Hope or hype? Aducanumab as a magic bullet for Alzheimer’s disease

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Since the first case was reported by Dr. Alois Alzheimer in 1906, Alzheimer’s disease (AD) has become the most reported form of dementia in the aging population worldwide [1]. Despite continuing efforts in basic research and clinical trials, AD remains the most devastating incurable neurodegenerative disorder. On June 7th, 2021, aducanumab (Aduhelm), a monoclonal-antibody-based treatment that decreases amyloid-plaque load in the brains of patients with AD, gained public attention not only because it could have provided the first AD therapeutic in nearly two decades but also because it is the first treatment that directly targets pathological amyloid-beta (Abeta), and effectively removes amyloid plaques and tau tangles in the brains in patients with AD [2]. Is aducanumab a new light at the end of the dark tunnel of AD treatment, or is its approval simply the result of a misinterpretation of clinical data?

Amyloid plaques, the pathological feature of AD

The pathological hallmarks of AD are characterized by progressive accumulation of Abeta plaques in affected brains [3]. Increasing evidence from clinical studies and animal models supports the pathological roles of Abeta in inducing and accelerating neuronal dysfunction, neuroinflammation and cognitive deficits, whereas Abeta-mediated alterations in neuronal activity have also been linked to increased phosphorylation of tau, a major component of the neurofilament tangles found in the diseased brains of patients with AD [3]. Strategies that target and modify the generation or clearance of pathological Abeta peptides, including BACE1 and gamma-secretase inhibitors, which target the production of toxic Abeta, have been shown to be effective in decreasing Abeta load, preventing pathological changes and/or improving cognitive performance in AD animal models [4,5]. These findings have raised hope that AD could eventually be cured by precision strategies targeting the pathological burden of amyloid plaques and neurofibrillary tangles. However, later attempts to translate the success in animal models into clinical trials have continually failed, owing to a lack of cognitive improvement or the manifestation of serious adverse effects in patients with AD, probably as a result of insufficient understanding of the biology of Abeta-processing secretases and their physiological roles in maintaining brain functions in addition to Abeta production [6–9].

Vaccination-based strategy to treat AD through direct Abeta targeting

The concept of using the immune system to clear pathological plaques in the brain was first reported by Schenk et al. in 1999. In that study, Abeta peptide 42 (Abeta42) was used to vaccinate both young (6-week-old) and old (11-month-old) PDAPP mice, a transgenic mouse model showing progressive accumulation of amyloid plaques in the brain as a result of overexpression of human familial APP mutant protein. This Abeta-based vaccination strategy, also called active immunization, significantly decreased cerebral loading of amyloid plaques, dystrophic neurites and astrogliosis in the PDAPP mice [10]. This groundbreaking work provided the first suggestion that targeting of pathological Abeta42 could be used to prevent or treat AD through a vaccination strategy. This simple but powerful idea quickly increased hope in the field. Additionally, the observation of a high titer...
of anti-Abeta42 in Abeta42-vaccinated PDAPP mice, a prerequisite for immune-response-mediated plaque clearance, also suggested the feasibility of an alternative therapeutic strategy through direct treatment with an anti-Abeta antibody (also called passive immunization).

Because the Abeta antibody may react against patients’ own endogenous Abeta peptides and APP proteins, questions and concerns remained regarding possible autoimmune encephalitis after vaccination-based treatment. Indeed, microhemorrhage is evident in AD mice after anti-Abeta immunotherapy treatment [11]. Phase 2 clinical studies have also shown that approximately 6% of Abeta-vaccinated patients develop T-cell-mediated meningeal inflammation; consequently, the studies were terminated early [12]. Nonetheless, post-mortem examination of patients who died years after the Abeta vaccination trial has indicated notable clearance of amyloid plaques and diminished neuritic dystrophy [13], thus supporting the therapeutic potential of Abeta vaccination. Considering both active and passive immunization strategies against Abeta, the advantage of tightly controlled titers and frequencies of monoclonal-antibody administration has gained favorable attention from pharmaceutical companies and has resulted in the development of several recombinant anti-Abeta monoclonal antibodies, as discussed in the next section.

