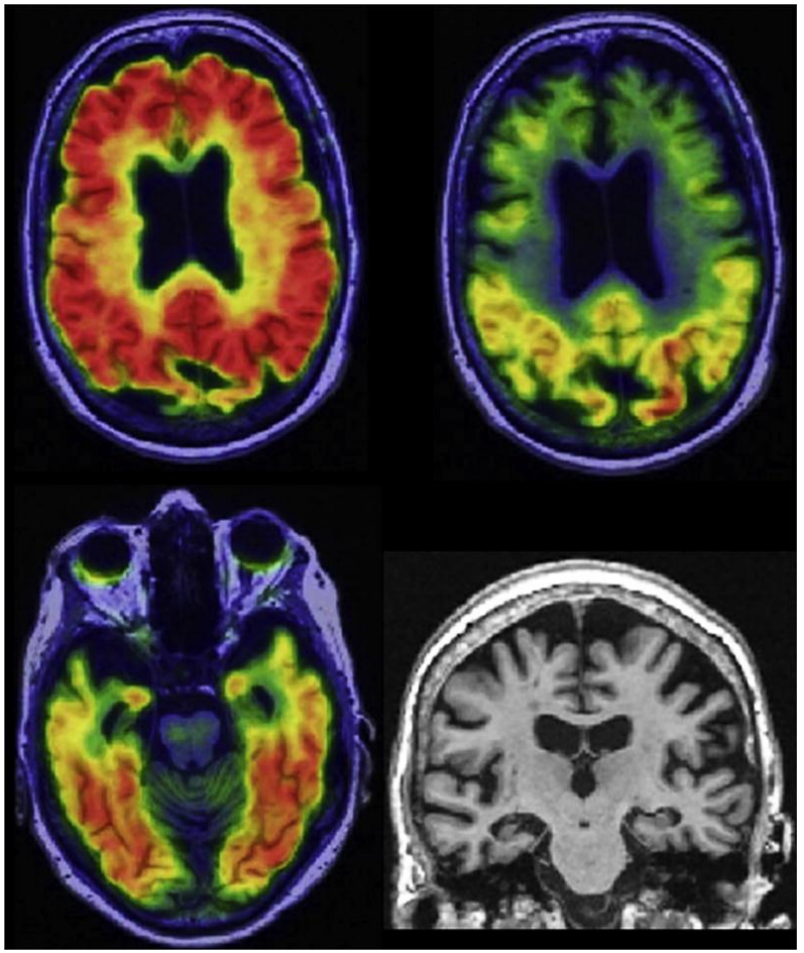
- A-PET scan = positive for amyloid
- T-PET scan = negative for tau
- MRI scan = negative for neurodegeneration



