

Aducanumab for Alzheimer disease: the amyloid hypothesis moves from bench to bedside

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For decades, a battle has raged in the Alzheimer disease (AD) research community. On one side, adherents to the amyloid hypothesis, an evolving body of evidence that abnormal accumulation and aggregation of β -amyloid (A β) peptides (the main component of amyloid plaques) plays a key role in triggering a cascade of pathological events that leads to the clinical syndrome of AD dementia (1). On the other side, opponents contend that amyloid deposition is an epiphenomenon that has distracted the field from the true causes of AD, which remain generally obscure. Nearly indisputable human genetics data, as well as considerable biochemical, histological, and animal model evidence, point to A β as a critical player in AD. Furthermore, brain amyloid can be detected at least 15 years prior to the onset of cognitive symptoms in AD and is associated with substantially increased risk of developing AD dementia in the ensuing decade (2), shaping the concept of a long preclinical or asymptomatic stage of AD (3). Removing amyloid is generally considered a highly promising target for primary and secondary prevention of clinical disease, and the first presymptomatic trials are now ongoing. However, the relationship between amyloid pathology, neurodegeneration, and dementia in AD is complex, as clinico-pathological correlation studies have demonstrated that neither the regional distribution nor the burden of amyloid plaques correlate well with the ante-mortem severity of cognitive deficits nor the amount of postmortem

neuronal loss in AD (4, 5). Thus, the utility of targeting amyloid in symptomatic disease is uncertain. Pharmaceutical companies have doggedly pursued amyloid. Up to now, there have been a myriad of failed clinical trials of anti-amyloid therapies for mild to moderate AD dementia over the past two decades. The failure of these drugs, which include antibodies targeting different forms of A β and inhibitors of enzymes that generate A β (gamma- and beta-secretases), has been crushing to patients, families, researchers, and pharmaceutical companies. These repeated failures have undermined faith in amyloid as a therapeutic target for symptomatic AD, and have fueled skepticism of the amyloid hypothesis in general.

More recently, two major advances have revived the anti-amyloid strategy for symptomatic AD. The first advance was the development of accurate human biomarkers of amyloid deposition, including amyloid positron emission tomography (PET) imaging, cerebrospinal fluid (CSF) A β and tau, and emerging plasma A β and tau measurements, all of which can detect the presence of amyloid plaques and tau pathology in the brain in both preclinical and symptomatic AD. This biomarker revolution has allowed the implementation of clinical trials which can (a) reliably enroll patients with amyloid pathology, (b) enroll patients with very mild symptoms, and (c) monitor target engagement (e.g., brain plaque removal). The second advance was the development of a new

generation of anti-amyloid antibodies, led by Biogen's aducanumab. This new group of antibodies, which also includes Roche's gantenerumab, Biogen/Eisai's lecanemab (aka BAN2401), and Lilly's donanemab, all target aggregated forms of A β (rather than monomeric) and all robustly reduce the burden of existing amyloid plaques in the human brain. Biogen's phase Ib PRIME trial of aducanumab, which enrolled patients with biomarker evidence of amyloid plaques and very mild cognitive symptoms, demonstrated striking dose-dependent removal of amyloid pathology (6). While the study was small and not designed to test for clinical efficacy, patients treated with the highest dose of drug showed less decline in cognitive function than the placebo group. These results created hope that plaque-removing antibodies, if employed correctly, could help in early-stage symptomatic AD. Since then, both lecanemab and donanemab have also demonstrated potent plaque-clearing effects and have shown evidence of modest slowing of cognitive decline in phase II studies of very mild AD (7, 8).

The complicated sequence of events surrounding the phase III trials and eventual approval of aducanumab has been the topic of considerable recent controversy. Briefly, two 18-month phase III studies, ENGAGE and EMERGE, were launched, through which each recruited more than 1600 people with mild cognitive impairment or very mild AD dementia (Clinical Dementia Rating [CDR] of 0.5) and positive amyloid PET scans. Biogen discontinued both trials in March 2019 based on an interim futility analysis, then resubmitted the drug a few months later after additional data accrued. EMERGE had demonstrated robust plaque clearance and a 22% slowing of cognitive decline on its primary endpoint at the highest (10 mg/kg) dose (9). ENGAGE, however, showed no effect on cognition at any

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dose. This conflicting result between the two phase III trials lies at the heart of the controversy over aducanumab.

