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Emerging Experimental Therapeutics in Alzheimer's Disease: Monoclonal Antibodies to Amyloid and Beyond

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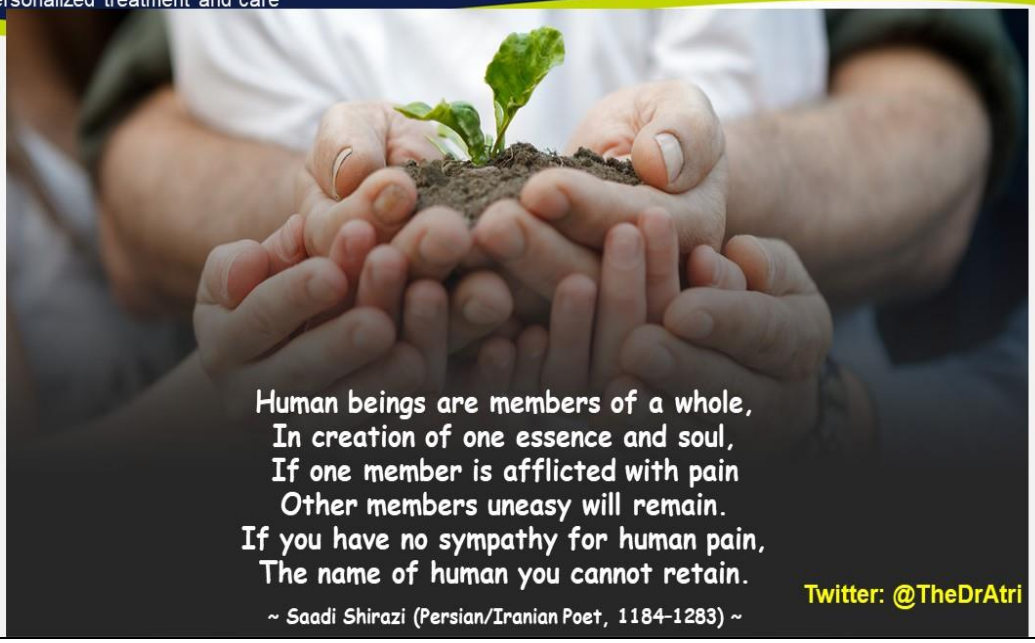
Disclosure/conflict of interest

- Institutional Research Grants, observational or biomarker studies or clinical trials:
  - Alzheimer's Disease Consortia, Coordinating Research Institutes or Government Funding (ACTC, ADCS, ATRI, NIH), Indiana University (observational cohort), Johns Hopkins (clinical trial), Global Alzheimer's Platform, Biohaven (with ADCS), Eisai (with ATRI/ACTC), Lilly (with ACTC/NIH), PEACE-AD study (with ADCS), Athira, Alzheon, Vivoryon (with ADCS), NIH
  - Receives institutional research grant/contract funding from NIA/NIH 1P30AG072980, AZ DHS CTR040636, Washington University St Louis, and Gates Ventures.
  - At my previous institution, served as site PI for the Biogen EMERGE study (clinical trial contract with institution), and at my current institution serve as site PI for ACTC/ATRI/Eisai AHEAD 3-45 AD prevention trial (clinical contract with my institution)
- Scientific, Medical or Data Monitoring Advisory Boards; Consulting; lectures, CME, or disease state education programs; or Work Groups/Committees:
  - AbbVie, Acadia, Allergan, the Alzheimer's Association, Axovant, AZ Therapies, Biogen, Eisai, Grifols, Harvard Medical School Graduate Continuing Education, JOMDD, Lundbeck, Merck, Roche/Genentech, Novo Nordisk, Qynapse, Sunovion, Suven, and Synexus.
- Book/Authorship Royalty:
  - Oxford University Press (OUP)

- Clinicians care for the particular person (individual) in front of us – not populations
- Infer & are informed by science & measurements (proteins, PET scans, p-values) – with data and treatments that are imperfect and incomplete – to estimate likelihoods about what may be reasonable and meaningful → incremental advances
- To help make shared and patient-centered decisions about <u>how to incrementaly and relatively improve the life of the person</u> → personalized treatment and care



Amyloid-beta Plaques and Neurofibrillary (Tau) Tangles as defining hallmarks of Alzheimer's disease

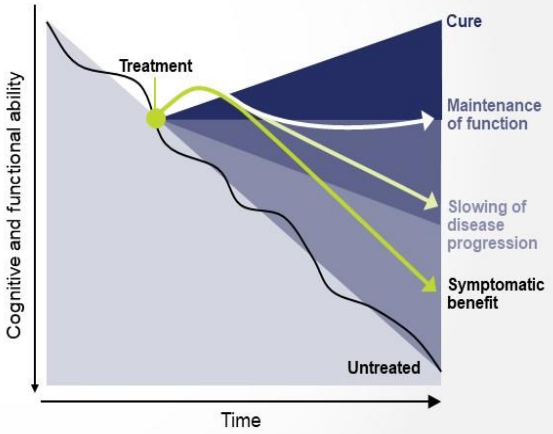
Cummings J, et al. *Alzheimers Dement (NY)*. 2017;3:367-384.