Jack et al, Alz & Dem, 2018

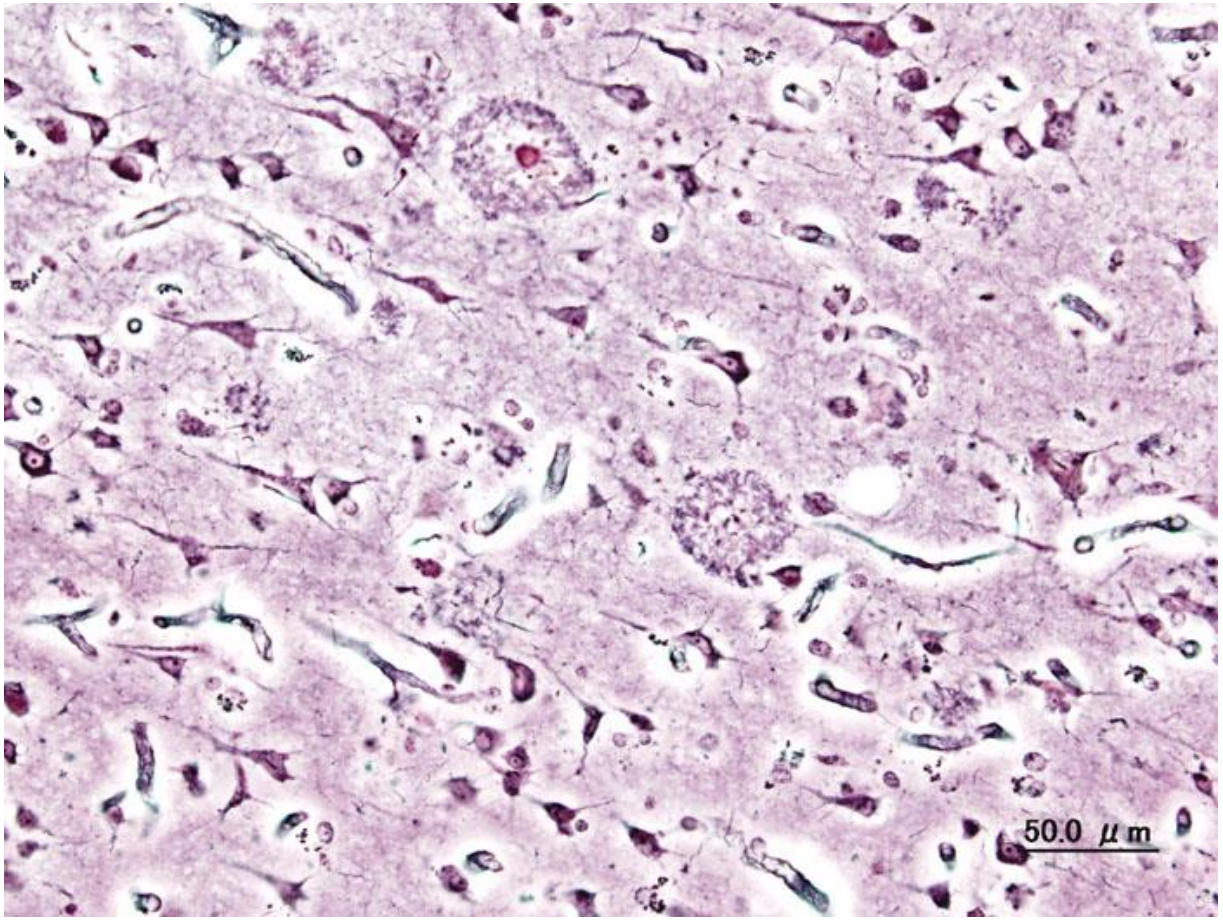
AD pt with A+ T+ N+ changes

- Amyloid-PET = positive
- Tau – PET = positive
- MRI = positive for neurodegeneration