Biogen presented a possible explanation for this dichotomy: due to an early protocol change, fewer patients in the ENGAGE trial had prolonged exposure to the most efficacious 10 mg/kg dose of the drug. Biogen's post hoc analyses showed that a subset of patients in ENGAGE who received at least 14 consecutive months of high-dose therapy exhibited similar slowing of cognitive decline, as observed in EMERGE (9, 10). However, many experts expressed serious concerns about the validity of these post hoc subgroup analyses. Accordingly, the FDA Peripheral and Central Nervous System Drugs Advisory Committee felt that the conflicted trial data did not meet the standard for approval, with 10 of 11 members voting against approval (the eleventh was "uncertain"). However, the FDA decided to take a broader approach to the data, drawing not only from the data presented by Biogen, but also from previous trials from other anti-amyloid agents, the phase Ib PRIME study data, and in-house analyses to argue that efficacious reduction in amyloid plaques burden was likely to be associated with slowing of clinical decline. The FDA also seemed to acknowledge concerns from patients and advocacy groups that another phase III trial of aducanumab would consume several more precious years. While the FDA did not approve the drug outright, they took a different and surprising track—accelerated approval. They argued that aducanumab was clearly effective at lowering amyloid plaque burden, and that lowering plaque burden was "reasonably likely to predict clinical benefit." This tactic allowed the FDA to make the drug available to patients immediately, while Biogen has nine years to conduct a phase IV study to prove clinical efficacy. This decision showed tacit approval of the amyloid hypothesis, but opponents argue that it sets a troubling precedent that drugs impacting a biomarker without demonstrably changing clinical disease are made available to patients. This decision not only makes aducanumab available now, it also opens the door for other plaque-clearing anti-amyloid antibodies, such as donanemab and lecanemab, to pursue similar accelerated approval with-

out having to first demonstrate clinical efficacy. Thus, the FDA decision transcends the clinical data and expert opinions and ushers in a near future in which multiple plaque-reducing antibody therapies for AD will likely be available, none of which is firmly proven to have clinically meaningful efficacy.

For these reasons, the approval of aducanumab has opened fault lines in the AD research community, which has long debated the veracity of the amyloid hypothesis. In reality, the issue at hand is whether removing amyloid in already symptomatic people can be clinically beneficial, rather than whether the amyloid hypothesis is valid.

It is worth noting that many proponents of the amyloid hypothesis still have strong reservations about aducanumab, and think that its approval was premature and ill-advised. However, some interpret the ambiguous clinical data more generously (as the FDA did), considering the success of EMERGE and PRIME, and drawing inference from other encouraging studies of similar agents (10). Small subgroup analyses from ENGAGE and EMERGE also showed improvement in tau biomarkers, suggesting that plaque removal may impact downstream aspects of AD pathogenesis. Longitudinal studies show that amyloid plaques arise more than a decade before the onset of symptoms and may serve as early instigators of AD pathogenesis, triggering changes in tau and downstream processes that ultimately lead to neurodegeneration (1). However, it is unclear how early amyloid impacts pathogenesis, or how late in the process is too late for amyloid plaque removal to have a clinical effect. The general mantra is "the earlier, the better," and advances in AD biomarkers now allow identification of plaque pathology in asymptomatic humans, in some cases many years before symptom onset. Thus, aducanumab approval may move us closer to the era of preclinical diagnosis and preventative therapy for AD. Indeed, several studies of presymptomatic therapy for AD with anti-amyloid antibodies are currently ongoing. Ultimately, plaque-removing antibodies may find their greatest utility in the prevention of symptomatic AD, rather than the treatment of patients with symptomatic AD dementia. Yet, several chal-

lenges lie ahead in such trials given the absence of additional reliable surrogate markers capable of accurately predicting if and when asymptomatic amyloid-positive individuals will become symptomatic. The approval and use of plaque-removing agents may also accelerate development of combination therapies that may synergize with plaque removal to improve efficacy.