Symptomatic and disease-modifying treatments

- The current fully approved treatments for AD (ChEIs, memantine) are mostly symptomatic;[1] only the newly FDA accelerated pathway-approved drug aducanumab is disease-modifying but has uncertain clinical benefit[2]

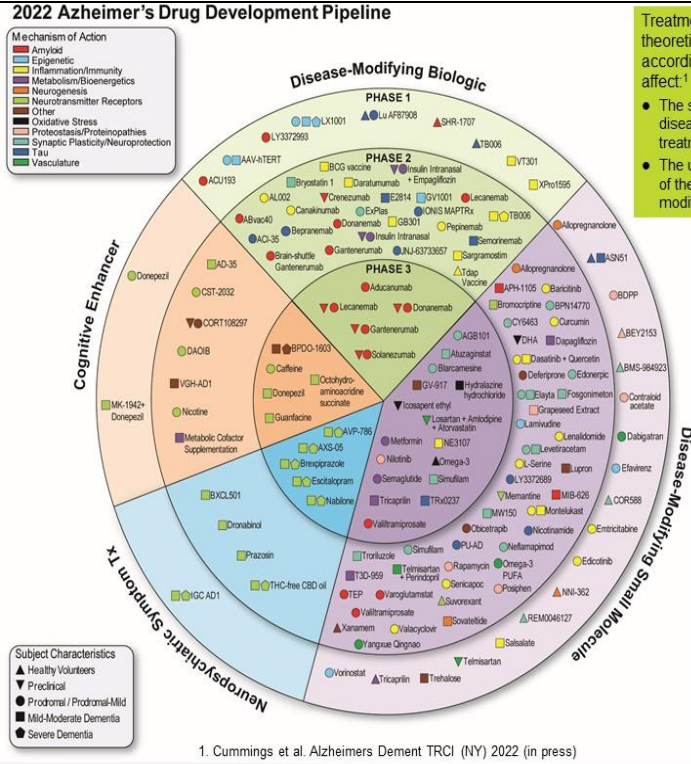
  - A **symptomatic treatment** can provide an initial benefit with symptoms but does not change the pathobiology of AD - ultimately the patient will continue to decline at the same rate (slope)[3,4]
  - A **disease-modifying treatment** impacts the underlying pathobiology of AD, and would stop or slow the rate (slope) of progressive decline of the patient[3,4]
  - A **cure** for AD would reverse the disease progress and restore the patient to their original level of functioning[4]

Theoretical ways in which a treatment could affect the course of AD[4]



1. Winblad et al. Lancet Neurol 2016;15(5):455–532; 2. Cummings et al. Alzheimers Res Ther 2021;13(1):98;
3. Cummings & Fox. J Prev Alzheimers Dis 2017;4(2):109–115; 4. Adapted from: Van Dam & De Deyn. Nat Rev Drug Discov 2006;5(11):956–970

2022 Azheimer's Drug Development Pipeline



1. Cummings et al. Alzheimers Dement TRCI (NY) 2022 (in press)

Treatments for AD can be theoretically classified according to whether they affect:[1]

- The symptoms of the disease ('symptomatic treatments')
- The underlying pathology of the disease ('disease-modifying treatments')