Jack et al, "NIA-AA Research Framework," Alz & Dem, 2018

AD= amyloid plaques + neurofibrillary tau tangles

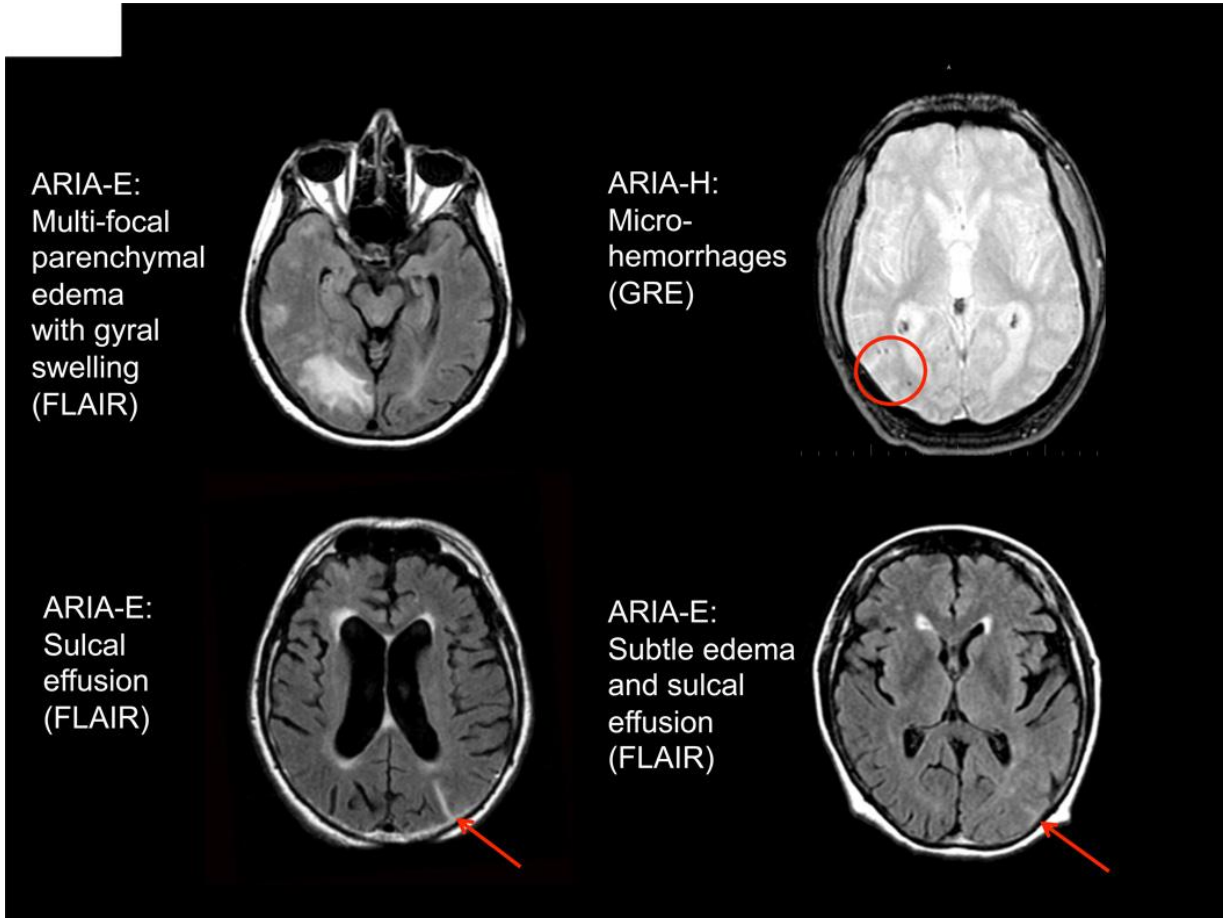


Aducanemab for early AD

- Aducanumab = a monoclonal antibody that targets brain amyloid. It was given to those with aMCI or mild AD (candidates in the first RCT trials were amyloid + by amyloid PET scans; MMSE=24-30).
- Contraindications = absence of a caregiver, **ARIA-H (CMB>4),** bleeding disorder, unstable med cond, anticoagulant use, substance/alcohol abuse.
- It was given in monthly 1 hr IV infusions starting at 1mg/kg and ending at 10mg/kg over 24 wks.
- MRI scans were at wks 7, 15, 23 during titration.

