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REVIEW ARTICLE

Amyloid-Lowering Monoclonal Antibodies for the Treatment of Early Alzheimer's Disease

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Abstract
Alzheimer's disease (AD) is the leading cause of dementia worldwide. Numerous biomarker studies have clearly demonstrated that AD has a long asymptomatic phase, with the development of pathology occurring at least 2 decades prior to the development of any symptoms. These pathological changes include a stepwise development of amyloid-β (Aβ) plaques, followed by tau neurofibrillary tangles and subsequently extensive neurodegeneration in the brain. In this review, we discuss the first class of drugs intended to be disease modifying to be approved by the US Food and Drug Administration (FDA) for AD—anti-Aβ monoclonal antibodies—and the scientific rationale with which they were developed.

Key Points

Early Alzheimer's disease (AD) is defined as mild cognitive impairment or mild dementia with evidence of elevated brain amyloid.

Anti-amyloid monoclonal antibodies that reduce brain amyloid have demonstrated amyloid-lowering effects and have received accelerated approval by the US Food and Drug Administration.

Appropriate use recommendations have been published to help implement these treatments into clinical care.

1 Introduction

Alzheimer's disease (AD) is a progressive neurologic disease that is the most common cause of dementia. Dementia is one of the top ten leading causes of death globally [1]. Nearly 10 million new dementia cases are diagnosed annually with 55 million known cases worldwide [1]. The prevalence of dementia increases substantially with age; 5.3% of individuals aged 65–74 years old are affected with the disease, in contrast to almost 35% of adults aged 85 years and older [2]. As a result of an aging population, it is expected that the number of people affected by AD will increase to close to 115 million worldwide by 2050 [2]. In addition to the emotional burden to patients, their families, and caregivers, the financial cost of AD in the US was estimated to be more than US$300 billion in 2020 [3]. The FDA has granted accelerated approval for aducanumab and traditional approval for lecanemab, both amyloid-directed monoclonal antibodies, and both members of a new class of disease-modifying treatments for early AD [4]. Another amyloid-lowering monoclonal antibody, donanemab, is in late-stage development and expected to receive approval once phase III results are presented. In this review, we discuss these treatments and the studies supporting their clinical use.

2 Alzheimer's Disease (AD) Continuum

The progression of AD is known to be a continuum that has sequential but overlapping components [5]. While AD is a continuum, staging is necessary to specify disease status and to provide prognosis. Staging also allows for tailored therapies to be used for the appropriate pathological stage. The three main clinical stages of AD are termed preclinical,

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prodromal, and dementia. The preclinical stage of AD is characterized by the absence of any cognitive impairment but with evidence of Aβ pathology present on neuroimaging and cerebrospinal fluid (CSF) biomarkers. Patients enter the prodromal stage of AD once they begin to experience mild cognitive impairment (MCI). The cognitive problems of MCI do not affect activities of daily living (ADLs) at this stage of AD. The last stage, AD dementia, is characterized by impairment across multiple cognitive domains and when functioning is invariably impacted [5].

3 Staging of AD

In 2018, the US National Institute on Aging and the Alzheimer's Association updated their diagnostic recommendations for the three stages of AD into a biologic-based system to more accurately define and stage patients with AD in clinical research [6]. This staging scheme is referred to as the ATN framework—amyloid deposition (A), tau (T), and neurodegeneration (N)—and was created to reflect the understanding that both cognitive decline and the progression of pathology is continuous but can be divided into discrete stages using biomarkers. The ATN classification system has three biomarker categories and eight possible biological combinations. The ATN system classifies an individual patient based on presence of Aβ (in CSF or amyloid positron-emission tomography [PET] [A+/–]), hyperphosphorylated tau species (CSF p-tau or tau PET [T+/–]), and neurodegeneration (on structural MRI, PET, FDG, or CSF total tau [N+/–]) [7]. Certain ATN combinations, such as A+T+N+, A+T-N+, and A+T+N-, have been shown to have more rapid memory decline compared with the other five ATN combinations [8].