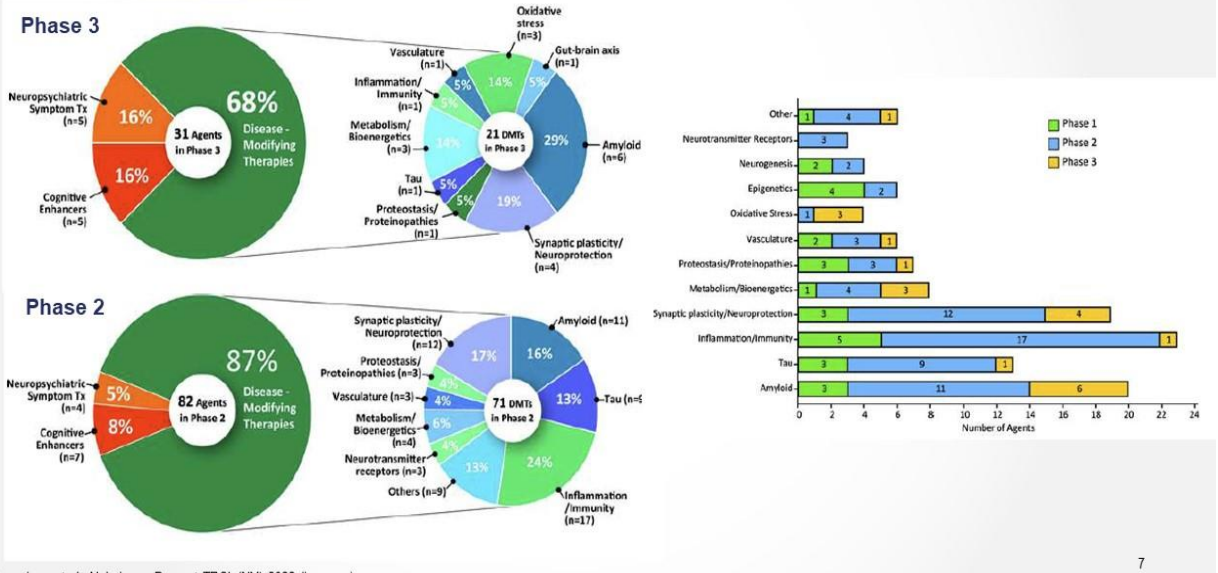
AD drug development pipeline, as at January 2022 on clinicaltrials.gov[1]

143 agents in 172 AD clinical studies[1]

- 31 agents in Phase 3 trials
- 82 agents in Phase 2 trials
- 30 agents in Phase 1 trials

- **104 agents (83.2 % of total pipeline) target disease modification** ('DMTs'), **13 agents (9.8%)** target cognitive enhancement ('symptomatic')[1], **9 agents (6.9%)** target behavioural/neuropsychiatric symptoms[1]
- Total number of participants needed in all currently recruiting trials – **50,575**[1]
- Long duration of recruitment 1.5-3.8 times longer than study durations
- There is a high failure rate of drug development for AD[1]
- Despite setbacks, drug development continues robustly at all phases[1]
- The **continuing unmet needs** of AD treatment **requires a commitment to growing and accelerating** the drug development **pipeline**; and **a robust alliance of all stakeholders** to coordinate, collaborate, and reach consensus regarding what matters, can be expected, and how to translate therapies into improving lives of patients

Mechanism of action of agents for the treatment of AD in Phases 1-3



Cummings et al. Alzheimers Dement TRCI (NY) 2022 (in press)

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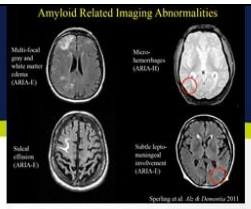
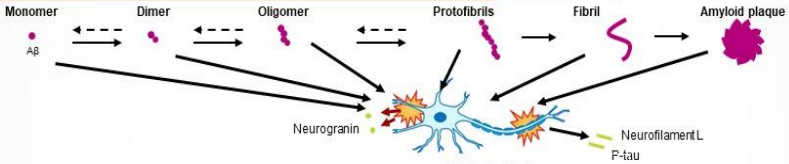
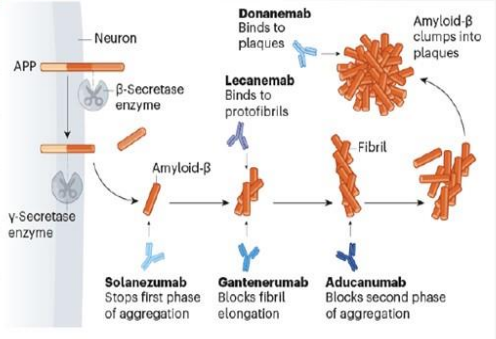
Anti-amyloid mAbs (monoclonal antibody) drugs in AD



Donanemab*	N-terminal pyroglutamate Abeta epitope present only in plaque Ph2 positive – met prespecified primary outcome (iADRS) → Ph3 Trailblazer2 (Q2 2023)	A



mAb	Target	Aβ Selectivity (Monomer, Aggregate)
Aducanumab*	Soluble and insoluble aggregated forms of Aβ: oligomers, protofibrils, fibrils Mixed Ph3 - stopped after futility analysis (fail) → + biomarker effect → FDA accelerated approval – EMBARK (Q4 2023), ENVISION, iCARE	A >> M
Lecanemab	Aggregated Aβ: **selectively binds to protofibrils** Ph 3 in prodromal AD (CLARITY AD Q3/4 2022) and preclinical AD	A >> M
Bapineuzumab*	All forms of Aβ Failed Ph3- A+ not required; ~17% A-, ARIA noted, some Plaque lowering	A, M
Crenezumab*	All forms of Aβ Failed Ph3 Failed Ph2/3 DIAN-TU Study, In study in ADAD prevention trial (Q3 2022)	A, M
Gantenerumab	Aggregated Aβ Futility → increase dose, Ph3 proAD (GRADUATE Q3/4 2022) in DIAN-TU	A > M
Solanezumab*	Monomeric Aβ; Failed Ph3 – no plaque lowering; 9-14% slope mitigation in EXP3 80 mos Under study in A4 secondary prevention trial	M >>A