Coerver, Yu, D'Abreu, et al, Neurol Clin Practice, April 2022

ARIA= Amyloid Related Imaging Abnormality
E = edema; H= hemorrhage



Sperling et al, Lancet Neurology, 2012

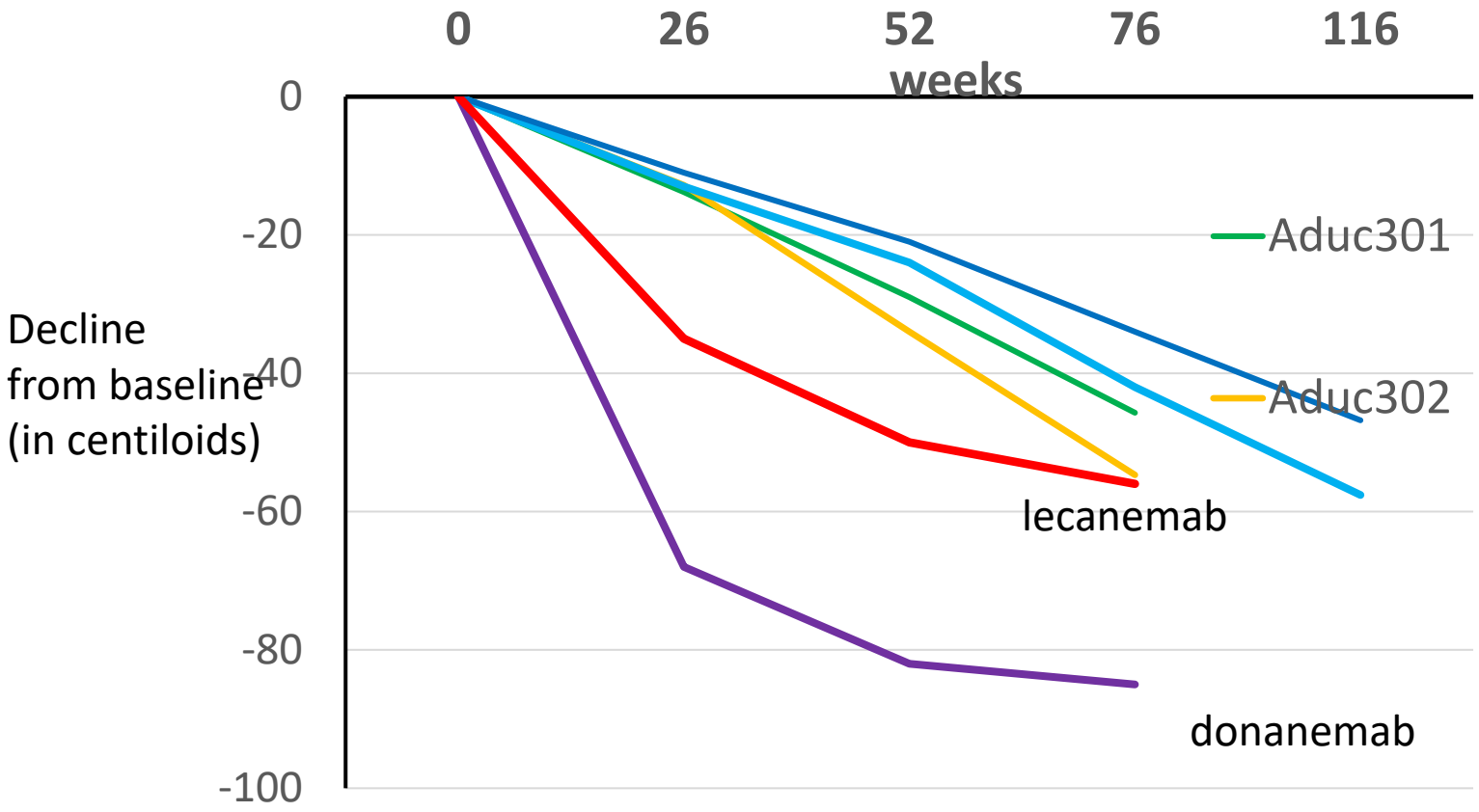
News as of Feb 1, 2024

- Aducanumab will no longer be sold or distributed by the manufacturer, and their post-marketing study will be ended.

- The manufacturer will continue to market their other mono-clonal amyloid antibody, lecanemab.

J Calfas & C Kallaher, Wall Street Journal, Feb 1, 2024

Comparison of monoclonal antibodies in their ability to remove brain amyloid



Knopman & Hershey, Neurology, 2023

The lecanemab phase 3 trial

- **Who was eligible?**
- Early AD (aMCI or mild dementia with Amyloid+ PET or Amyloid + CSF)
- 1795 pts were enrolled (898 = L; 897 = P).

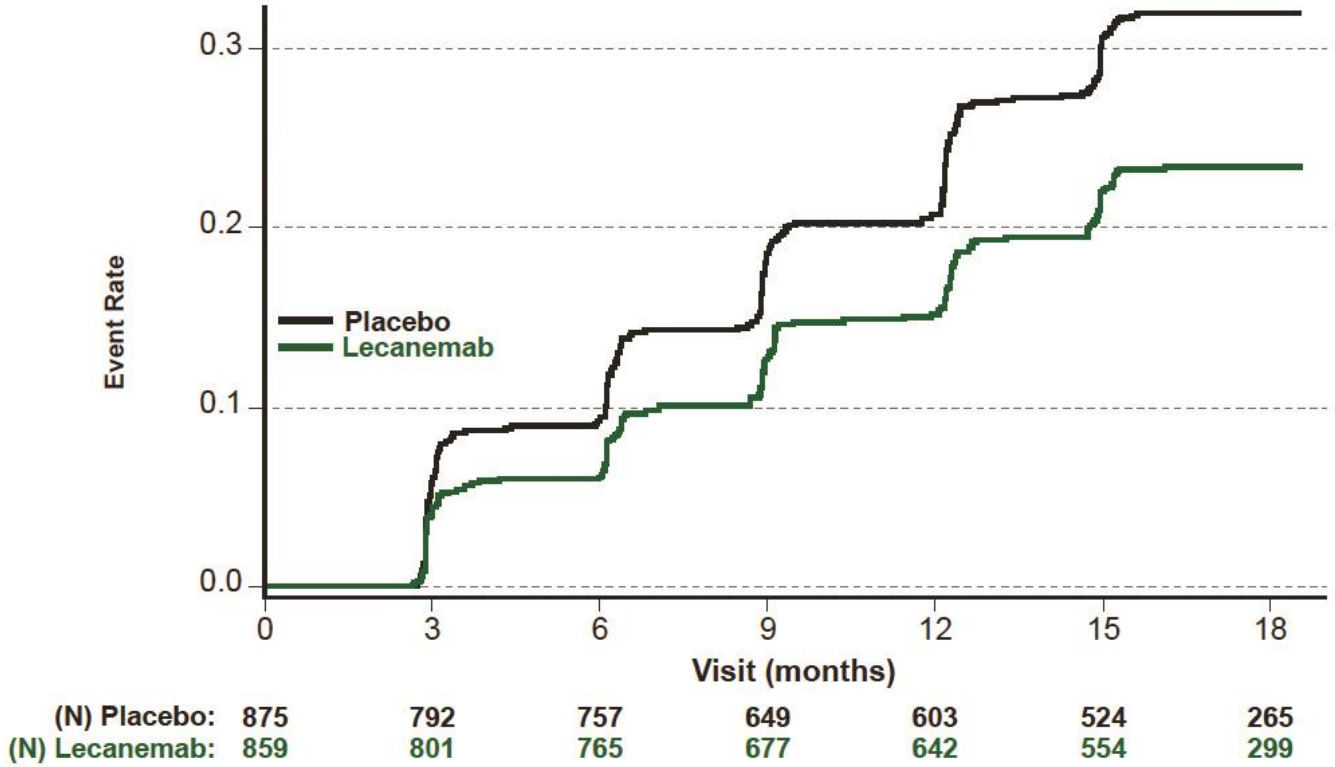
- **What was the primary endpoint?**
- Change in CDR-sb scores at 18 mo, compared to placebo.