Many other experts, however, take a more sobering view of aducanumab's potential impact. Amyloid opponents believe that no drug targeting amyloid can work, no matter how early it is given, because they argue that amyloid does not play a direct role in AD pathogenesis. Many experts fear that the availability of aducanumab will jeopardize ongoing and future clinical trials of other, potentially more effective AD drugs. Some experts are concerned that patients will be put at unnecessary risk of vasogenic edema or brain microhemorrhages, collectively termed amyloid-related imaging abnormalities (ARIAs), which occurred in 40% of trial participants (though Biogen has reported that 75% of these were asymptomatic; ref. 9). Even if the drug works, the modest slowing of cognitive decline observed in EMERGE may not be clinically meaningful (11) and may not merit the high cost. The Institute for Clinical and Economic Review asked one of its expert panels to consider the aducanumab data and vote on whether there was sufficient evidence of a net benefit of aducanumab. All 15 panelists voted no. Finally, widespread use (or misuse) of the drug could have dire financial consequences for the healthcare system. Aducanumab itself costs \$56,000 per year, plus considerable associated clinical costs. If administered broadly, aducanumab therapy could cost in excess of \$100 billion annually. There is currently no evidence that these drug costs will be offset by future savings. Aducanumab may also exacerbate health disparities. Currently, only wealthy patients can afford the out-of-pocket costs. Even if the Centers for Medicare & Medicaid Services approves the drug, scarce access to dementia experts and the presumed 20% annual drug cost for those with traditional Medicare will likely put aducanumab out of reach of low- and middle-income patients.

Only convincing clinical efficacy data from another large study can put many of

these issues to rest. Even then, the debate may continue. Large clinical effect sizes are needed to reduce costs of AD-related care to make these drugs financially net-positive for a health system. For patients, however, even a modest effect, if it truly exists, may be well worth the cost. In the meantime, clinicians and patients must navigate this complex and difficult environment on their own.

Clinical considerations

From the standpoint of memory care clinicians, aducanumab's approval comes with little information on how to appropriately screen patients and monitor safety. At our specialized memory care centers (Washington University, St. Louis, Missouri, USA, and Massachusetts General Hospital, Boston, Massachusetts, USA), there was consensus that if aducanumab has a clinical effect, it will only be in a select subset of patients who have very mild, biomarker-proven AD, are otherwise healthy, and are not likely to have coexistent neuropathologies. However, as of the writing of this article, it is still unknown whether and how aducanumab will be covered by Medicare and private insurers. Clinicians are scrambling to develop policies and workflows to offer aducanumab to the most appropriate patients and to monitor safety. A few centers have refused to offer the drug at this time. Many centers, including our own, are developing screening and safety monitoring protocols based closely on those used in the ENGAGE and EMERGE trials, and expert guidelines are emerging (12). There is general agreement that patients should have mild cognitive impairment due to AD or very mild AD dementia, have undergone standard screening for reversible causes of dementia, and must have a CDR of 0.5, indicating very mild but consistent cognitive changes. Some centers plan to use psychometric test cutoffs for inclusion, such as scores greater than 20–24 on the Mini Mental Status Examination. Others prefer to avoid hard cutoffs altogether. Our centers will also require biomarker evidence of amyloid plaque pathology, which was not mandated by the FDA. While Biogen required amyloid PET imaging, we will also rely on cerebrospinal fluid and possibly plasma AD biomarkers in the future. Patients must be able to undergo appropriate MRI imag-

ing to exclude mass lesions, acute infarcts, evidence of brain hemorrhage or siderosis, or numerous microhemorrhages. Those on anticoagulants would be ineligible until safety data emerges.

While these criteria may appear straightforward, there is immense clinical “gray area.” Assessment of the degree of impairment is subjective, even with use of tools such as the CDR. Many patients have complex medical histories, coexisting psychiatric disease, or atypical symptoms that may cloud the diagnostic picture. Biomarker studies often give borderline results. Other neurodegenerative diseases can mimic AD or coexist with it. At our centers, patients will be evaluated by experienced dementia experts prior to consideration of treatment, and expert panels will help adjudicate challenging cases. However, this level of expertise and oversight is unlikely to be widely available. Moreover, frank conversations between patient and clinician will be needed to ensure that the best decision is made.