Aducanumab

- Aducanumab is an anti-amyloid antibody therapy (human mAb) (AAA mAbs), administered as a monthly 1-hour infusion, that has **accelerated approval** by the FDA for the treatment of early AD[1]
  - **Based on reduction in beta-amyloid plaques** observed in patients treated with aducanumab[2]
- **Aducanumab is far from a cure – expectation is clearing of amyloid plaques with potential signal for modest slowing of clinical progression/decline** (expectation is not potential symptomatic improvements)
- **Side effects of treatment include ARIA** (~20–40% of treated individuals, depending on APOE-e4 status) – treatment with aducanumab requires multiple brain MRIs for monitoring for potential ARIA[2]
- Treatment access will likely be very limited (due to cost & coverage considerations) in the U.S.
- CMS National Coverage Determination (NCD) on April 7, 2022 determined for the class of AD anti-amyloid mAbs would not cover freely but would cover (pay for)
  - FDA traditionally(fully)-approved drugs under a CED (coverage with evidence development; such as a Registry)
  - FDA accelerated approved drugs (e.g. aducanumab) in FDA- or NIH-approved trials[5]
- What's accelerated approval?
  - Mechanism established in 1992 to accelerate drug approval (as a response to HIV/AIDS) **for serious conditions** that have unmet treatment needs to make available drugs, **without definitively proven clinical benefit, based on effects on a biomarker considered reasonably likely to predict clinical benefit**
  - Used to accelerated treatments in HIV/AIDS (viral load biomarker), **multiple sclerosis (MRI plaque burden biomarker)**, many cancer therapeutics (e.g. tumor size as biomarker) → still requires confirmatory clinical trial to definitively show efficacy for full approval

1. Aduhelm. Prescribing Information. June 2021; 2. Aduhelm. Prescribing Information. July 2021;
3. Cummings et al. J Prev Alz Dis 2021. doi: http://dx.doi.org/10.14283/jpad.2021.41 ; 4. Cummings et al. J Prev Alz Dis 2022;5. CMS.gov website. https://www.cms.gov/newsroom/press-releases/cms-finalizes-medicare-coverage-policy-monoclonal-antibodies-directed-against-amyloid-treatment

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Aducanumab Phase 3 Studies EMERGE and ENGAGE Background – mixed and controversial results after a failed futility analysis and truncated studies

- **ENGAGE negative** study
- **EMERGE positive** study– all primary & secondary (and tertiary) endpoints analyses were consistent per prespecified sequential testing procedure (prespecified that 10mg/kg was target dose - page 4[1])
- Positive biological effect of target engagement in both studies:
  - Amyloid plaques lowered → upstream biomarker effect
  - Signals for downstream biomarker impact (plasma p-tau)
- Safety: AE's of ARIA (20-40%) – managed with strict protocols
  - mostly asymptomatic - 74% of ARIA-E
  - when symptomatic, mostly mild (67.7% mild, 28.3% moderate, 4% severe, 0.3% serious)
  - mostly resolved between 12-16 weeks (~83%)

Budd Haeberlein et al JPAD 2022; Salloway et al . JAMA Neurol 2022

Evolution of 2nd generation AAA mAb that remove amyloid plaques

- Evolution of AAA mAbs and trials: Second generation AAA "plaque lowering" mAbs different from each other (and very different from BACE-inhibitors) but
  - **Tested in A+ individuals**
  - **Tested in earlier clinical stages** – in Early AD (MCI and mild dementia due to AD) as opposed to in mild to moderate AD dementia
  - Used higher doses
  - **Remove amyloid plaques**
  - **Modest signals of efficacy appearing** (20-40% slowing of decline over 18 months tested)
  - **ARIA side effect** (more at higher drug doses and for e4+ carriers)

Cummings et al. Alzheim Research Therap. 2021.