  27% reduction in rate of progression of CDR-sb scores at 18 months, compared to placebo.

- What were the main side effects?
- ARIA-H = 17% and ARIA-E = 13% w lecanemab (2.8% symptomatic)
- " " = 9% and " " = 2% w placebo

CH Van Dyck, et al, Lecanemab in early Alzheimer's disease, NEJM, 2022

Does lecanemab slow symptom progression?



vanDyck et al, "Lecanemab in early AD", NEJM, 2022 (w permission)

What are the risks of ARIA?

	Lecanemab	Placebo
• ARIA-E	113 (12.6%)	15 (1.7%)
• **APOE-e4 homozyg**	**13/141 (9.2%)**	0/133 (0%)
• APOE-e4 heterozyg	8/479 (1.7%)	0/478 (0%)

• ARIA-H	155 (17.3%)	81 (9.0%)
• ARIA-microhem	126 (14.0%)	68 (7.6%)

vanDyck et al, "Lecanemab in early AD," NEJM, 2022

What should be the guidelines for stopping lecanemab?

- Severe radiographic signs of ARIA
- Severe symptoms of ARIA (HA, seizures, N/V, etc)
- Any macro-hemorrhage
- >10 micro-hemorrhages since starting treatment
- Any condition requiring anticoagulant therapy

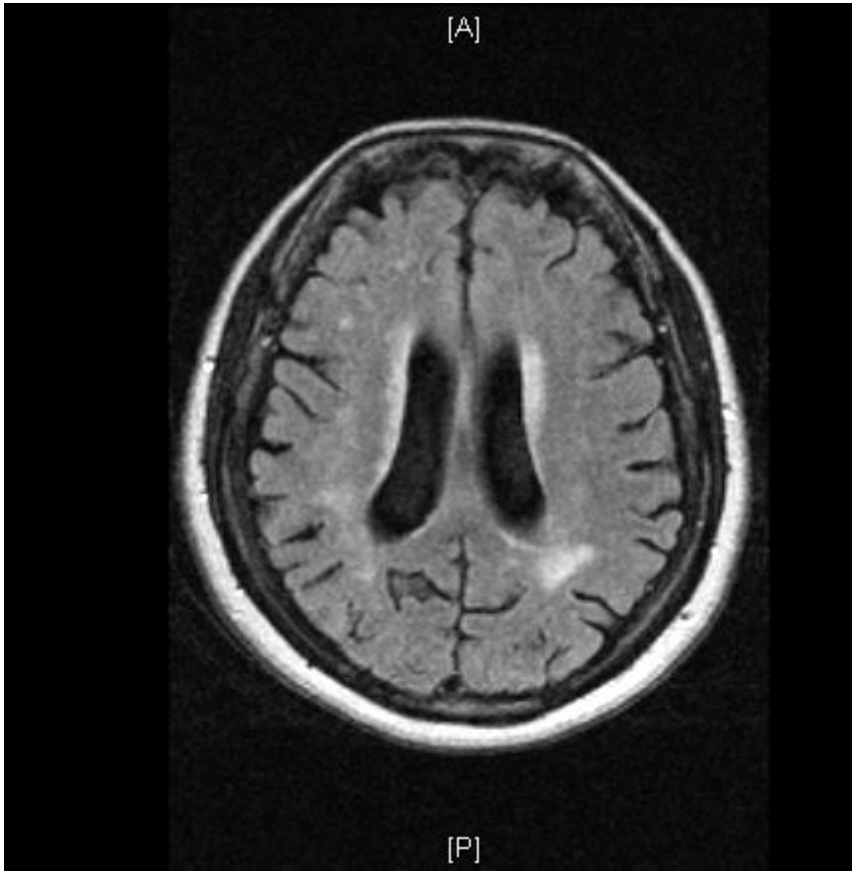
J Cummings et al, "Lecanemab: Appropriate Use", J Prev Alz Dis, 2023

Visit #1: Do I qualify?