Once a patient decides on aducanumab therapy and meets all criteria, the complexities do not end. Repeated MRI imaging is needed to evaluate for ARIAs, though the exact frequency is still debated and insurance coverage is uncertain. ARIAs are postulated to be triggered by cerebral amyloid angiopathy (CAA), and multiple studies have shown that CAA is an important determinant of AD dementia and may act additively or synergistically with concomitant AD pathology to produce more severe cognitive dysfunction (13). The duration of therapy is also a question. While patients in ENGAGE and EMERGE were treated indefinitely, it may be possible to temporarily suspend therapy once amyloid pathology is decreased below a certain threshold. The details of how or whether this would work and what that threshold might be are still unknown, though this strategy is being evaluated for other anti-plaque drugs (14). It is also unclear at what point the drug should be discontinued as the disease progresses, or whether biomarkers and/or repeated clinical testing should be used to monitor target engagement and clinical response.

The debate over the amyloid hypothesis has now moved from the lab to the clinic, as the era of amyloid plaque-removing agents for AD is upon us. Whether this will

be the first step toward successful treatment and perhaps prevention of AD, or an expensive setback to the field, remains to be seen. The real clinical trial is now taking place in clinics across the nation. We have the opportunity (and the responsibility) to rigorously design and harmonize protocols across institutions that can allow us to clearly answer what has been a pressing question for too long: is amyloid plaque removal from the brain sufficient to provide meaningful clinical benefit to our patients with symptomatic AD? Our commitment should be to continue offering hope and best care to our patients and their families, but hope and care based on solid science.

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1. Musiek ES, Holtzman DM. Three dimensions of the amyloid hypothesis: time, space and ‘wing-men’. *Nat Neurosci*. 2015;18(6):800–806.
2. Donohue MC, et al. Association between elevated brain amyloid and subsequent cognitive decline among cognitively normal persons. *JAMA*. 2017;317(22):2305–2316.
3. Jack CR Jr, et al. NIA-AA research framework: toward a biological definition of Alzheimer’s disease. *Alzheimers Dement*. 2018;14(4):535–562.
4. Arriagada PV, et al. Distribution of Alzheimer-type pathologic changes in nondemented elderly individuals matches the pattern in Alzheimer’s disease. *Neurology*. 1992;42(9):1681–1688.
5. Gómez-Isla T, et al. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer’s disease. *Ann Neurol*. 1997;41(1):17–24.
6. Sevigny J, et al. The antibody aducanumab reduces A β plaques in Alzheimer’s disease. *Nature*. 2016;537(7618):50–56.
7. Swanson CJ, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer’s disease with lecanemab, an anti-A β protofibril antibody. *Alzheimers Res Ther*. 2021;13(1):80.
8. Mintun MA, et al. Donanemab in early Alzheimer’s disease. *N Engl J Med*. 2021;384(18):1691–1704.
9. Haeblerlein SB, et al. Evaluation of aducanumab efficacy in early Alzheimer’s disease. Paper presented at: AD/PD 2021, Virtual Conference; March 9–14, 2021; Virtual. <https://investors.biogen.com/static-files/74641e1b-cd23-495e-8f29-f4ecac0a1126>. 2021. Accessed September 8, 2021.
10. Cummings J, et al. Aducanumab produced a clinically meaningful benefit in association with amyloid lowering. *Alzheimers Res Ther*.

- 2021;13(1):98.
11. Andrews JS, et al. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimers Dement (N Y)*. 2019;5:354-363.
12. Cummings J, Salloway S. Aducanumab: appropriate use recommendations [published online July 27, 2021]. *Alzheimers Dement*. <https://doi.org/10.1002/alz.12444>.
13. Viswanathan A, Greenberg SM. Cerebral amyloid angiopathy in the elderly. *Ann Neurol*. 2011;70(6):871-880.
14. Shugart J. On donanemab, plaques plummet. Off donanemab, they stay away. Paper presented at: Alzheimer's Association International Conference; July 26-30, 2021; Denver, Colorado, USA. <https://www.alzforum.org/news/conference-coverage/donanemab-plaques-plummet-donanemab-they-stay-away>. Accessed September 8, 2021.