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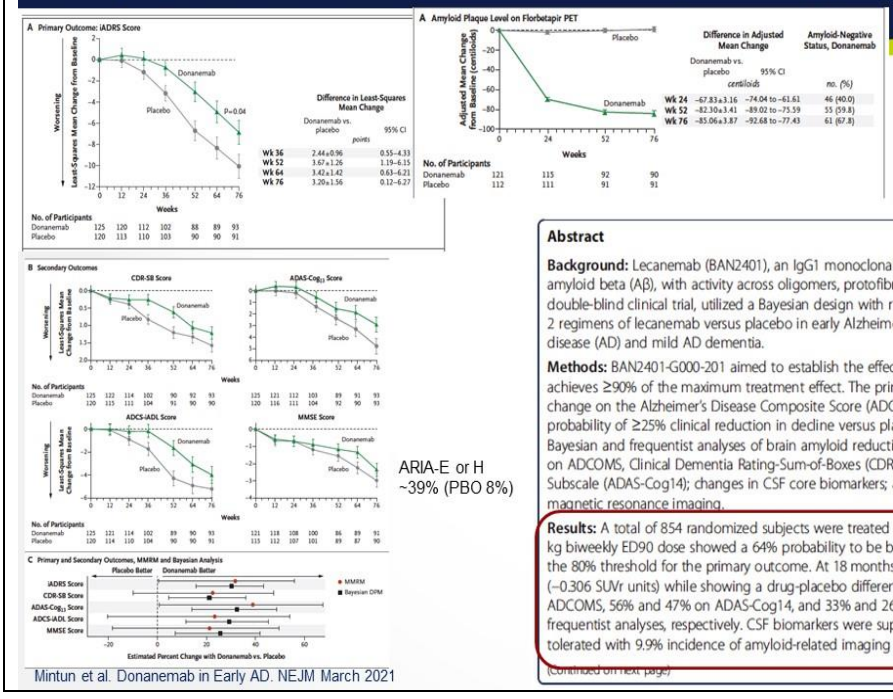
Donanemab and lecanumab (anti-amyloid mAb AD drugs) Ph2b studies show lowering of brain amyloid fibrillar plaques and associated signals of clinical benefit (20-40% range) over ~18 months



ARIA-E or H ~39% (PBO 8%)

Mintun et al. Donanemab in Early AD. NEJM March 2021

Alzheimer's Research & Therapy

RESEARCH Open Access

A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody

Abstract

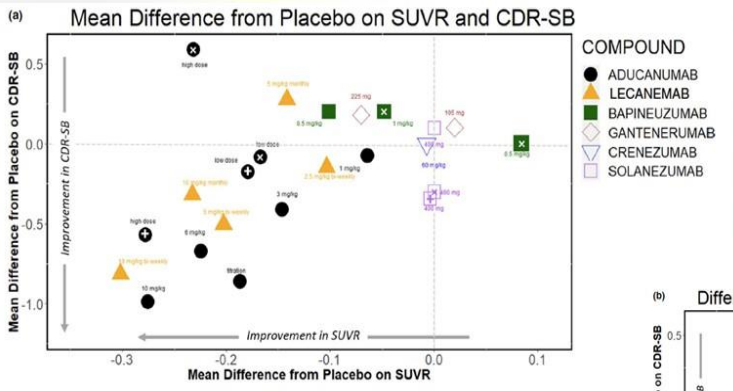
Background: Lecanemab (BAN2401), an IgG1 monoclonal antibody, preferentially targets soluble aggregated amyloid beta (Aβ), with activity across oligomers, protofibrils, and insoluble fibrils. BAN2401-G000-201, a randomized double-blind clinical trial, utilized a Bayesian design with response-adaptive randomization to assess 3 doses across 2 regimens of lecanemab versus placebo in early Alzheimer's disease, mild cognitive impairment due to Alzheimer's disease (AD) and mild AD dementia.

Methods: BAN2401-G000-201 aimed to establish the effective dose 90% (ED90), defined as the simplest dose that achieves ≥90% of the maximum treatment effect. The primary endpoint was Bayesian analysis of 12-month clinical change on the Alzheimer's Disease Composite Score (ADCOMS) for the ED90 dose, which required an 80% probability of ≥25% clinical reduction in decline versus placebo. Key secondary endpoints included 18-month Bayesian and frequentist analyses of brain amyloid reduction using positron emission tomography; clinical decline on ADCOMS, Clinical Dementia Rating-Sum-of-Boxes (CDR-SB), and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog14); changes in CSF core biomarkers; and total hippocampal volume (HV) using volumetric magnetic resonance imaging.

Results: A total of 854 randomized subjects were treated (lecanemab, 609; placebo, 245). At 12 months, the 10-mg/kg biweekly ED90 dose showed a 64% probability to be better than placebo by 25% on ADCOMS, which missed the 80% threshold for the primary outcome. At 18 months, 10-mg/kg biweekly lecanemab reduced brain amyloid (−0.306 SUVr units) while showing a drug-placebo difference in favor of active treatment by 27% and 30% on ADCOMS, 56% and 47% on ADAS-Cog14, and 33% and 26% on CDR-SB versus placebo according to Bayesian and frequentist analyses, respectively. CSF biomarkers were supportive of a treatment effect. Lecanemab was well-tolerated with 9.9% incidence of amyloid-related imaging abnormalities-edema/effusion at 10 mg/kg biweekly.