- MMSE …. > or = 22/30 (MCI or mild dementia)
- NO anticoagulants.
- MRI must show no signs of macro-hemorrhage, diffuse WMHs, CBS, NPH, bvFTD, tumor.
- **CMB…must be < 4.**
- Platelets must be > or = 50,000.
- No TIA or stroke within the last 12 months.
- **No APOE-e4/e4** (higher risk for developing ARIA).
- No unstable medical conditions (DM, CHF, CRF, etc).

J Cummings et al, "Lecanemab: Appropriate use recommendations." J of Prev of Alz Dis, 30: 14283, 2023.

Does this patient qualify?



This 65 yo woman has chronic HTN & high cholesterol.

She had a TIA a few weeks ago.

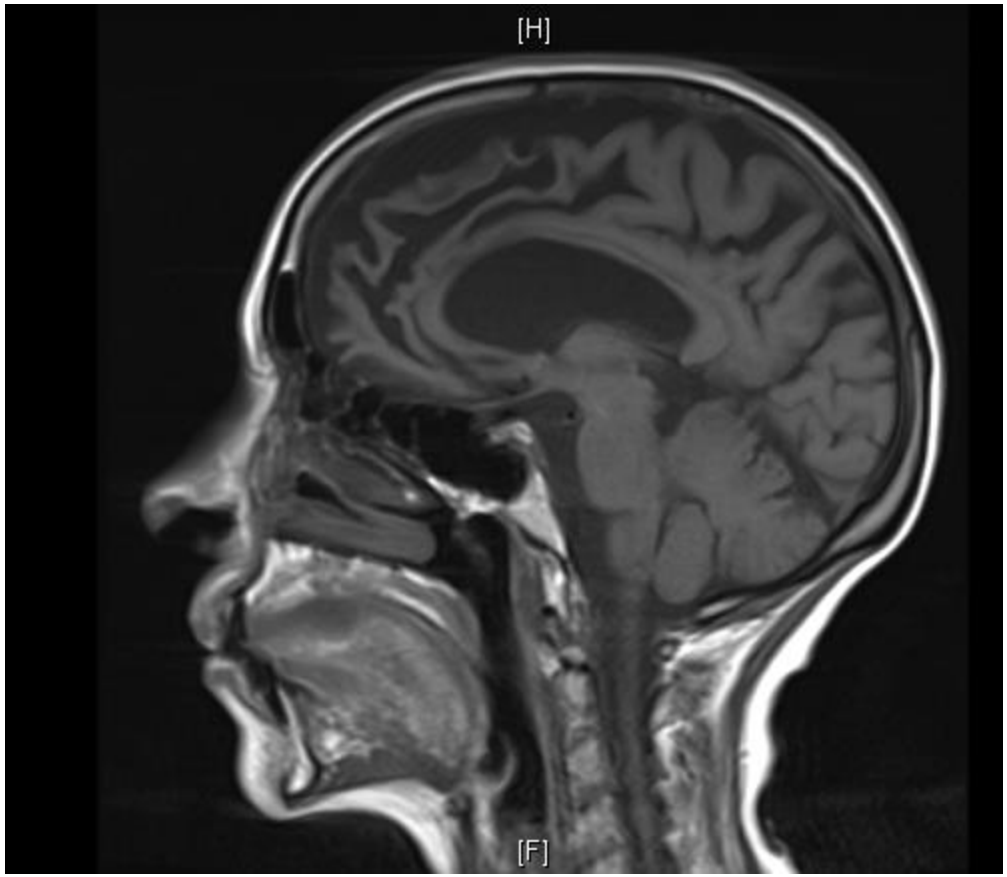
HPI: Her memory has been declining, and she has had problems with her balance and gait. She needs help with everyday chores.

Exam: 18/30 on the MMSE. Mild BL hyperreflexia, postural instability & gait apraxia.

Dx: Vascular cognitive Impairment .

No…she doesn't qualify.

Does this patient qualify?



63 yo woman w 3 yr Hx of poor judgement & apathy.