Aducanumab, a recombinant anti-Abeta monoclonal antibody

Since the Food and Drug Administration (FDA) approved memantine in 2003, no new drugs for AD treatment entered the market before aducanumab was approved (Figure 1) [14–23]. Clinically available treatments are mainly designed to attenuate cognitive decline, either with acetylcholinesterase inhibitors such as donepezil, which delays the breakdown of acetylcholine, or N-methyl-D-aspartate receptor antagonists such as memantine, which blocks the receptor’s excitotoxic effects. Aducanumab is a recombinant human IgG monoclonal antibody that binds Abeta oligomers and fibrils with high affinity [24,25]. In passive immunization against Abeta in the brain, the titer of the antibody can be tightly controlled to decrease the risk of meningoencephalitis. Aducanumab has been found to cross the blood-brain barrier in a Tg2576 AD mouse model, probably because of permeability changes resulting from amyloid-related pathology [25]. In this animal model, chronic peripheral administration of aducanumab significantly decreased the plaque load in the brain parenchyma. Support for the therapeutic potential of aducanumab for clinical use was first provided by a phase 1b study in 2016, in which a 54-week treatment with aducanumab dramatically decreased plaque load and slowed cognitive decline in patients with mild cognitive impairment (MCI) and early-stage AD [25]. As a disease-modifying treatment, aducanumab directly targets pathological Abeta and removes amyloid plaques and neurofilament tangles in the brains of patients with AD, as confirmed by two phase 3 clinical trials: ENGAGE and EMERGE.

Almost immediately after the FDA approval of aducanemab, another monoclonal antibody from Biogen, lecanemab, was granted a breakthrough therapy designation by the FDA, through a program designed to expedite the development and review of potential drugs for serious diseases. Lecanemab works similarly to aducanemab by targeting oligomeric and fibrillar types of Abeta, and its phase 2b study in 856 participants with MCI or early-stage AD showed positive results [26]. In this study, a consistent decrease in clinical decline and amyloid pathology was shown after lecanemab treatment at the highest dose (10 mg/kg, the same as the aducanemab dose). Two phase 3 studies are currently

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**Figure 1** Timeline of highlights in the development of Alzheimer’s disease drugs.
underway; one of these studies is exploring preventive treatment with lecanemab in patients with preclinical AD who have elevated levels of amyloid plaques in their brains but are clinically normal. Notably, Amyloid-related imaging abnormalities suggestive of vasogenic edema (ARIA-E) induced by lecanemab were much lower than those induced by aducanumab, a phenomenon suggesting variation in the potential of different anti-Abeta monoclonal antibody treatments to induce ARIA-E. These findings showed promise for improving in antibody-based therapeutic efficacy while decreasing the adverse effects. Notably, patients who received treatment with either antibody and experienced ARIA-E were either mostly (in the aducanemab trial) or all (in the lecanemab trial) carriers of the APOE4 gene variant, thus indicating a possible cross-reaction between monoclonal-antibody-mediated edema and an APOE4 effect [25,26].

Studies of the recently identified lymphatic-meningeal lymphatic system, a waste-transportation pipeline in the brain, have revealed its critical role in decreasing the interstitial Abeta load and neuroinflammation. Improved function of the lymphatic-meningeal lymphatic system has been shown to increase the efficiency of antibody-mediated Abeta clearance in the brain in an AD mouse model [27]. These findings may lead to a new direction in amyloid-based treatment in conjunction with antibody-based therapy, through modification of the waste-drainage system of the diseased brain.