(Continued on next page)

FDA Clin Pharm Group: Across multiple studies and multiple different anti-amyloid mAb AD drugs, higher amyloid plaque removal is associated with more clinical benefit on CDR-sb



Study Legend:

Aducanumab	lecanemab	Bapineuzumab	Gantenerumab	Crenezumab	Solanezumab
103	201	Car	Scar	CREAD/2	Exp 1
301		NonCar			Exp 2
302					Exp 3

Study Legend:

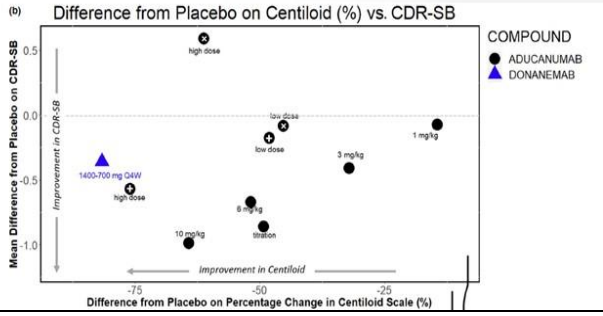
Aducanumab	Donanemab
103	AIZ
301	
302	

Zhu et al. Clin Pharm Therapeutics 2022

Toward Bridging Unmet Medical Need in Early Alzheimer's Disease: An Evaluation of Beta-Amyloid (Aβ) Plaque Burden as a Potential Drug Development Tool

Hao Zhu[1,*], Mehul Mehta[1], Shiew-Mei Huang[1] and Yaning Wang[1]

This piece expresses our views on the use of reduction in beta-amyloid (Aβ) plaque as a potential tool to facilitate new drug development and patient access to promising therapies for Alzheimer's disease. By summarizing literature from seven anti-Aβ antibodies investigated in late-phase trials, we demonstrate a potential threshold of Aβ plaque reduction for clinical effect. The reduction in Aβ plaque of sufficient extent shows a relationship with clinical improvements as measured by a standard end point.



Challenges & Opportunities – implications for clinical practice and need for earlier multi-stakeholder coordination, collaboration and consensus and a robust alliance

- Readouts for several 2nd generation AA mAb for treatment of early AD expected in Q3/4 2022 (gantenerumab, lecanumab) and Q2 2023 (donanemab)
- Translational dilemma and generalizability from clinical trials to clinical practice:
  - Biological Effect (e.g. impact on upstream or downstream biomarker(s)
  - Clinical Efficacy (clinical trial – idealized conditions and restricted populations)
  - Clinical Effectiveness in Real-World (clinical practice)
- What should our expectations be treatments given complexity of disease (and likely co-pathology in brain), no silver bullet? What benefit-risk levels are needed (and by who)?
- Accelerated approval – will AD treatments be the exception and be treated differently by payers potentially limiting access to accelerated approved AD drugs?
  - Impact of biomarkers --> what constitutes "reasonably likely to predict clinical benefit"?
- Traditional approval – what constitutes a "clinically meaningful health outcome" in AD and is "reasonable and necessary" to be covered? For who, when, what outcome, and how much and for how long (relative, absolute?)
  - AD has heterogeneous clinical presentations and impacts different aspects of multiple domains - cognition (memory, executive functions, language, visuospatial functions), activities of daily living (complex, instrumental, basic), neuropsychiatric/behavioural - differentially across persons and over its clinical course
  - Each trial has own population & design (specific inclusion/exclusion, biomarkers, outcome measures, duration

Challenges & Opportunities – implications for clinical practice and need for earlier multi-stakeholder coordination, collaboration and consensus and a robust alliance

- What benefit effect size?
  - On a scale? On a composite?
  - Which scales/outcomes?
  - Fixed # or difference?
  - % difference (20% slowing over 18 months, 20% over 2 years?)?
  - "Gaining" more time at a relatively higher state of cognition/function? How many months relative benefit over how long – e.g. over 2 years the treatment provides equivalent of 6 months of "time" compared to expected decline without treatment?
- Generally, most persons with AD prioritize quality of life (has not been easy to measure with standard measures), retention of greater independence, and "gaining time"
- What are acceptable safety, risks and burden profiles? (stage dependent, individual differences)
- Use of biomarkers – which ones, for what purposes (diagnosis, prognosis, treatment response, safety)? (C - A/T/N/V/I/O/S/N); Iteratively learn to personalize biomarkers to have greater impact on benefit and safety
- Multidisciplinary integrated comprehensive hub and spoke models of diagnosis and care with clinical trials as a coordinated extension of clinical practice - akin to oncology model
- Clinical Registries and Clinical Consortia
- Improve timely detection; DEI; choice and access (autonomy and justice)

