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Advancements in Alzheimer's Disease Therapy: The Role of Anti-Amyloid Monoclonal Antibodies - A Literature Review

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Abstract

Alzheimer's disease is a neurodegenerative disorder characterized by progressive cognitive decline and neuronal damage. Anti-amyloid monoclonal antibodies such as aducanumab, lecanemab, and donanemab, represent the first disease-modifying therapies for Alzheimer's disease, specifically targeting amyloid-β plaques, a hallmark of the disease. This review examines the pathogenesis of Alzheimer's disease, the mechanism of action of these anti-amyloid therapies, and their potential benefits and associated risks, particularly amyloid-related imaging abnormalities (ARIA). While these therapies have demonstrated statistically significant efficacy in reducing amyloid plaques and decelerating cognitive decline, further research is required to confirm their long-term clinical benefits and establish a precise safety profile. Nonetheless, the approval of these monoclonal antibodies constitutes a significant advancement and potentially heralds the beginning of a new era in the treatment of Alzheimer's disease.

Keywords: Alzheimer's disease, anti-amyloid monoclonal antibodies, aducanumab, lecanemab, donanemab, ARIA

Introduction

Alzheimer's disease (AD) is a progressive brain disorder that leads to damage to the neurons responsible for the proper functioning of the brain. The first symptoms include problems with memory, language, and thinking, and the changes in the brain that cause them may begin as much as 20 years earlier [1].

Dementia represents a major challenge for contemporary medicine, affecting over 55 million people worldwide, with more than 60% living in low- and middle-income countries. Nearly 10 million new cases are diagnosed annually. Alzheimer's disease accounts for approximately 60-70% of cases [2]. It is the seventh leading cause of death and a significant contributor to disability and dependency among older adults. Furthermore, the global economic impact of this condition in 2019 was estimated at US$ 1.3 trillion [2]. AD, being the most common form of dementia, is progressively becoming one of the most expensive, fatal and burdensome diseases of the present era [3]. Patients with Alzheimer's dementia may exhibit changes in their mood, personality, or behavior. One of them is wandering, which can result in severe injuries and, in some cases, even death [1, 4].

Disease-modifying therapies (DMTs), specifically anti-amyloid monoclonal antibodies, appear to offer promising potential for the treatment of Alzheimer's disease [5, 6]. Three of these, aducanumab, lecanemab, and donanemab

had received approval from the FDA [22, 33, 38]. However, currently, only lecanemab and donanemab remain available on the market following the discontinuation of aducanumab, announced in January 2024 [7]. Another drug, remternetug, is presently undergoing evaluation in phase III trial (NCT04451408) [8].

In this review, we briefly describe the pathogenesis of Alzheimer's disease with regard to the mechanism of action of anti-amyloid monoclonal antibodies, present aducanumab, lecanemab, and donanemab, and discuss the potential of these innovative treatments for AD, while acknowledging the risks they may pose.

Pathogenesis of Alzheimer's Disease

Alzheimer's disease is a complex and progressive neurodegenerative disorder characterized by cortical atrophy and a gradual deterioration of cognitive functions, including memory, thinking, and problem-solving abilities. Advanced age is a significant risk factor for AD, likely due to studies showing the accumulation of oxidative damage, which appears to be most pronounced during the early stages of the disease, with a subsequent reduction in its intensity as the disease progresses [9]. AD is characterized by distinct histopathological features, including the extracellular accumulation of amyloid-beta (Aβ) plaques and intracellular aggregation of neurofibrillary tangles (NFTs), composed of hyperphosphorylated tau protein. These pathological features disrupt proper neuronal communication, leading to neuronal degeneration and ultimately contributing to a decline in cognitive function [10, 11]. Remarkably, studies indicate that higher levels of Aβ deposition correlate with a reduction in oxidative damage [9]. Initially, Aβ plaques develop in the basal, temporal, and orbitofrontal regions of the neocortex. As the disease progresses, these plaques spread throughout the neocortex, hippocampus, amygdala, diencephalon, and basal ganglia. In more advanced stages, Aβ deposits are also observed in the mesencephalon, lower brain stem, and cerebellar cortex. The deposition of Aβ triggers the formation of tau tangles, which first appear in the locus coeruleus and transentorhinal and entorhinal areas. As the disease advances, tau tangles extend to the hippocampus and neocortex. Both Aβ plaques and NFTs are considered central to the pathogenesis and progression of AD [10]. Alzheimer's disease is a heritable condition; therefore, genetic risk factors, especially the APOE alleles, play a role in the development of AD [12, 13]. Additional genetic variants linked to Alzheimer's disease include TREM2, CR1, CD33, CLU, BIN1, CD2AP, PILRA, SCIMP, PICALM, SORL1, SPI1, and RIN3 [14].

