Alzheimer's Disease Center at the Sanders-Brown Center on Aging

Alzheimer's Tennessee

Advances in Alzheimer's & Dementia Research: Understanding Anti-Amyloid Therapies

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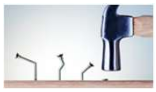
University of Kentucky ADRC




1

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Disclosures

(Only those related to Aβ treatments listed here)

- **Grants**
  - NIH P30 AG072946, U24 AG057437, R01 AG053798, R01 AG063689, U19 AG010483, R01 AG054029, R01 AG061848
- **Contract Research**
  - Cassava, Cyclerion, Eisai, Lilly, Suven, Vivoryon
- **Educational Programming**
  - Medscape, CEConcepts/ AAFP, Mid-America Institute on Aging and Wellness
- **Leadership Roles**
  - Alzheimer's Association ALZ-NET, ACTC, ADCS, AAN Education, ADRC Clinical Steering Committee & Task Force
- **Consulting/Speaker's Bureau**
  - None
- **Stock, Royalties, or Intellectual Property**
  - None

2

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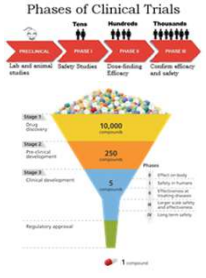
Learning Objectives

1. **Discuss discoveries related to anti-amyloid therapy for AD**
2. **Analyze clinical trial results in order to understand potential disease modifying properties that may make a medication suitable for FDA approval**
3. **Demonstrate an understanding of the potential benefits and risks of approved anti-amyloid therapy for AD**



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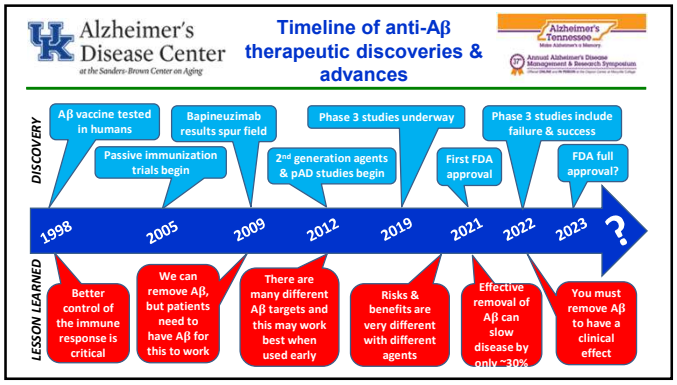
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Timeline of anti-Aβ therapeutic discoveries & advances
Alzheimer's Tennessee
DISCOVERY
Aβ vaccine tested in humans
Bapineuzimab results spur field
Phase 3 studies underway
Phase 3 studies include failure & success
Passive immunization trials begin
2nd generation agents & pAD studies begin
First FDA approval
FDA full approval?
1998
2005
2009
2012
2019
2021
2022
2023
?
LESSON LEARNED
Better control of the immune response is critical
We can remove Aβ, but patients need to have Aβ for this to work
There are many different Aβ targets and this may work best when used early
Risks & benefits are very different with different agents
Effective removal of Aβ can slow disease by only ~30%
You must remove Aβ to have a clinical effect

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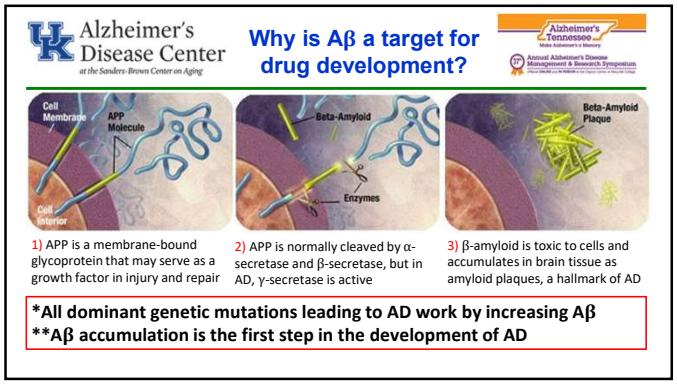
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Why is Aβ a target for drug development?
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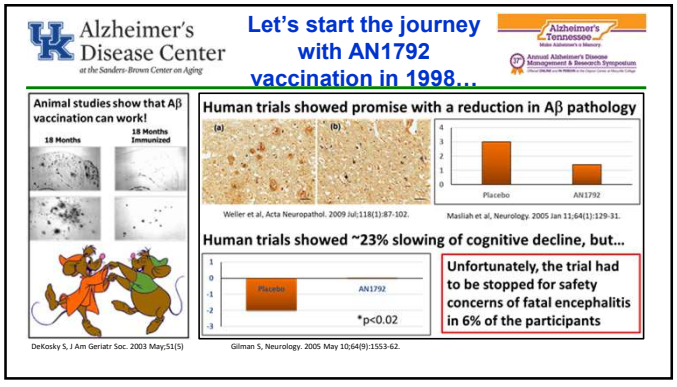
Cell Membrane
APP Molecule
Cell Interior
Beta-Amyloid
Enzymes
Beta-Amyloid Plaque
1) APP is a membrane-bound glycoprotein that may serve as a growth factor in injury and repair
2) APP is normally cleaved by α-secretase and β-secretase, but in AD, γ-secretase is active
3) β-amyloid is toxic to cells and accumulates in brain tissue as amyloid plaques, a hallmark of AD
*All dominant genetic mutations leading to AD work by increasing Aβ
**Aβ accumulation is the first step in the development of AD