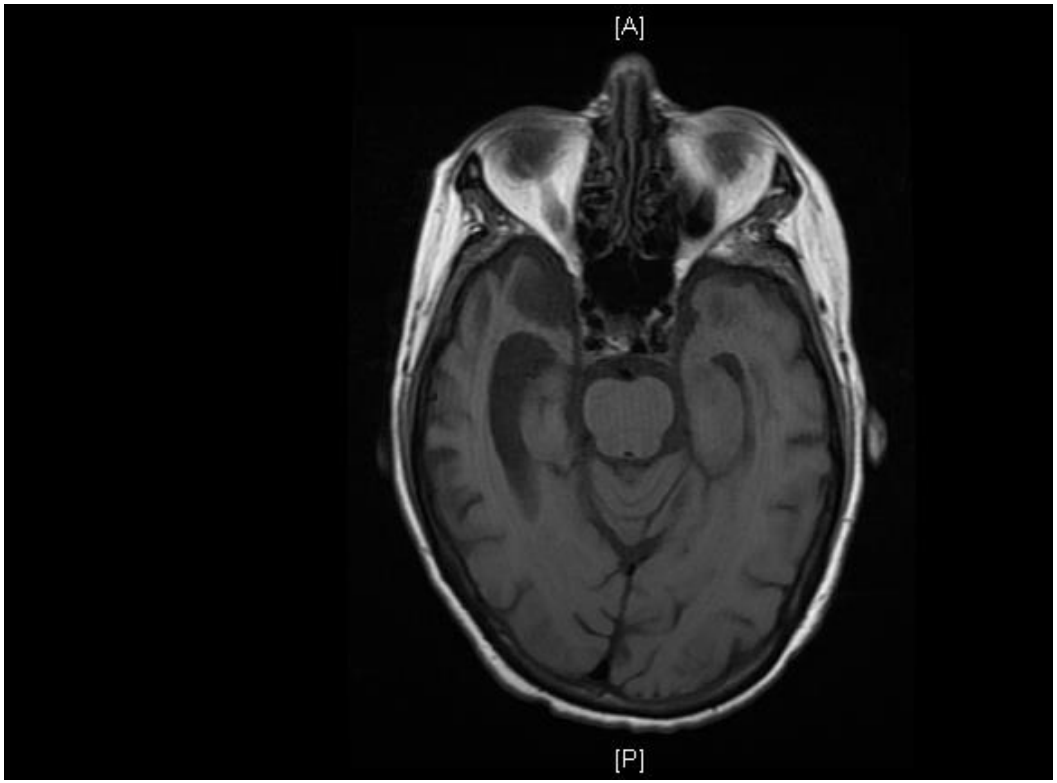
CC: Apathy…she does not get dressed until her husband comes home for dinner.

Exam: MMSE = 6/30

Dx: behavioral variant-Fronto-temporal dementia

No…she doesn't qualify.

Does this patient qualify?



This 68 yo woman has a 3 yr Hx of memory loss, language prob, and behavioral changes.

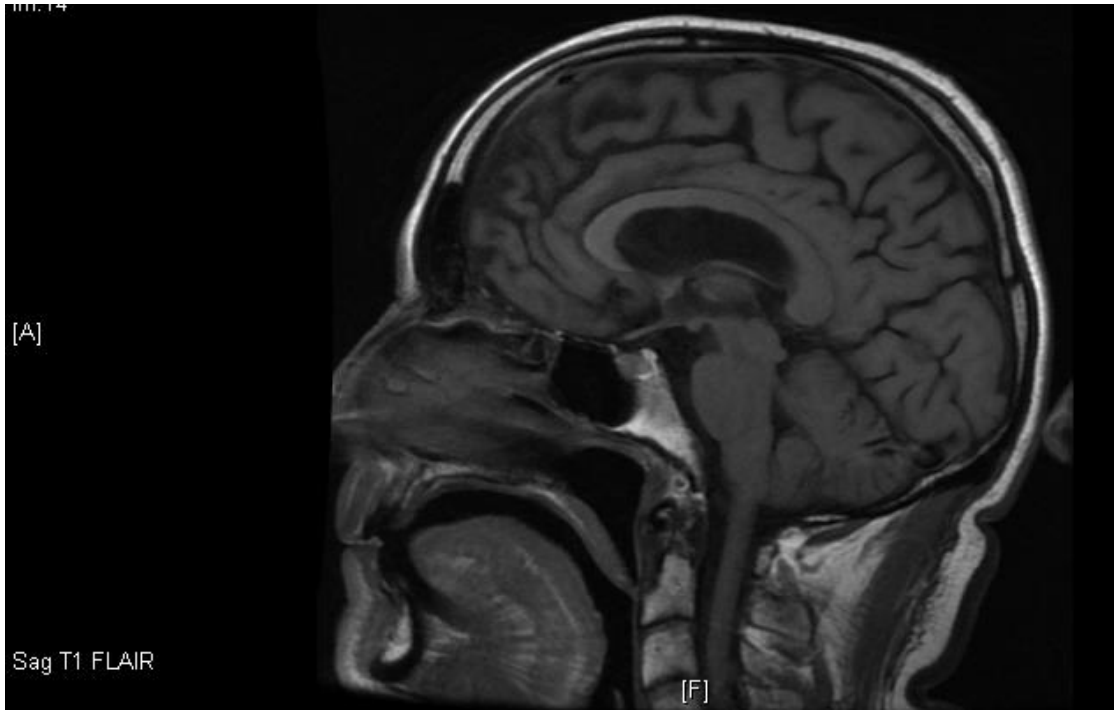
CC: She has lost 15 # in the last 6 months (she is not eating right or attending to self-care).