Further Insights into Amyloid-β in Alzheimer's Disease Pathogenesis

Amyloid-β pathogenesis begins with the abnormal cleavage of amyloid precursor protein (APP) by β-secretases (BACE1) and γ-secretases, producing insoluble Aβ fibrils. These fibrils oligomerize, diffuse into synaptic clefts, and disrupt synaptic signaling, impairing neuronal communication [15, 16]. Aβ aggregates into plaques, which activate kinases, leading to tau protein hyperphosphorylation and the formation of neurofibrillary tangles. The presence of amyloid plaques and tau tangles triggers the recruitment of microglia, activating these cells and initiating a localized inflammatory response that contributes to neurotoxicity. These processes collectively accelerate the neurodegenerative mechanisms observed in Alzheimer's disease [10].

For many years, no disease-modifying therapies were available for AD, until the advent of anti-amyloid monoclonal antibodies targeting amyloid-β accumulation in the brain. These treatments hold the potential to revolutionize current therapeutic approaches and pave the way for new directions in AD management.

Targeting Amyloid-β in Alzheimer's Disease: Mechanism of Action of Anti-Amyloid Monoclonal Antibodies

Although the key pathological features of Alzheimer's disease are well understood, their precise role in disease progression remains unclear. It is uncertain whether the accumulation of Aβ plaques and tau protein is a cause of the disease or rather a consequence of it. However, targeting Aβ accumulation in the brain remains the primary strategy for disease-modifying treatments [17]. The hypothesized mechanism for Aβ plaque reduction by all monoclonal antibodies involves the activation of microglia, which then phagocytose fibrillar Aβ and degrade it through the endosomal/lysosomal pathway [5]. Aβ occurs in several forms, such as monomers, oligomers, protofibrils, and insoluble fibrils within plaques. Studies have shown that oligomers and protofibrils are toxic, and eliminating these aggregates could provide an effective strategy for treating Alzheimer's disease whereas monomeric Aβ demonstrates positive neurological effects [18, 19]. Based on the conducted research, lecanemab and aducanumab exhibited minimal binding to monomers. Notably, lecanemab demonstrated a tenfold higher binding affinity for protofibrils in comparison to fibrils. In contrast, aducanumab showed a clear preference for binding to fibrils over protofibrils [18]. Plaque Aβ, which is the only form of amyloid detectable by amyloid PET, is significantly decreased by all approved monoclonal antibodies. The levels of Aβ in plasma and cerebrospinal fluid (CSF) indicate the presence of monomeric Aβ. However, there is no universally accepted method for measuring protofibrils or oligomers [5].

Aducanumab

Aducanumab (Aduhelm™) is a fully human IgG1 monoclonal antibody with high affinity, targeting a specific conformational epitope present on both soluble oligomers and insoluble fibrils of β-amyloid, which is involved in the pathogenesis of Alzheimer's disease [20]. Based on biochemical and structural analyses, aducanumab binds to a linear epitope composed of amino acids 3–7 of the Aβ peptide in an extended conformation, differentiating it from other antibodies that recognize N-terminal epitopes in Aβ. Weak monovalent affinity, fast binding kinetics, and strong avidity for epitope-rich aggregates are the factors, which enable aducanumab to selectively target pathologic oligomeric and fibrillar forms of Aβ [21].

Aducanumab was granted accelerated approval by the FDA in June 2021, marking it as the first Aβ-targeting monoclonal antibody and the first approved disease-modifying treatment for Alzheimer's disease [22]. Aducanumab was approved for the treatment of AD in patients diagnosed with mild cognitive impairment due to Alzheimer’s disease (MCI-AD) or those who are in the mild dementia stage of the disease [23]. Regarding its off-label use, a month after the FDA's accelerated approval of aducanumab, leaders of the International CAA Association raised significant concerns about its safety and efficacy in patients with cerebral amyloid angiopathy (CAA) [24]. The Appropriate Use Recommendations (AUR) for aducanumab were published in July 2021 to provide comprehensive guidance complementing the package insert. Subsequently, in 2022, these recommendations were updated to refine patient selection, decision-making, and safety monitoring [25, 26].