3.1 Defining 'Early AD'

The US Food and Drug Administration (FDA) released guidance in 2018 entitled 'Early Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industry', which aids sponsors in developing drugs for earlier stages of AD before the presentation of substantial dementia symptoms [9]. The guidance proposes three stages to classify early AD. In all stages, the patient is required to have the characteristic pathophysiologic changes of AD. In stage 1, patients are asymptomatic with no evidence of clinical impact. In stage 2, there is no functional impairment with slight detectable abnormalities on neuropsychological measures. The emergence of subtle functional impairment indicates a transition to stage 3. Thus, stage 3 manifests detectable abnormalities on neuropsychological measures, and mild functional impairment. The functional impairment in this stage is not severe enough to warrant a diagnosis of overt dementia (considered stage 4 in the guidance) [9]. The FDA also established that endpoints can be considered clinically meaningful and could be utilized when seeking FDA approval for drugs in AD trials [9]. By defining 'early AD', the FDA facilitated drug development to move earlier in the AD continuum by providing a regulatory pathway that allows clinical trials in patients with mild cognitive impairment and mild dementia in whom elevated brain amyloid is confirmed.

3.2 Alzheimer's Disease Pathogenesis

When amyloid precursor protein (APP) is cleaved by secretases, monomers of Aβ are formed. The monomers aggregate into oligomers which can form insoluble protofibrils, fibrils, and, subsequently, plaques [10–12]. Oligomers are soluble, synaptotoxic and can spread throughout the brain following a prion-like pattern [13]. They are associated with an inflammatory response leading to synapse failure and neuronal death. Amyloid plaques accumulate extracellularly and disrupt neurons such that there is neurodegeneration.

Pathogenic mutations in the *APP* gene or *presenilin* genes cause the overproduction of Aβ and early-onset familial AD [14]. In addition, trisomy 21 (Down syndrome) is due to an extra copy of chromosome 21 on which the *APP* gene resides. Individuals with Down syndrome over-produce Aβ and also develop early-onset AD dementia [15]. In sporadic AD, impaired clearance of Aβ is considered to be the main cause for its accumulation in the brain [16]. The amyloid cascade hypothesis has been the leading theory for explaining the etiology and pathogenesis of AD [17]. For these reasons, Aβ has been the main therapeutic target for AD during the past 20 years.

Neurofibrillary tangles (NFTs) are composed of hyperphosphorylated tau protein. Normally, tau protein is synthesized within the neuron and is a major microtubule-binding protein. The mechanism of tau production is not clear, but it is thought to be triggered by deposition of Aβ plaques. Tau pathology, which arises from hyperphosphorylation of the tau protein, results in NFTs within neurons. Presence of NFTs is more proximally related to cognitive decline in AD, which is also accompanied by a number of pathologies including neuroinflammation, oxidative stress, and insulin resistance [18].

4 Rationale for the Amyloid-Lowering Mechanism of Action

Drug development for AD has therefore been focused on the notion that Aβ is the causative agent for most AD pathology, such as NFT formation, vascular damage,

and neurodegeneration [19]. Because of the recognition of Aβ's important role in AD pathogenesis from genetic forms of AD, for the past two decades, AD drug development efforts have focused on disease modification that targets Aβ. Therapeutic strategies aimed at preventing Aβ formation, lowering its soluble levels in the brain, blocking its aggregation into plaques, and disassembling existing Aβ plaques are among the most advanced approaches employed to slow the progression of AD. Immunotherapy, namely passive immunization with monoclonal antibodies, has been the forefront of late-stage drug development (Fig. 1).

Consequently, two amyloid-lowering monoclonal antibodies (aducanumab and lecanemab) have received FDA approval with one more (donanemab) expected to be approved later in 2023.