5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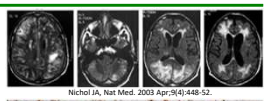
Let's start the journey with AN1792 vaccination in 1998…
Alzheimer's Tennessee
Animal studies show that Aβ vaccination can work!
18 Months
18 Months Immunized
DeKosky S, J Am Geriatr Soc. 2003 May;51(5)
Human trials showed promise with a reduction in Aβ pathology
(a)
(b)
Weller et al, Acta Neuropathol. 2009 Jul;118(1):87-102.
Placebo
AN1792
Masliah et al, Neurology. 2005 Jan 11;64(1):129-31.
Human trials showed ~23% slowing of cognitive decline, but…
Placebo
AN1792
*p<0.02
Unfortunately, the trial had to be stopped for safety concerns of fatal encephalitis in 6% of the participants
Gilman S, Neurology. 2005 May 10;64(9):1553-62.

6

AN1792 Lessons Learned

- **Active vaccination cannot be controlled precisely**
  - Some did not develop antibodies against Aβ
  - 13 patients died of "encephalitis" (~6%) of uncertain cause
- **Aβ in plaques moved into the blood vessels before it was removed from the brain causing worsening CAA**



Nichol JA, Nat Med. 2003 Apr;9(4):448-52.

Weller et al, Acta Neuropathol. 2009 Jul;118(1):87-102.

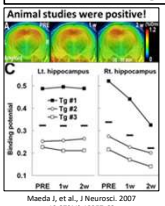
Passive immunization is the path forward as we can precisely control the immune response by adjusting dose and timing

7

Let's continue the journey with Bapineuzumab 2006…

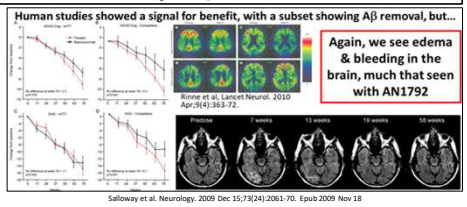
- **Recombinant (manufactured) antibodies administered by infusion using the exact same Aβ target as AN1792**

Animal studies were positive!



Maeda J, et al., J Neurosci. 2007 10;27(41):10957-68

Human studies showed a signal for benefit, with a subset showing Aβ removal, but…



Rinne et al, Lancet Neurol. 2010 Apr;9(4):363-72.

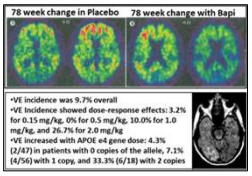
Again, we see edema & bleeding in the brain, much that seen with AN1792

Salloway et al. Neurology. 2009 Dec 15;73(24):2061-70. Epub 2009 Nov 18

8

Bapineuzumab Lessons Learned 2009

- **Passive immunization can remove Aβ from human brains**
  - This was only shown in a subset of patients
- **Removal of Aβ may be associated with slowing of decline in cognition**
- **Edema and bleeding remains a problem**
  - Associated with dose & ApoE e4 status

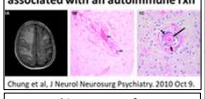


We need to be careful with dosing, take ApoE status into consideration, and make sure we are measuring amyloid reduction in everyone

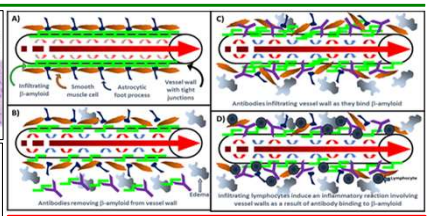
9

ARIA-E & ARIA-H?

