

## Aducanumab: The first targeted Alzheimer's therapy

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**SUMMARY** Alzheimer's disease (AD) is an irreversible brain disorder associated with severe progressive dementia and is characterized by deposits of amyloid plaques in the brain. Over the past 20 years, the mortality of strokes and heart disease has decreased, but deaths from AD have increased. The four drugs used clinically to treat AD can only relieve symptoms but cannot slow the progression of the disease. Aducanumab, a human monoclonal antibody that preferentially binds to aggregated amyloid- $\beta$  to reduce the number of amyloid plaques and slow disease progression, was approved to treat AD by the US Food and Drug Administration on June 7, 2021. It is the first disease-modifying therapy for AD, but there is considerable controversy regarding the drug's approval. Aducanumab offers hope for millions of patients.

**Keywords** Alzheimer's disease, aducanumab, amyloid- $\beta$ , clinical trials

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with memory loss and decline in cognitive function. It is the most common cause of dementia and accounts for 60-70% of dementia cases (1). In the US, approximately 6.2 million people suffer from AD, and the number is predicted to reach 13.8 million by 2060. From 2000 to 2019, deaths from AD increased more than 145%, so AD has become the sixth-leading cause of death in the US (2). However, current treatments do not meet clinical need. By June this year, just four drugs were approved by the US Food and Drug Administration (FDA) for the treatment of cognitive impairment and dysfunction in symptomatic AD, including three cholinesterase inhibitors (donepezil, rivastigmine, and galanthamine) and a glutamate regulator memantine. However, these drugs can only help lessen symptoms, such as memory loss and confusion (3).

On June 7, 2021, the FDA announced that aducanumab was approved to treat patients with AD. Aducanumab is the first novel therapy approved for AD since 2003. More significantly, it is the first treatment directed at the underlying pathophysiology of AD (4). The key pathological changes that are observed in AD brain tissue are increased levels of both the amyloid- $\beta$  (A $\beta$ ) peptide and hyperphosphorylated tau (p-tau). A $\beta$  is a tiny protein fragment that forms and accumulates in the brain as a plaque. These plaques disrupt communication between nerve cells and may also activate immune system cells, triggering inflammation and phagocytosis

of damaged nerve cells (5). The amyloid hypothesis holds that A $\beta$ -related toxicity is the main cause of synaptic dysfunction and subsequent neurodegeneration, which is the basis of AD progression (6). Although scientists are not sure what causes cell death and tissue loss in the process of AD, amyloid plaques are one of the potential factors. Aducanumab is a type of human monoclonal antibody that can selectively interact with A $\beta$  aggregates, including soluble oligomers and insoluble fibrils, and that then clears A $\beta$ . Aducanumab is the first therapy to prove that removing A $\beta$  leads to better clinical outcomes (7).

Thirty-seven years have passed since when A $\beta$  was first proposed as the pathogenesis of AD (8) and when aducanumab was approved. Over the past 20 years, several drugs that decrease the production of A $\beta$  (mainly  $\gamma$ -secretase and  $\beta$ -secretase inhibitors) or increase A $\beta$  brain clearance (anti-A $\beta$  monoclonal or polyclonal antibodies and A $\beta$  antigens) have been identified. Unfortunately, in all clinical trials to date, these treatments have failed to improve cognitive outcomes despite reducing brain A $\beta$  (9). Aducanumab's approval was also a long and arduous journey. Biogen and Eisai conducted two global Phase 3 trials on aducanumab in 2015 – ENGAGE and EMERGE. Both trials were terminated in March 2019 due to previous invalid analyses using smaller datasets. Afterwards, the researchers obtained a large dataset and analyzed it again. Results of the EMERGE trial indicated that the cognitive ability of patients treated with high-

dose aducanumab improved significantly (10). On October 22, 2019, they announced their plan to seek regulatory approval for aducanumab. On July 8, 2020, Biogen announced the completion of its application to the FDA for a Biologics License for aducanumab for the treatment of AD. On November 6, 2020, the FDA Peripheral and Central Nervous System Drugs Advisory Committee voted against the proposal (11). Later, three members of the committee, G. Caleb Alexander, Scott Emerson, and Aaron S. Kesselheim, expressed their opposition to the drug in an article in the Journal of the American Medical Association (12). Their paper focuses on the contradictory results of the two trials and aducanumab's potential safety hazards. On June 7, 2021, the FDA approved aducanumab as the first and only drug to reduce A $\beta$  plaques in the brain to solve the pathological problems of dementia plaques. As part of the accelerated approval, Biogen will conduct a controlled trial to verify the clinical benefits of aducanumab in patients with AD (4).