Aducanumab is a monoclonal antibody to Aβ and was the first drug intended to be disease modifying that was approved by the US FDA to treat early AD. Accelerated approval of aducanumab was based on the results of one of two phase III clinical trials. The accelerated approval pathway allows for clinical use of a drug with effects on a surrogate marker considered reasonably likely to predict clinical benefit and requires additional post-approval studies to confirm clinical benefit. The EMERGE and ENGAGE trials were two phase III, 18-month studies in early AD (prodromal and mild AD). However, both studies were terminated after an interim futility analysis demonstrated that one of the trials (ENGAGE) met futility criteria while the other (EMERGE) was trending positive [20].

While data from the two trials were extracted for futility analysis, participants continued for an additional 3 months before the studies were halted. In the additional data that included these 3 additional months, high-dose aducanumab in the EMERGE study showed benefits in the primary outcome, Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB), slowing cognitive decline by 22%, and in each of the other secondary outcomes, while low-dose aducanumab did not show benefits compared with placebo [20]. No benefits were seen for low-dose or high-dose aducanumab in the ENGAGE study in the larger dataset. In both the EMERGE and ENGAGE trials, Aβ PET imaging showed dose-related reductions in brain Aβ, indicating target engagement.

Although identical in design, the EMERGE and ENGAGE trials differed in the duration of exposure to high-dose aducanumab. The total duration of exposure to high-dose aducanumab was longer in the positive EMERGE study and is thought to have accounted for the divergent outcomes. The US FDA gave accelerated approval to aducanumab based on the surrogate endpoint of reduction of Aβ, which is a measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. The US Centers for Medicare & Medicaid Services (CMS) has currently declined coverage of aducanumab outside of approved clinical trials, resulting in limited clinical access. Nonetheless, approval of aducanumab was a pivotal event in the field of AD therapeutics and has ushered in a new era in AD therapeutics capping nearly 25 years of testing the amyloid hypothesis.

Lecanemab is an Aβ-targeting monoclonal antibody with relative selectivity for the protofibrillar species of Aβ protein. The antibody has also demonstrated Aβ removal and slowing in AD-related cognitive decline correlating with exposure [21]. Lecanemab has completed its phase III trial in early AD (CLARITY AD). Clarity AD was a global confirmatory phase III placebo-controlled, double-blind, parallel-group, randomized study in 1795 people with early AD (lecanemab group: $n = 898$, placebo group: $n = 897$) at 235 sites in North America, Europe, and Asia. The participants were randomized 1:1 to receive either placebo or lecanemab 10-mg/kg intravenously (IV) biweekly, and the randomization was stratified according to clinical subgroup (MCI due to AD or mild AD) and presence or absence of concomitant approved AD symptomatic medication at baseline. Topline results from the phase III trial demonstrated a highly significant slowing of clinical decline as measured by the CDR-SB, with concordant results on all key secondary outcomes [22]. Mean change of CDR-SB from baseline at 18 months as the primary endpoint was 1.21 and 1.66 for lecanemab and placebo groups, respectively. Lecanemab treatment resulted in highly statistically significant results, reducing clinical decline on the global cognitive and functional scale compared with placebo at 18 months by − 0.45 (95% confidence interval [CI] − 0.67 to − 0.23; $p = 0.00005$), representing a 27% slowing of decline. Starting as early as 6 months (difference: – 0.17 [95% CI − 0.29 to − 0.05]; $p < 0.01$), and increasing in absolute difference over time across all time points every 3 months, the treatment showed highly statistically significant changes in CDR-SB from baseline compared with placebo (all p-values are <0.01).