Cerebral amyloid angiopathy (CAA) occurs in ~80% AD patients & can be associated with an autoimmune rxn



Chung et al, J Neurol Neurosurg Psychiatry. 2010 Oct 9.



- A working group of experts in 2011 coined the term ARIA
- Amyloid Related Imaging Abnormalities include both:
- Vasogenic edema – ARIA-E
- Microhemorrhage – ARIA-H

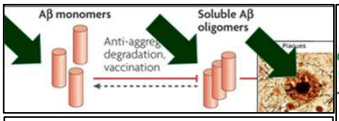
We're still trying to better understand ARIA so we can avoid it and or learn to manage it more effectively!

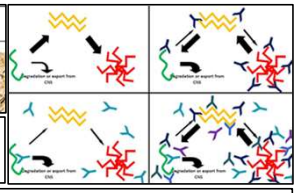
Jicha GA. Is passive immunization for Alzheimer's disease 'alive and well' or 'dead and buried'? Expert Opin Biol Ther. 2009 Apr;9(4):481-91.

10

Targeting different types of Aβ

- Both safety & efficacy concerns prompted a closer look at the Aβ targeted by the antibodies, and new generation of antibodies were developed





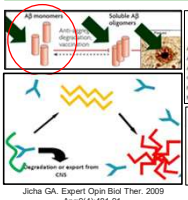
We didn't know or understand if it mattered?
If all antibodies would be the same?
Or if they might be different?

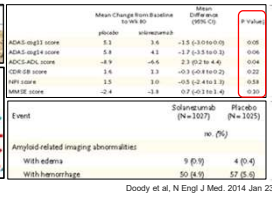
This gave rise to 2nd generation antibodies that target monomers, oligomers, plaques, or all types of Aβ

Jicha GA. Is passive immunization for Alzheimer's disease 'alive and well' or 'dead and buried'? Expert Opin Biol Ther. 2009 Apr;9(4):481-91.

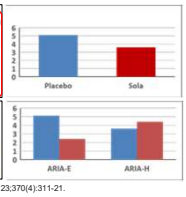
11

Let's continue the journey with Solanezumab 2007…





	Mean Change from Baseline to Wk 80		Mean Difference (95% CI)	P Value
	placebo	solanezumab		
ADAS-cog13 score	5.1	3.6	-1.5 (-3.0 to 0.0)	0.05
ADAS-cog14 score	5.9	4.1	-1.7 (-3.5 to 0.1)	0.06
ADCS-ADL score	-4.9	-6.5	2.3 (0.2 to 4.4)	0.04
CDR-SB score	1.6	1.3	-0.3 (-0.8 to 0.2)	0.22
NPI score	1.5	1.0	-0.5 (-2.4 to 1.3)	0.58
MMSE score	-2.4	-1.8	0.7 (-0.1 to 1.4)	0.10



Event	Solanezumab (N=1027)	Placebo (N=1025)
	no. (%)	
Amyloid-related imaging abnormalities		
With edema	9 (0.9)	4 (0.4)
With hemorrhage	50 (4.9)	57 (5.6)

Jicha GA. Expert Opin Biol Ther. 2009 Apr;9(4):481-91.

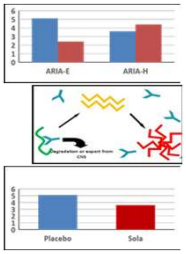
Doody et al, N Engl J Med. 2014 Jan 23;370(4):311-21.

- The study failed overall, but did show a 29% slowing of cognitive decline with Sola
- No significant change in Aβ levels between groups was seen

12

Solanezumab Lessons Learned 2014

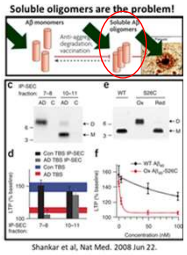
- **Targeting only monomeric Aβ is as safe as placebo**
  - While ARIA-E was increased by 0.7%, ARIA-E was lower by 0.5%
- **Targeting only monomeric Aβ does not reduce Aβ plaque levels**
  - The "Sink" hypothesis was disproven
- **There may be a clinical benefit of removing monomeric Aβ**
  - Slowing by about 31% on ADAS-cog11



13

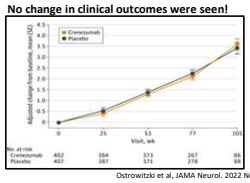
Let's continue the journey with Crenezumab 2012…

Soluble oligomers are the problem!