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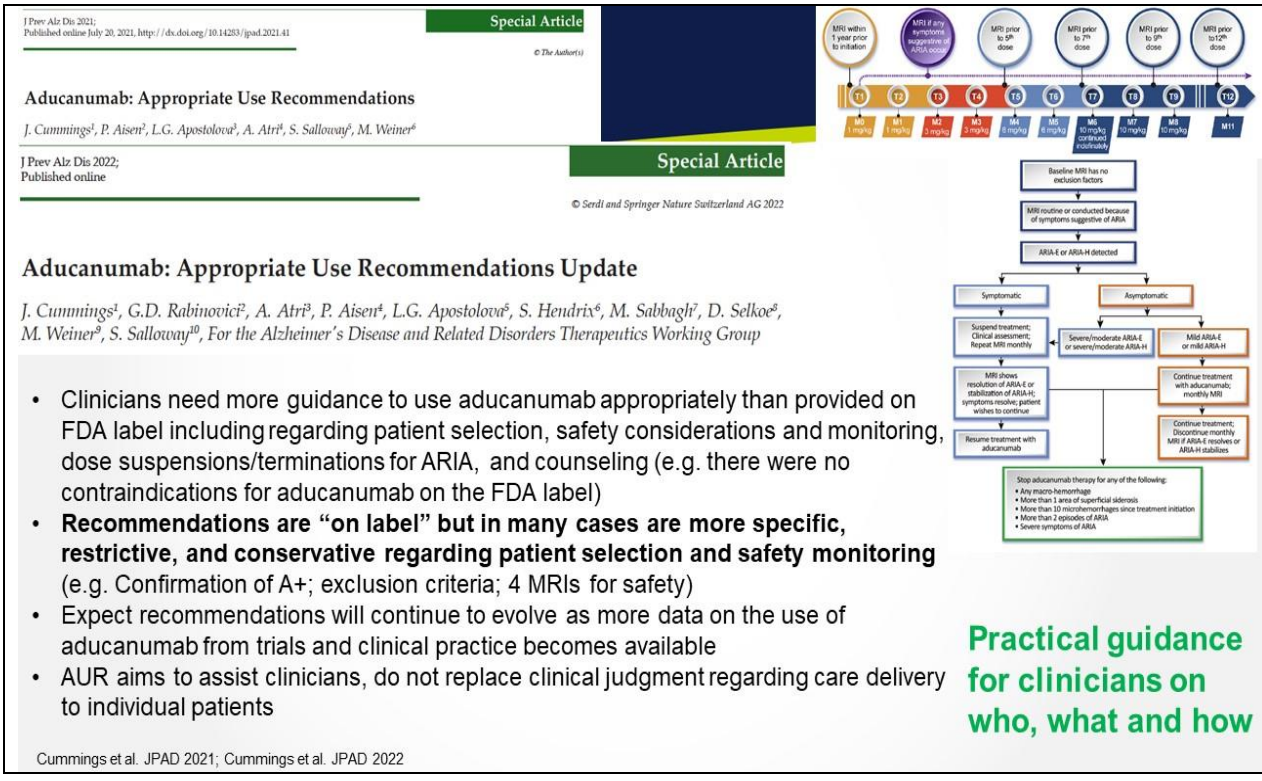

- Clinicians need more guidance to use aducanumab appropriately than provided on FDA label including regarding patient selection, safety considerations and monitoring, dose suspensions/terminations for ARIA, and counseling (e.g. there were no contraindications for aducanumab on the FDA label)
- **Recommendations are "on label" but in many cases are more specific, restrictive, and conservative regarding patient selection and safety monitoring** (e.g. Confirmation of A+; exclusion criteria; 4 MRIs for safety)
- Expect recommendations will continue to evolve as more data on the use of aducanumab from trials and clinical practice becomes available
- AUR aims to assist clinicians, do not replace clinical judgment regarding care delivery to individual patients

Practical guidance for clinicians on who, what and how

Cummings et al. JPAD 2021; Cummings et al. JPAD 2022

Summary

- There are many learnings from the amyloid clinical trials odyssey – and **we are at the precipice of a new and exciting era of biomarker-informed combination treatments**[1-4]
  - **Have better understanding of what does not work and when, that amyloid is only part of the equation and that we will not have any magic bullets – but will need biomarker supported combination therapies – abnormal tau, neurodegeneration, inflammation, and other mechanisms are also thought to be involved in the pathobiology of AD**[1-4]
  - **When, and to what extent, and for how long would clearing of amyloid from the brain be needed to potentially produce meaningful changes for patients with early AD**[1-3]
  - The totality of the evidence provides hope for the promise of amyloid therapies:
    - Potentially ~20-40% reduction in clinical decline over ~18 months in early clinical AD – more Ph3 readouts are nearing (end of 2022/early 2023)
    - Likelihood of adverse-effects that require proficiency and resources for careful patient selection, close monitoring and management
    - Need to learn and optimize benefit and safety using biomarkers in clinical trial and real-world settings
- Need robust alliance of all stakeholders to coordinate, collaborate, reach consensus, and establish clinical care and effectiveness research partnerships, infrastructure and resources