All key secondary endpoints also showed highly statistically significant results compared with placebo ($p < 0.001$). In the amyloid PET sub-study, treatment with lecanemab showed statistically significant reduction in amyloid plaque burden at all timepoints starting at 3 months. Mean change in centiloids at 18 months was − 55.5 and 3.6 for lecanemab and placebo groups, respectively (mean difference: − 59.1 [95% CI − 62.6 to − 55.6]; $p < 0.00001$). Lecanemab slowed decline of cognitive function by 26% on the Alzheimer's Disease Assessment Scale–Cognitive subscale 14 (ADAS-Cog14) at 18 months (mean difference: − 1.44 [95% CI − 2.27 to − 0.61]; $p = 0.00065$). In the AD composite score (ADCOMS) assessment, lecanemab slowed disease progression by 24% at 18 months (mean difference: − 0.050 [95% CI − 0.074 to − 0.027]; $p = 0.00002$). Lecanemab slowed

decline of activities of daily living by 37% on the Alzheimer's Disease Cooperative Study (ADCS) MCI-ADL at 18 months (mean difference: 2.016 [95% CI 1.208–2.823]; $p < 0.00001$). In addition, the primary stratified analysis showed consistent results in CDR-SB, ADAS-Cog14 and ADCS MCI-ADL at 18 months of treatment with lecanemab in all subgroups of disease stage (MCI due to AD or mild AD), ApoE4 status (non-carriers, carriers), presence or absence of concomitant approved AD symptomatic medication, and region (North America, Asia, Europe).

The most common adverse events (>10%) in the lecanemab group were infusion reactions (lecanemab: 26.4%; placebo: 7.4%), amyloid-related imaging abnormalities (ARIA)-H (combined cerebral microhemorrhages, cerebral macrohemorrhages, and superficial siderosis; lecanemab: 17.3%; placebo: 9.0%), ARIA-E (edema/effusion; lecanemab: 12.6%; placebo: 1.7%), headache (lecanemab: 11.1%; placebo: 8.1%), and fall (lecanemab: 10.4%; placebo: 9.6%). Infusion reactions were largely mild to moderate (grade 1–2: 96%) and occurred on the first dose (75%).

During the study period, deaths occurred in 0.7% and 0.8% of participants in the lecanemab and placebo groups, respectively, and no deaths were related to lecanemab or occurred with ARIA in the 18-month double-blind study period. Serious adverse events were experienced by 14.0% of participants in the lecanemab group and 11.3% of participants in the placebo group. The drug received accelerated approval in 2022 and is expected to receive full approval in 2023. Additionally, lecanemab is being studied in even earlier stages of AD, namely preclinical AD as well as pre-preclinical AD, where participants have intermediate elevations in brain Aβ [23].

Donanemab targets the Aβ(p3-42), a N-terminal pyroglutamate Aβ epitope, which is the predominant component among all truncated Aβ species in AD brain. Donanemab is considered to be the most potent amyloid-lowering therapy and rapidly reduces plaque through microglial-mediated phagocytosis [24]. According to results presented at the 2022 Clinical Trials on Alzheimer's Disease (CTAD) conference, donanemab removed four times more plaque than aducanumab in the first 6 months of treatment (CTAD 2022). Thirty-eight percent of people on donanemab fell below the amyloid positivity threshold by 6 months, compared with 2% for aducanumab. A phase Ib trial showed a significant reduction in Aβ plaque that was seen after even a single dose [24]. A phase II trial in patients with early symptomatic Alzheimer's disease who had tau and amyloid deposition on PET was also conducted. Patients were randomly assigned in a 1:1 ratio to receive donanemab (700 mg for the first three doses and 1400 mg thereafter) or placebo intravenously every 4 weeks for up to 72 weeks. The primary outcome was the change from baseline in the score on the Integrated Alzheimer's Disease Rating Scale (iADRS; range 0–144, with lower scores indicating greater cognitive and functional impairment) at 76 weeks. A total of 257 patients were enrolled; 131 were assigned to receive donanemab and 126 to receive placebo. The baseline iADRS score was 106 in both groups. The change from baseline in the iADRS score at 76 weeks was − 6.86 with donanemab and − 10.06 with placebo (difference: 3.20 [95% CI 0.12–6.27]; $p = 0.04$). At 76 weeks, the reductions in the amyloid plaque level and the global tau load were 85.06 centiloids and 0.01 greater, respectively, with donanemab than with placebo. The positive results on its primary cognitive/functional composite outcome was accompanied by a nearly complete clearance of Aβ plaques within 6 months [25]. Neutralizing antibodies are seen with donanemab and will need to be further studied to understand impact on efficacy. The TRAILBLAZER-ALZ-2 phase III trial is determining the safety and efficacy of donanemab in early AD.