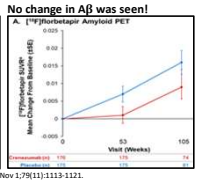


Shankar et al, Nat Med. 2008 Jun 22.

No change in clinical outcomes were seen!



No change in Aβ was seen!



Ostrowitzki et al, JAMA Neurol. 2022 Nov 1;79(11):1113-1121.

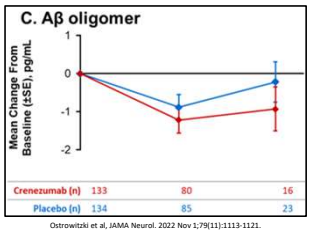
*ARIA was the same for both placebo and treated patients in the study

Both Phase 3 studies were stopped for neg efficacy

14

Crenezumab Lessons Learned 2022

- **There are two possible explanations for the complete lack of effect seen in these two Phase 3 trials**
  - The antibody did not actually capture oligomeric Aβ in humans
  - Oligomeric Aβ toxicity has little to do with AD progression



Ostrowitzki et al, JAMA Neurol. 2022 Nov 1;79(11):1113-1121.

15

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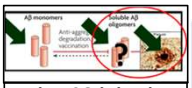
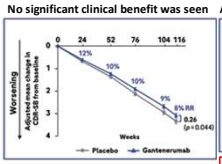
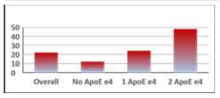
Let's continue the journey with Gantenerumab 2017…



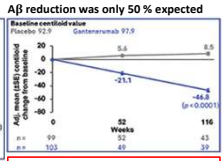
- First SQ injection rather than infusion delivery
- Prelim studies showed good Aβ removal and probable efficacy

No significant clinical benefit was seen





Aβ reduction was only 50 % expected



- Development was stopped as a result of these negative findings Dec 2022
- It remains unclear if dose reductions or SQ methods led to this failure?

16

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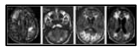
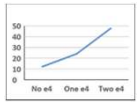
Gantenerumab Lessons Learned 2022

- Efficacy appears to be dependent on Aβ plaque clearance, not on other targets
- Safety appears to be somewhat dissociable from Aβ removal effectiveness, although this remains poorly understood
- ARIA occurrence is clearly dependent on ApoE e4 status in a dose-dependent manner as has been seen with many other antibodies
- SQ was able to deliver the same levels of antibodies as IV treatments





It is hopeful that we can use this method of delivery to reduce burden on healthcare systems and on patients

17

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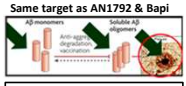
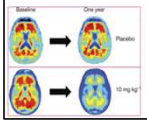
Let's continue the journey with Aducanumab 2017…

Same target as AN1792 & Bapi



- This worried me, and we chose not to participate in clinical trials because…
- We didn't know if it would it be safe?
- We didn't know if it would be of benefit?
- It has the same target as Bapineuzumab so are we just repeating history's mistakes?

- ENGAGE and EMERGE, tested aducanumab in ~1600 mild AD patients
- The drug removed amyloid plaques from the brain
- The FDA concluded that benefits on slowing cognitive decline were inconclusive and the conditional approval requires an additional study
- ~41% subjects had brain swelling/stroke or bleeding in the brain and 25% of those had symptoms including worsening of cognitive decline



BIOMEDICINE

Doubts persist for claimed Alzheimer's drug

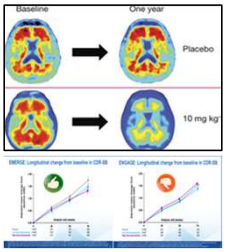
Once declared a failure, Biogen's antibody drug to be submitted for U.S. approval in 2020

http://science.sciencemag.org/content/366/6471/1298

18

Aducanumab Lessons Learned 2021

- **Definitive proof that such agents can fully remove amyloid from the brain!**
  - Removal of Aβ plaque clearly demonstrated in both Phase 3 studies leading to accelerated FDA approval
- **With one positive and one negative study on clinical outcomes it remained unclear what the benefit might be?**
- **Do another definitive studies was the FDA mandate! (conditional approval)**



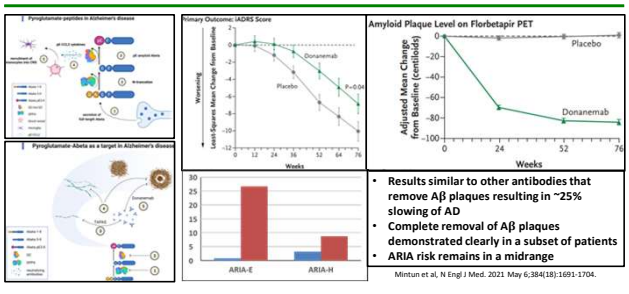
19

Accelerated & or Conditional FDA Approval?