According to statistics, in 2021, 126 drugs for the treatment of AD are undergoing clinical trials. One hundred and four drugs (82.5%) target the pathophysiology of AD, with 17 (13.5%) targeting A $\beta$  and 11 (8.7%) targeting the tau protein. A point worth noting is that there are 19 drugs for inflammation/infection/immunity and 17 drugs for synaptic plasticity/neuroprotection in the clinical stage; these 2 groups represent the largest proportion (13). Reviews of clinical trials indicate that there is progressive emphasis on non-amyloid targets, such as synaptic plasticity, inflammation, metabolism, and proteostasis (13-15). Over the past few years, researchers have found new targets for AD. Wang *et al.* confirmed that an imbalance in intestinal microbiota promotes the infiltration of peripheral immune cells in a mouse model of amyloidosis, which is related to behavioral and AD-related pathological changes. A drug to address this mechanism, GV-971, is in a phase 3 clinical trial in China (16). APOE4 accelerates blood brain barrier (BBB) decomposition and neurodegeneration in AD mice via the cyclophilin A pathway in pericytes, which is crucial to the pathogenesis and treatment of vascular and neurodegenerative disorders in AD (17). Lau *et al.* found that an IL-33-PU.1 axis is involved in transcriptional regulation and that it promotes beneficial microglial functions in AD (18). Their findings provided important insight into the therapeutic potential of targeting glial- and endothelial-specific pathways to restore brain homeostasis in AD (19). Long-term delivery of antibodies blocking CD22 in the central nervous system reprograms microglia into stable transcription and improves cognitive function in older mice (20). TREM2 enables the microglial response in AD by maintaining cell energy and biosynthesis (21). Reducing the time between finding targets and developing effective drugs may accelerate the approval of new drugs for AD.

There are other reasons for the difficulty of developing drugs for AD. AD develops well before patients develop the symptoms associated with Alzheimer's dementia. In fact, research suggests that brain changes associated with the disease may begin 20 or more years before symptoms appear (22). Therefore, early screening and prevention of AD is vital. Guidelines on preventing AD based on meta-analyses were published in 2018 (23). The guidelines suggest that a combination of evidence-based clinical recommendations may be the best choice for the prevention of AD. That said, a comprehensive and individually tailored strategy to prevent and treat AD should also be formulated. Therefore, personalized prevention and treatment should be developed for high-risk groups.

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## References

- Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer's disease. *Lancet*. 2016; 388:505-517.
- 2021 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2021; 17:327-406.
- Long JM, Holtzman DM. Alzheimer disease: An update on pathobiology and treatment strategies. *Cell*. 2019; 179:312-339.
- FDA's Decision to Approve New Treatment for Alzheimer's Disease. <https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease>. (accessed June 7, 2021).
- Kent SA, Spires-Jones TL, Durrant CS. The physiological roles of tau and A $\beta$ : implications for Alzheimer's disease pathology and therapeutics. *Acta Neuropathol*. 2020; 140:417-447.
- Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002; 297:353-356.
- Sevigny J, Chiao P, Bussiere T, *et al.* The antibody aducanumab reduces A $\beta$  plaques in Alzheimer's disease. *Nature*. 2016; 537:50-56.
- Glennner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun*. 1984; 120:885-890.
- Panza F, Lozupone M, Logroscino G, Imbimbo BP. A critical appraisal of amyloid- $\beta$ -targeting therapies for Alzheimer disease. *Nat Rev Neurol*. 2019; 15:73-88.
- Knopman DS, Jones DT, Greicius MD. Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. *Alzheimers Dement*. 2021; 17:696-701.
- Biogen. Aducanumab. (Combined FDA and Applicant PCNS Drugs Advisory Committee Briefing Document). [https://fdareport/media/143503/PCNS-20201106-CombinedFDA Biogen Backgrounder\\_0pdf](https://fdareport/media/143503/PCNS-20201106-CombinedFDA Biogen Backgrounder_0pdf) (accessed June 20, 2021).

12. Alexander GC, Emerson S, Kesselheim AS. Evaluation of aducanumab for Alzheimer disease: Scientific evidence and regulatory review involving efficacy, safety, and futility. *JAMA*. 2021; 325:1717-1718.
13. Cummings J, Lee G, Zhong K, Fonseca J, Taghva K. Alzheimer's disease drug development pipeline: 2021. *Alzheimers Dement (N Y)*. 2021; 7:e12179.
14. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2020. *Alzheimers Dement (N Y)*. 2020; 6:e12050.
15. Alzheimer's disease drug development pipeline: 2019. *Alzheimers Dement (N Y)*. 2019; 5:272-293.
16. Wang X, Sun G, Feng T, *et al*. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. *Cell Res*. 2019; 29:787-803.
17. Montagne A, Nikolakopoulou AM, Huuskonen MT, *et al*. APOE4 accelerates advanced-stage vascular and neurodegenerative disorder in old Alzheimer's mice via cyclophilin A independently of amyloid- $\beta$ . *Nature Aging*. 2021; 1:506-520.
18. Lau SF, Chen C, Fu WY, Qu JY, Cheung TH, Fu AKY, Ip NY. IL-33-PU.1 transcriptome reprogramming drives functional state transition and clearance activity of microglia in Alzheimer's disease. *Cell Rep*. 2020; 31:107530.
19. Lau SF, Cao H, Fu AKY, Ip NY. Single-nucleus transcriptome analysis reveals dysregulation of angiogenic endothelial cells and neuroprotective glia in Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2020; 117:25800-25809.
20. Pluvinage JV, Haney MS, Smith BAH, *et al*. CD22 blockade restores homeostatic microglial phagocytosis in ageing brains. *Nature*. 2019; 568:187-192.
21. Ulland TK, Song WM, Huang SC, *et al*. TREM2 maintains microglial metabolic fitness in Alzheimer's disease. *Cell*. 2017; 170:649-663.e613.
22. PhRMA. Alzheimer's Medicines: Setbacks and Stepping Stones. <https://www.phrma.org/alzheimer-s-medicines-setbacks-and-stepping-stones>. (accessed June 12, 2021).
23. Yu JT, Xu W, Tan CC, *et al*. Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. *J Neurol Neurosurg Psychiatry*. 2020; 91:1201-1209.

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