5 Amyloid-Related Imaging Abnormalities (ARIA)

Amyloid-related imaging abnormalities (ARIA) are part of AD pathophysiology but also associated with the amyloid-lowering class of therapeutics [26]. There are two types of ARIA: ARIA-E (vasogenic edema) and ARIA-H (microhemorrhages and hemosiderosis), that can occur spontaneously in patients with AD mainly due to the inflammatory response secondary to amyloid angiopathy in the brain [27].

ARIA-H is essentially a small leakage of blood from vessels affected by amyloid angiopathy into the parenchyma tissue. Cerebral amyloid angiopathy (CAA) weakens the endothelia, increasing the risk of micro bleeding [28]. Microhemorrhage is an age-related finding also seen in healthy individuals without amyloid pathology. ARIA, either as part of the natural history of AD or with amyloid immunotherapy, is typically transient and asymptomatic. Symptomatic ARIA can vary in severity and can present with additional symptoms including headaches, dizziness, confusion, visual disturbances, seizures and rarely, death. Management of ARIA depends on symptoms and severity, and it can vary from monthly monitoring with MRI for asymptomatic patients to temporary or permanent suspension of the treatment for moderate to severe ARIA. Preclinical studies have shown that recovery of vessel integrity and perivascular drainage may be possible in patients who continue with treatment, reducing the risk of developing ARIA in later stages of treatment. If neuroinflammation is associated with ARIA, intravenous corticosteroids are used as treatment to reduce ARIA symptoms and severity.

Clinical trials with monoclonal antibody therapies have demonstrated that the risk of developing ARIA-E is usually

seen early in treatment, is higher among apolipoprotein E (APOE) ε4 carriers, and is dose dependent [29]. Participants receiving higher doses present higher risk for develop ARIA-E, especially if participants have shown to have more than four microhemorrhages at baseline. Titration with some of these treatments has been shown to reduce the risk of ARIA [29].

6 Appropriate Use Recommendations

Each of the anti-Aβ monoclonal antibodies has its own safety and efficacy profile despite belonging to the same class (Table 1). Appropriate use guidelines (AURs) have been published for both aducanumab and lecanemab [30, 31]. The guidelines will help integrate these treatments into clinical practice and it is expected that we will gain further understanding of long-term safety and efficacy using real-world data as they enter clinical practice. In addition, the CMS has announced that monoclonal antibody treatments for AD that received traditional approval will receive coverage only if patients are enrolled into a registry that will collect long-term, real-world evidence on safety and efficacy. The AURs advise that all patients considered for therapy meet clinical criteria for MCI due to AD or mild AD dementia and have biomarker confirmation (amyloid PET or CSF) of elevated brain amyloid. In addition, the current AURs advise against treatment with anti-Aβ monoclonal antibodies in patients on anti-coagulation and that patients on anti-Aβ monoclonal antibodies not be treated with acute thrombolytics (see Fig. 1).

The expert panels also recommend performing APOE genotyping and discussion with patients about their APOE status and risk of developing ARIA. The AURs include guidance on surveillance MRIs for ARIA which is similar to that used in the clinical trials. Treating physicians are advised to be vigilant for symptoms of ARIA, obtain an MRI when there is suspicion and, if indicated, hold treatment as per the criteria in the AURs. Understanding the long-term efficacy and safety profile of amyloid-lowering monoclonal antibodies in real-world settings will be critical for successful incorporation into clinical practice.