- **"Accelerated" FDA Approval**
  - Accelerated means the FDA knows how much we need something
  - Approval was based on evidence of removing Aβ only
- **"Conditional" FDA Approval**
  - There is a requirement for an additional study to prove clinical benefit by 2026 or the drug approval will be pulled
  - This is really still an experimental research drug, similar to the many others we are working with in the field
- **What it takes for "Full" FDA Approval?**
  - Definitive evidence for significant clinical benefit, not just Aβ brain removal

20

Let's continue the journey with Donanemab 2017…



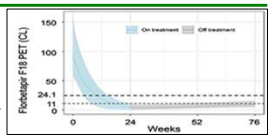
- **Results similar to other antibodies that remove Aβ plaques resulting in ~25% slowing of AD**
- **Complete removal of Aβ plaques demonstrated clearly in a subset of patients**
- **ARIA risk remains in a midrange**

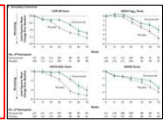
Mintun et al, N Engl J Med. 2021 May 6;384(18):1691-1704.

21

Donanemab Lessons Learned 2022

- **Clearly reduces Aβ, but the protocol stopped Aβ-PET once clear of Aβ, and so not all patients had EOS Aβ-PET**
  - This led the FDA to not grant accelerated approval given the disparate timelines for establishing Aβ clearance
- **A clinical benefit of ~32% was seen in the Phase 2 study, similar to other studies using agents that reduced Aβ**
  - A simailr clinical benefit was seen across all secondary clinical measures in the study

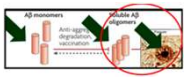




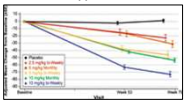
ARIA rate was intermediate between that seen with Aducanumab and that seen with Lecanumab

22

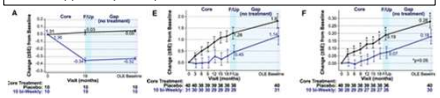
Let's continue the journey with Phase 2 Lecanemab 2012…



Phase 2b/3 study showed removal of Aβ leading to FDA accelerated approval



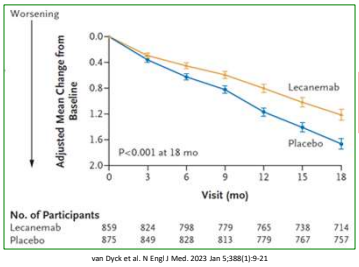
- **The trial demonstrated 10 mg/kg biweekly was optimal**
  - It eliminated Aβ
  - There was positive clinical benefit
- **But the trial ended and all patients went into a gap period before an OLE was started**
  - This taught us so much about disease modification and what happens if you stop these medicines

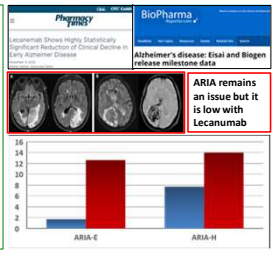


- **A slow rise in Ab-PET is seen, but this is really slow**
- **Cognitive decline continues, but parallel slopes indicate it has changed the disease course permanently**

23

Lecanemab Phase 3 Results…





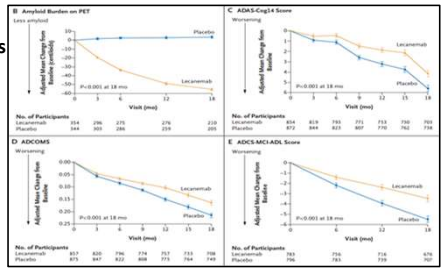
ARIA remains an issue but it is low with Lecanumab

van Dyck et al. N Engl J Med. 2023 Jan 5;388(1):9-21

24

Lecanemab secondary endpoints?