Exam: She is oriented x 2, but cannot follow a 2-step command. She cannot name simple objects or repeat: “no ifs ands or buts”.

Dx: Primary progressive aphasia

No …she does not qualify.

Does this patient qualify?



75 yo man w 6 mo of memory loss and functional decline

CC: 3 mo of visual hallucinations, slowness and shuffling gait

Exam:
MMSE = 22/30
Speech = slow, hypophonic
Face = loss of expression
Motor = slow, mild BL rigidity
Gait = slow, shuffling

Dx: Dementia w Lewy bodies

No…he doesn't qualify.

Eligibility for anti-amyloid treatment in a population-based study of cognitive aging

- **Objective** = Lecanemab is now approved for treatment of MCI and mild AD. Using the criteria for the lecanemab study, how many in the Mayo Clinic Study of Aging would qualify?

- **Results** = 237 participants (x age 80.9 yrs; 54.9% men). All had MCI or mild dementia and were Amyloid+ by Amyloid-PET.
- The lecanemab inclusion and exclusion criteria reduced the sample to 19 (8% of 237).
- Using the aducanemab inclusion/exclusion criteria, the sample was reduced even further to 12 (5% of 237).

Conclusion = Patients with MCI and mild AD dementia need to be carefully screened before being considered for treatment with anti-amyloid Rx.

RR, Pittock et al, "Eligibility for anti-amyloid treatment", Neurology, 2023.

What about data registries?

- You have screened your patients and have found 8% who meet the lecanemab entry criteria….
- CMS requires that a record be kept of your patient's longitudinal data using 1 of 3 registries:

- 1) CMS's Anti-Abeta mAb CED study…unfunded
- 2) The Emory University Registry…unfunded
- 3) The Alz Assoc's ALZ-NET Registry…funded

G Shaw, "Alzheimer monoclonal antibody registries….", Neurology Today, 2024

What data are in the registries?

- Cognitive outcomes? …..MoCA for CMS registry (MMSE is also permitted).

- Functional outcomes? ….FAQ for CMS registry (Lawton is also permitted).

The data need to be useable and of good quality. It cannot require too much staff time. It is a minimal data set (and sharable), much like what is collected in cancer research/practice.

G Shaw, “Alzheimer monoclonal antibody registries…..”, Neurol Today, 2024

Symptomatic therapies for AD

- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)

- Memantine (Namenda)

- Medical control of HTN, DM, LDL

Symptomatic Therapy for MCI?

- According to an AAN workgroup on MCI (2019), no RCTs have demonstrated clinical benefit for the cholinesterase inhibitors or memantine in patients with MCI.

- There is, of course, good evidence for the long-term benefit of medical management of HTN, DM and LDL in MCI pts.

- N Foster et al, Quality improvement in neurology: mild cognitive impairment measurement set, Neurology, 2019

Non-pharmacological therapies

- Smoking cessation
- Avoiding falls, head injury
- Mediterranean diet
- Regular physical activity
- Regular cognitive activity
- Regular social activity
- Regular sleep habits

Conclusions

- The “amyloid cascade” is the best current explanation for the pathophysiology of Alzheimer’s disease.
- Amyloid accumulation in the brain triggers tau deposits, which in turn brings on the process of neurodegeneration.
- MCI symptoms develop around the same time as tau accumulation. Functional decline (dementia) accompanies signs of neurodegeneration.
- The anti-amyloid drugs that are most effective in treating symptoms of AD (lecanemab and donanemab) are the ones that are most effective at removing amyloid from the brain.
- Careful patient screening (especially including APOE testing) and routine f/u with MRI is imperative for the safe administration of anti-amyloid drugs for MCI and mild AD pts.

Questions?