In an integrated safety data set of 2 phase 3 clinical trials (EMERGE and ENGAGE), which included 3285 participants, 425 patients (41.3%) in the 10 mg/kg aducanumab group (n = 1029) developed amyloid-related imaging abnormalities (ARIA). Specifically, ARIA-edema was observed in 362 patients (35.2%), with 94 of them

(26.0%) experiencing symptoms such as headache, confusion, dizziness, and nausea. Additionally, ARIA-microhemorrhage was found in 197 patients (19.1%), and ARIA–superficial siderosis occurred in 151 patients (14.7%). To summarize, amyloid-related imaging abnormalities were observed in about 40% of participants in the phase 3 clinical trials of aducanumab, with roughly a quarter of these patients presenting symptoms [27].

In January 2024, Biogen announced that Aduhelm would be discontinued by November 2024. Clinical trial participants would have access to the drug until May 1, 2024, while those receiving it via prescription could continue treatment until November 1, 2024 [7]. The company's statement in this case claims that the discontinuation of aducanumab in order to "reprioritize its resources in Alzheimer's disease." This decision was not driven by safety or efficacy concerns [7, 28].

Lecanemab

Lecanemab (Leqembi®) is a humanized monoclonal antibody based on the mouse mAb158 [29], specifically targeting the soluble protofibril form of Aβ protein [5, 30].

The FDA approved lecanemab for the treatment via the Accelerated Approval pathway in January 2023, making it the second of a new category of medications approved for Alzheimer's disease [31], to be initiated in the early stages of the disease, including mild cognitive impairment (MCI) caused by AD or mild AD dementia, with confirmed amyloid pathology in the brain [30-32]. The phase 3 CLARITY trial demonstrated a smaller decline in cognitive function among participants receiving lecanemab compared to the placebo group. The study also revealed a significant reduction in brain amyloid levels over 18 months of lecanemab treatment, along with decreases in cerebrospinal fluid levels of phosphorylated tau and markers of neuroinflammation [30]. All these data contributed to the FDA's decision to convert traditional approval for lecanemab in July 2023, making it the first amyloid beta-directed antibody to be converted from an accelerated approval to a traditional approval for the treatment of AD [30, 33].

The recommended dose of lecanemab in AD is 10 mg/kg given as an intravenous infusion every two weeks [34]. Lecanemab treatment can lead to side effects, such as ARIA and infusion reactions [32]. ARIA includes two types of MRI signal abnormalities: ARIA-E and ARIA-H. The first one, ARIA-oedema/effusion (ARIA-E), refers to the extravasation of fluid resulting in interstitial vasogenic oedema or sulcal effusion in the leptomeningeal/subpial space. The other one, ARIA-haemosiderosis/microhaemorrhages (ARIA-H) refers to microhaemorrhages (mH) or macrohaemorrhages observed as hypointense haemosiderin deposition [35]. Most cases of ARIA associated with lecanemab are asymptomatic, although a small number can be severe or, in rare instances, fatal. Patients on lecanemab may experience microhemorrhages and, less frequently, macrohemorrhages. The use of anticoagulants increases the likelihood of hemorrhages, so the AUR advises against administering lecanemab to patients on anticoagulant therapy until more information on this interaction becomes available [32]. Individuals carrying the APOE ε4 variant (APOE4) are at a markedly higher risk of experiencing ARIA compared to noncarriers [32, 36]. Furthermore, patients with two copies of the APOE4 allele are more likely to develop ARIA than those with only one copy of the allele [30, 36]. Therefore, the AUR recommends APOE genotyping to better assess and communicate the risks to potential lecanemab recipients [32].

Donanemab

Donanemab (Kisunla™) is a monoclonal antibody that specifically targets N-terminal pyroglutamate Aβ, promoting the removal of amyloid deposits [8].

The TRAILBLAZER-ALZ 2 (NCT04437511) study assessed donanemab's efficacy and safety in early symptomatic AD, stratifying participants by tau protein levels. The results demonstrated that donanemab significantly slowed clinical progression at 76 weeks in those with low/medium tau and in the combined low/medium and high tau pathology population [37].

In July 2024, donanemab was approved for use in patients with mild cognitive impairment or mild dementia, the population in which treatment was studied in the clinical trials [38].

Donanemab is available in single dose vials of 350 mg in 20 mL (17.5 mg/mL). The recommended dosage is 700 mg every four weeks for three doses, then 1400 mg every four weeks. Regularly scheduled evaluations for efficacy and safety must be provided. Discontinuation of treatment may be considered if amyloid PET imaging reveals reduction of amyloid plaques to minimal levels [39].