Table 1 Comparison of amyloid-lowering monoclonal antibodies based on phase III data (except donanemab which currently only has phase II data)

	Aducanumab	Lecanemab	Donanemab
Cognitive slowing on primary outcome measure (%)	22	27	32
Amyloid removal as measured by PET SUVr (%)	70	77	80
ARIA incidence rates (%)	33	13	28

ARIA amyloid-related imaging abnormalities, *PET* positron emission tomography, *SUVr* standardized uptake value ratio

7 Conclusions

Based on the late-stage results, the amyloid-lowering monoclonal antibodies used in the early AD stage of the AD continuum slow cognitive decline by approximately 25–30% over 18 months [20, 22, 25]. They have received US FDA approval and are slowly entering clinical practice. Currently, the Alzheimer's National Registry for Treatment and Diagnostics (ALZ-NET) is collecting long-term

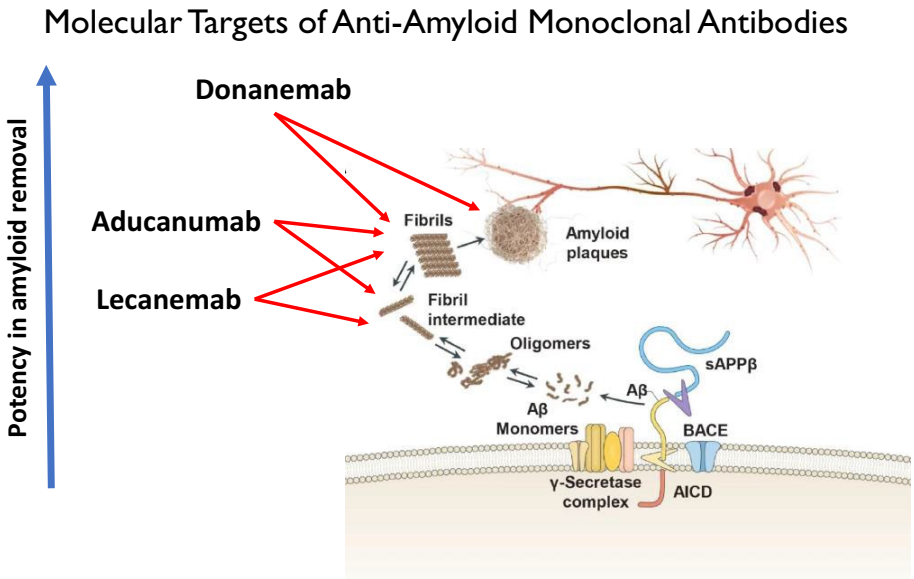

Fig. 1 Molecular targets of the monoclonal antibodies

safety and efficacy data in real-world settings for approved AD therapies including amyloid-lowering monoclonal antibodies (www.ALZ-NET.org). Beyond Aβ as a target, the accumulation of tau aggregates in the brain is a key pathological hallmark of several neurodegenerative diseases including AD. Immunotherapy against pathological tau protein is being considered as a disease-modifying treatment for AD [18]. Given that tau lesions correlate better with the degree of dementia than Aβ plaques do, their clearance may also be clinically more efficacious once Aβ plaques develop. Future studies will likely need to test combinations of anti-Aβ and anti-tau therapies to further treatments for AD.

In this review, we have summarized the rationale and clinical progress with the most advanced therapeutics for early AD, namely amyloid-lowering monoclonal antibodies. Appropriate use recommendations and patient registries will help implementation of this new class of therapies into clinical practice. Work continues towards new options within the amyloid-lowering Aβ class including active vaccination, small molecule amyloid-lowering compounds as well as expansion into anti-tau approaches. Undoubtedly, the approval of amyloid-lowering monoclonal antibodies will mark a new era in AD clinical care. Phase IV studies and patient registries will help us to further understand the long-term safety and efficacy of these promising new treatments and provide for an assessment of clinical meaningfulness in a real-world setting.

Declarations

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Competing Interests Solana Leisher, Adriana Bohorquez, Marcus Gay, Victoria Garcia, Renarda Jones, and Dobri Baldaranov have nothing to disclose. Michael S. Rafii reports consulting for AC Immune, Alzheon, Aptah Bio, Biohaven, Ionis, and Keystone Bio.

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