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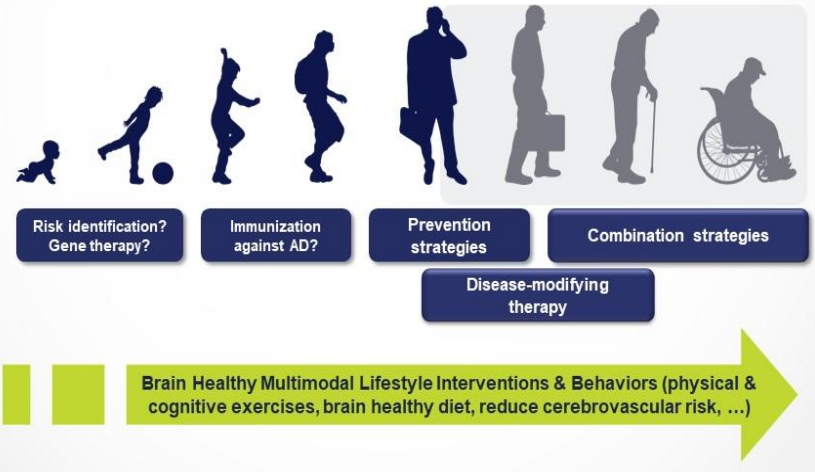
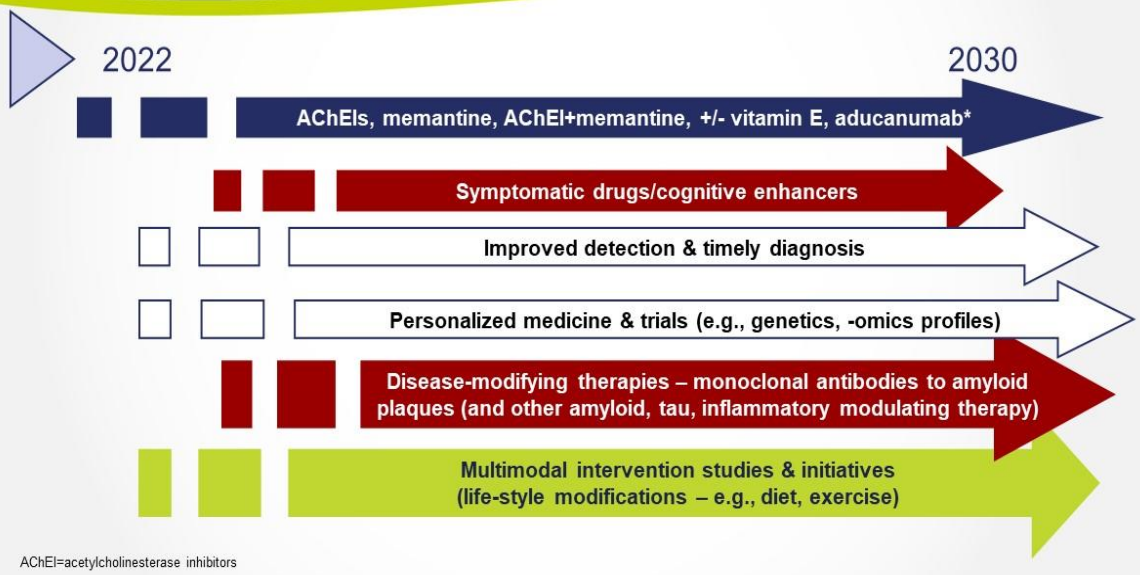
1. Atri. Semin Neurol 2019;39(2):227–240; 2. Atri. Med Clin North Am 2019;103(2):263–293; 3. Cummings J, Alzheim Res Therap 2021; 4. Cummings et al Alz Dement TRCI 2022 in press

Transformation: AD Prevention and Consideration Across the Life Span



Potential AD combination treatment approaches in 2022, in the coming decade, and beyond



AChEI=acetylcholinesterase inhibitors

Addapted from: Cummings et al. Alzheimers Res Ther 2021;13(1):98; Atri. Personal communication

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Collective global problems require collective global commitment, investments, and efforts

→ our problems require our solutions

Twitter: @TheDrAtri

"Where there is no hope, there can be no endeavour" ~ Samuel Johnson

"The journey of a thousand miles begins with one step" ~ *Lau Tzu*

THANK YOU!

No man is an island,
entire of
itself...
Any man's death
diminishes me,
because I am
involved in mankind;
and therefore never
send to know for

… the glass is
more than half full!