Donanemab and its potential benefits in cerebral amyloid removal and delay in cognitive decline are currently a topic of ongoing discussion. There is a serious concern that the absolute clinical benefits may be minimal and potentially outweighed by associated risks, such as ARIA and accelerated brain volume loss. Therefore, some experts oppose further approvals of anti-AD antibodies until additional research is conducted to clarify the long-term safety and efficacy of these treatments before they are more widely adopted [40].

Discussion

Anti-amyloid monoclonal antibodies are the first disease-modifying treatments for Alzheimer's disease. Examples of such therapies include aducanumab, lecanemab, and donanemab, which differ in their specificity, targeting various forms of amyloid-β such as oligomers, protofibrils, and pyroglutaminated Aβ. By reducing the pathological accumulation of Aβ plaques, these therapies contribute to slowing the progression of the disease. On average, treatment leads to a 25–40% reduction in the progression of cognitive decline, depending on the specific outcomes evaluated in clinical trials [5].

Anti-amyloid monoclonal antibodies are associated with significant adverse effects. The most common of these is ARIA (amyloid-related imaging abnormalities). ARIA can result in serious complications, such as headaches, seizures, and, in rare instances, death. Infusion reactions are also common, and the risk of ARIA is notably higher in patients with the APOE4 genotype, underscoring the need for careful patient selection for treatment. Considering this, clinicians must ensure that patients and caregivers are fully informed about both the benefits and risks of this therapy. Appropriate use recommendations are essential for proper patient selection, optimizing treatment outcomes, and minimizing the risks associated with monoclonal antibody therapy [5, 32].

The administration of monoclonal antibodies necessitates the use of infusion centers, PET imaging or cerebrospinal fluid sampling to evaluate amyloid levels, as well as MRI monitoring for safety, presenting a challenge for contemporary healthcare systems [5]. It is also important to train healthcare professionals, develop policies that enhance access to treatments, and promote public awareness and support for ongoing research on Alzheimer's disease [41].

Currently, many studies are underway targeting various pathological pathways leading to Alzheimer's disease, such as tau pathology and neuroinflammation. Great hope is also placed in the development of therapies targeting APOE [13]. This approach could pave the way for combination therapies [42].

In addition to pharmacological treatments, there is increasing interest in non-drug interventions for managing Alzheimer's disease. These include approaches such as cognitive training, physical activity, and dietary changes, all of which have the potential to improve cognitive function and reduce the risk of decline in older adults [43].

However, anti-Aβ therapies such as aducanumab, lecanemab, and donanemab are currently the subject of ongoing discussion regarding their clinical significance. While these monoclonal antibodies have demonstrated effectiveness in reducing amyloid plaques and slowing cognitive decline, some experts suggest that the overall clinical benefits may be limited and could be overshadowed by potential risks, including ARIA and accelerated brain volume loss. These concerns emphasize the need for further research to better understand the long-term safety and efficacy of these treatments before broader adoption [40]. Future research should prioritize more personalized, biomarker-guided treatments, along with comprehensive monitoring of side effects. Furthermore, there should be a focus on enhancing the diversity and representativeness of participants in clinical trials.

Conclusion

Anti-amyloid monoclonal antibodies represent a groundbreaking development as the first disease-modifying therapies for Alzheimer's disease, with lecanemab and donanemab currently approved by the FDA. The approval of these therapies has marked a new era treatment for AD, offering hope for slowing disease progression. However, these therapies are associated with significant risks, including amyloid-related imaging abnormalities (ARIA), which are particularly highlighted in the boxed warnings in their prescribing information. Clinical trials have demonstrated these antibodies' efficacy in reducing amyloid plaques and slowing cognitive decline, with statistically significant outcomes. Nevertheless, as these therapies become more widely available, questions have arisen regarding their long-term effectiveness and safety.

In summary, while monoclonal antibody therapies offer significant promise for improving the treatment landscape of AD, their clinical adoption necessitates further investigation. Future efforts should focus on enhancing efficacy, safety, and accessibility. Additionally, the integration of pharmacological and non-pharmacological interventions could provide a comprehensive approach to significantly improving the quality of life for AD patients and delaying disease progression.

Disclosure

Author's contribution:

Conceptualization, AS, NR; methodology, AS, NR; software: not applicable; check, BK, AKG, AK; formal analysis, AK, AKG, MK; investigation, BK, WW, MM ; resources: not applicable; data curation: not applicable; writing - rough preparation, AS, NR, AKG, MK; writing - review and editing, MMJ, AK, BK; visualization, AD, MMJ; supervision, AS, NR, AD; project administration, AS; receiving funding: not applicable

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