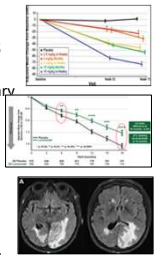
- **Full FDA approval expected in 3 mos**
- **VA has already chosen to cover this medicine**
- **It will be here at UK in the next 6 months**
- **Let's get ready…**



25

Lecanemab Lessons Learned 2022

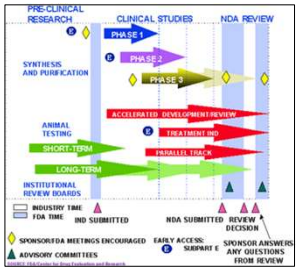
- **The Phase 3 CLARITY data is considered by most in the field to be definitive evidence of clinical benefit in addition to the previously accepted demonstration of Aβ removal**
  - The Phase 2b/3 data led to FDA accelerated approval on January 6, 2023 based solely on Aβ removal
- **Clinical benefit ranges from 27% to 40% based on outcomes similar to the many other studies with other agents**
  - Eisai immediately filed for full approval based on the Phase 3 CLARITY data
- **ARIA rates appear low despite full clearance of Aβ suggesting again a partial dissociation of risk from extent of amyloid removal**



26

FDA Full Approval?

- **Drug approval is based on the ultimate Phase 3 data**
  - Typically, 2 independent studies are needed
  - Surrogate outcomes can be used in some instances (i.e. BP lowering for antihypertensives
- **Aβ-PET lowering was a move to surrogate endpoints for AD**
  - Warranted "accelerated", but not full approval as of yet
- **Full FDA approval of Lecanemab was granted on July 6, 2023**
  - Medicare has stated they will cover the costs of Lecanemab (Leqembi®)

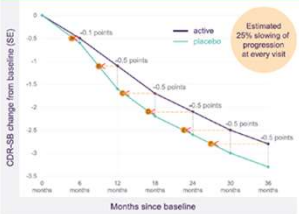


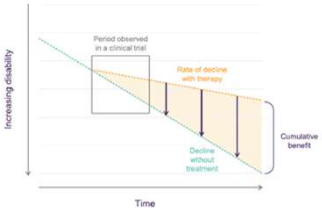
27

Alzheimer's Disease Center at the Sanders-Brown Center on Aging

How much time will this buy us? Is it clinically meaningful?

Alzheimer's Tennessee — Annual Alzheimer's Disease Management & Research Symposium





Petersen RC, Aisen PS, Andrews JS, Atri A, Matthews BR, Rentz DM, Siemers ER, Weber CJ, Carrillo MC. Expectations and clinical meaningfulness of randomized controlled trials. Alzheimers Dement. 2023 Feb 7. doi: 10.1002/alz.12959. Epub ahead of print. PMID: 36748826.

28

Alzheimer's Disease Center at the Sanders-Brown Center on Aging

Are these medicines all the same or are they different?

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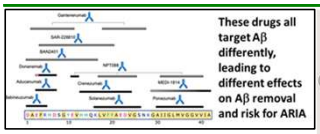
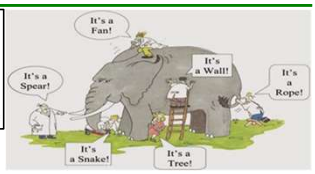


These drugs all target Aβ differently, leading to different effects on Aβ removal and risk for ARIA

Haass & Selkoe (2022) PLoS Biol 20(7): e3001694.



This conundrum is no different than the story of the blind men and the elephant

- Each part of the elephant is different depending on where you touch!
- These therapies all "touch" amyloid in different areas and are different!

29

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Are these medicines all the same or are they different?

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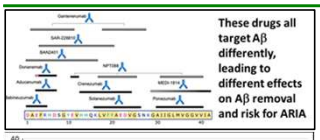

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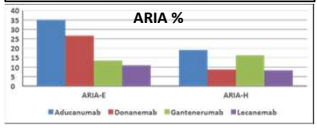

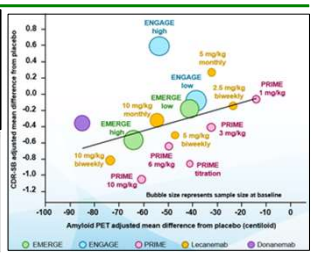

Haass & Selkoe (2022) PLoS Biol 20(7): e3001694.

30

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Why only ~30% clinical benefit despite full Aβ removal?