Controversial clinical outcomes for aducanumab

Controversy has emerged from conflicting findings, in which only one of the two phase 3 trials of aducanumab has met its primary efficacy endpoint of the dementia rating score for cognitive performance, i.e., the Clinical Dementia Rating-Sum of Boxes score [28]. Notably, in the trials of aducanemab, although the brain imaging results showed near-complete removal of amyloid plaques in the aducanumab-treated patients, 20 of the 165 enrolled patients dropped out early because of severe adverse events [22]. ARIA-E significantly increased in treated patients in a dose-dependent manner but usually resolved within 4–12 weeks after treatment without hospitalization [22]. The uncertainty regarding the therapeutic benefit of aducanumab for the prevention of cognitive decline has concerned the FDA advisory committee and led to a vote against aducanumab. However, the FDA still made the unusual decision to approve aducanumab through a process called the accelerated approval pathway, because of the unmet need and the agency’s expectation that the clinical benefits of aducanumab might outweigh its risks. Accelerated FDA approval of aducanumab will require subsequent completion of a phase 4 trial evaluating the safety, long-term clinical benefits and real-world effectiveness of the approved 100 mg/ml solution. For such a trial, the FDA usually requires randomization, controls and an acceptable endpoint. However, that endpoint was not specified for aducanumab, and enrolling patients who might be offered a placebo would present clear ethical and logistical challenges. Finally, Biogen has until August, 2022 to finalize the design of the trial, until August 2029 to complete it and another 6 months to report the results.

Immediately after the approval of aducanemab, Biogen designed and announced an observational clinical phase 4 study, called ICARE-AD-US, planned to follow 6,000 people receiving aducanemab for as long as 5 years. The ICARE-AD-US study will include participants from traditionally underrepresented communities, participants with comorbid health conditions, and no placebo or control group. The ICARE-AD-US study will provide important information regarding the safety and effectiveness of aducanemab but is likely to require as long 10 years to complete. However, a recent meta-analysis has concluded that no relationship exists between brain amyloid fibril burden and cognition, thus further calling into question the use of amyloid load to determine the efficacy of aducanumab and other monoclonal antibody-based therapies for AD [29].

Another assessment reported by the Institute for Clinical and Economic Review has concluded that the clinical evidence from both the EMERGE and ENGAGE studies is insufficient to determine the net health benefits of aducanumab in patients with MCI or early-stage AD [30]. Considering the clinical use of aducanumab, the Institute for Clinical and Economic Review has also provided several policy recommendations, including a call for accurate characterization of aducanumab and its potential benefits as slowing of cognitive decline instead of causing cognitive improvement; a suggestion for the FDA to clarify a specified threshold range for amyloid clearance that reasonably provides clinical benefit to patients; and a call for advocates among clinicians and specialty societies to lobby for fair pricing of aducanumab and equitable access to all available treatments for patients with AD.

Alternative strategies targeting tauopathy

Among the non-amyloid-based drugs in development for AD, antibody treatments targeting different domains of monomeric tau and its phosphorylated form, soluble tau oligomers, or neurofibrillary tangles in the brains of patients with AD are currently undergoing preclinical studies or clinical trials [31]. In the normal brain, the cellular function of tau protein is to bind tubulin and promote its polymerization, thus resulting in microtubule formation and stabilization. The tau protein can undergo multiple post-translational modifications, including phosphorylation, ubiquitination, acetylation and glycosylation. The excessive phosphorylation of tau protein results in tau aggregation, which accumulates in paired helical filaments and leads to neurofibrillary tangles, another pathological hallmark found in the brains of patients with AD. Aggregated tau loses its biological function to promote microtubule assembly and stability—a function critical for axonal transport and synaptic signaling in neurons—and thus can lead to neuronal dysfunction and death [32]. Preclinical studies of treatment with monoclonal antibodies against pathological tau protein have shown decreased neuroinflammation and neuronal loss, and functional preservation of spatial memory in human tau transgenic mice, and in mice with vascular dementia that show...
pathological features of tauopathy and cognitive deficits [32]. An active immunization strategy with tau peptide provides an alternative method to produce tau-targeting antibodies whose safety and efficacy have been demonstrated in pre-clinical animal models, but whose potential clinical efficacy and cognitive benefit remain unclear [33].

**Summary**

Although controversial, the approval of aducanumab has been considered a positive sign for AD research. The clinical use of aducanumab and the rapid approval pathway by regulatory agencies such as the FDA have encouraged further investment in developing new therapeutic strategies for AD by pharmaceutical companies. In our opinion, for further evaluation of the success and therapeutic effects of aducanumab or other Abeta monoclonal-antibody-based therapies, the ability for early diagnosis with biomarkers of AD and early intervention in patients who will later develop AD may be key to achieving clinical benefits in terms of preserving cognitive function and mitigating the pathological signs of Abeta. The fight against AD continues with a dim but perhaps slowly brightening light at the end of a long tunnel.

**References**