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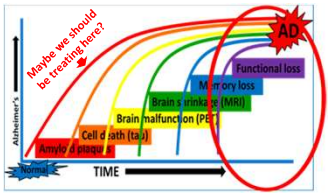
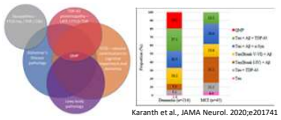
Two major possibilities exist…

#1 We are treating way too late in the disease and there is so much more injury this won't reverse



#2 We are only treating the Aβ & most cases of MCI and dementia are mixed disease states



Karanth et al., JAMA Neurol. 2020;e201741

"Pure" AD is only 27% to 40% of the pathology found in most MCI and or dementia cases at autopsy

31

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Let's continue the journey with Solanezumab for pAD 2012…

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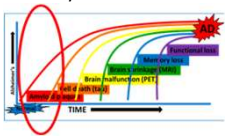
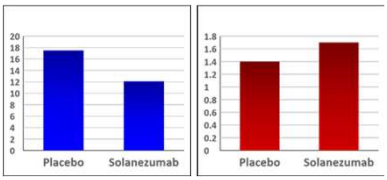
The A4 Study
NOW IS THE TIME

- **In 2011, the NIH funded the A4 *(anti-amyloid in asymptomatic AD)* study**
- **1,150 participants were treated for 3-9 years**





- **Aβ was not removed as was expected from prior Sola data**
- **Aβ accumulation was slowed**
- **No improvement in cognition was seen**
- **No difference in 36% transition rate to MCI was seen**

https://investor.lilly.com/news-releases/news-release-details/lilly-provides-update-a4-study-solanezumab-preclinical

32

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pAD Lessons Learned 2023

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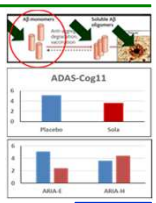
- **Slowing Aβ accumulation in those with AD levels of Aβ will not change disease progression**
  - Reinforces that Aβ removal is what matters
  - These medicines work the same way regardless of disease stage (safety and efficacy the same as in AD)
- **Rather than giving up, the field is pushing ahead with new pAD studies using Lecanemab**
  - A45 studies the same stage of pAD
  - A3 moves even earlier



AHEAD STUDY

Enrolling now at UK and across the globe!

33

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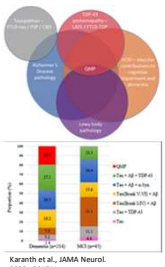
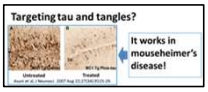
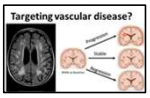
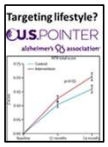
Do we need to add other medicines to Aβ agents?

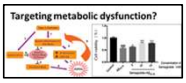


Karanth et al., JAMA Neurol. 2020;e201741









As these are developed it is likely we will enter an age of "precision medicine" where treatment is unique for every individual person!

34

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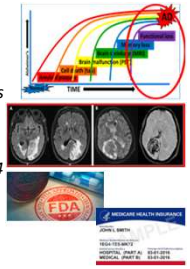
Imminent practical issues moving forward that we should all know…

Lecanemab is unfortunately not for everyone…

- *It is only for those with MCI and mild dementia*
- *Patients must be able to have an MRI scan for safety monitoring*
- *Patients cannot have significant past microhemorrhages or other bleeding in the brain*
- *Caution should be used for those on blood thinners (no concerns for anti-platelet blood thinners)*
- *Caution should be used for ApoE e4 homozygotes (e4/e4 carriers)*
- *If a person has only basic Medicare, 20% of the cost (~$5K) will be a co-pay needed (Eisai has a patient assistance program that may help?)*



35

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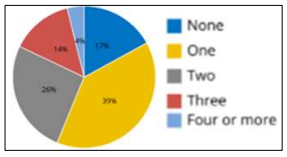
How few of our patients may be eligible?

- **Only 17% of our patients that appear eligible at first glance may actually be eligible…**
- **We need to be prepared to tell those that are not eligible why they are not eligible…**
- **Many may have exclusionary conditions…**
- **In the worst case scenario, with over 6 million persons on the US with AD, this still allows us to help over a million!!!**



COMMON EXCLUSIONARY CONDITIONS:

- Imaging exclusion (37.5%) including past ICH
- Cardiac exclusions if not well controlled (36%)
- Renal or liver disease (3.6%)
- Immunologic disease ever (10.7%)
- TIA or stroke in last year (6.3%)

Pittock et al. Neurology. 2023 Aug 16:10.1212/WNL.0000000000207770.

36

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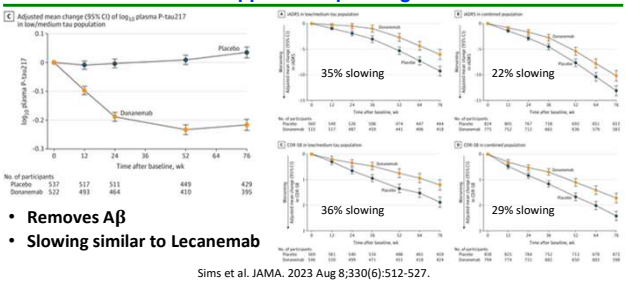
But that's not all as Donanemab full FDA approval is pending 1/24



- Removes Aβ
- Slowing similar to Lecanemab

Sims et al. JAMA. 2023 Aug 8;330(6):512-527.

37

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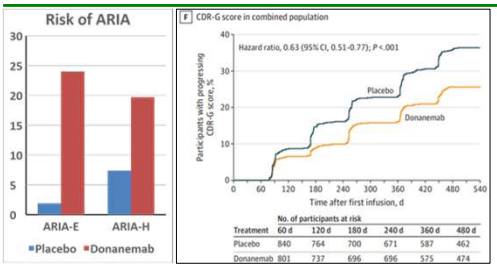
Risks vs. benefits?



- ARIA risks remain higher than placebo
- 4.4 month delay over the 1.5 year study period
- This difference could be much more significant if continued post-therapy

Sims et al. JAMA. 2023 Aug 8;330(6):512-527.

38

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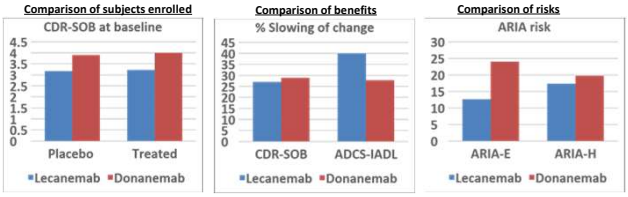
Comparing lecanemab & donanemab…

- Donanemab studies required tau-PET positivity whereas lecanemab studies did not (these populations are different)

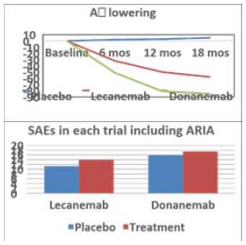


van Dyck et al. N Engl J Med. 2023 Jan 5;388(1):9-21; Sims et al. JAMA. 2023 Aug 8;330(6):512-527.

39

How to guide our patients?

- **Overall, the data show similar effects and risks**
- **Donanemab appears to clear amyloid faster**
- **Donanemab is also associated with slightly greater risk of ARIA & SAEs but this increased risk was also seen in the placebo group…**
- **These risks are manageable with either agent and SAEs are high irrespective of treatment in our patients with AD**



van Dyck et al. N Engl J Med. 2023 Jan 5;388(1):9-21; Sims et al. JAMA. 2023 Aug 8;330(6):512-527.

40

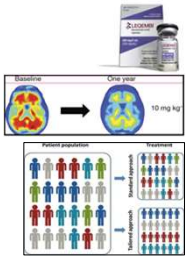
Advice to patients…

- **The medications have similar effects and similar safety profiles**
- **The safest approach may be to go with lecanemab, but the more aggressive approach is to go for donanemab**
  - This is like thinking of your retirement account investments…
- **Much of this may come down to what your patient's 3rd party payor will cover**
- **A consideration is that lecanemab is every two weeks and donanemab is only every 4 weeks**
  - With that said, missing an infusion or 2, or 3, or more is not as important as getting that amyloid out of their brains!
- **Our patients will ultimately have to make the choice for themselves as to whether these are right for them and if so, which one?**
  - We should be prepared to guide and educate on this important decision!

41

Impact on current & future clinical trials?

- **We have dozens of patients on lecanemab already, many for over 7 years now**
- **"The first person to be cured of Alzheimer's disease will be in a clinical trial"** *Dr. J 2012*
- **We still need to do better, and as we have seen, each successive generation of new experimental medicines brings us safer medicines that move us closer to the cure we are looking for!**
- **Many that are not eligible for Lecanemab or donanemab may still be eligible for these treatments**
- **It remains unclear how the field will begin to adapt to combination therapy with experimental medicines that are needed as we move towards precision medicine!**



42

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Questions? Discussion?

Alzheimer's Tennessee

- We are entering a new world for the care and treatment of those with MCI and or dementia
- It has been too long, and there has been too much suffering and death
- Change is finally here and I for one embrace this new world!

43