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Anti-amyloid Monoclonal Antibodies in Alzheimer's Disease: A New Hope

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Abstract
Objectives: The current review aimed to collect the updated clinical investigations of monoclonal antibodies (mAbs) in Alzheimer's disease (AD) patients and assess the feasibility and efficacy of the immunotherapies with mAbs in AD.
Design: A narrative review.
Participants: People with AD.
Outcome measures: The occurrence of AD.
Results: The failure of all attempts to cure AD during the previous decades by focusing on the pathogenic factors revealed that the pathophysiology of AD is multifaceted. In recent years, anti-amyloid mAbs that exhibit beneficial effects in AD treatment have been marketed, and different studies have attempted to assess their effects. We investigated the current research to determine the potential benefits and outcomes of clinical trials of mAbs in AD cases in the review.
Conclusions: This study concentrated on determining how these drugs affect AD pathology. It offers potential support for using anti-amyloid mAb immunotherapy for AD and evaluates the lessons learned from these clinical studies to conduct further research on the beneficial and harmful impacts of these therapeutic agents.
Keywords: Anti-amyloid, Monoclonal antibodies, Alzheimer's disease

Introduction

As a chronic neurodegenerative ailment, Alzheimer's disease (AD) is characterized by cognition impairment, loss of memory, and disruption of synaptic pathways.[1,2] Over one hundred million individuals on the planet by the year 2050, and 10% to 30% of those who are 65 or above will have AD.[3] The disease has a considerable influence on the economy as a global public health crisis.[2,4] The main primary hallmarks of the disease are neurofibrillary tangles and amyloid plaques caused by intracellular tau protein hyperphosphorylation.[5] The amyloidogenic cascade and its peptide byproducts play a significant role in the start of AD.[6] These peptides can accumulate in brain tissue and vasculature, leading to neuronal atrophy.[7] Furthermore, AD development may potentially be influenced by inflammation.[8] Scanty medicines, including non-competitive N-methyl-D-aspartate receptor antagonists and acetylcholinesterase blockers, have been used clinically to treat AD to date.[9] Nevertheless, these medications can only partially relieve symptoms, and they cannot stop the course of AD. According to the amyloid cascade theory, removing brain plaques may treat AD and halt the progression of the illness. This idea has sparked the creation of cutting-edge medications to stop amyloid beta aggregation in neural tissue in recent years. However, earlier attempts to cure AD by focusing on pathogenic amyloid or tau have all failed, suggesting that the disease's pathophysiology is more complicated and multifaceted.[10] Anti-amyloid treatments are currently being discussed. Although the neural system has traditionally been regarded as an immune-privileged location, there are mounting reports suggesting that innate immunity plays a significant role in AD's pathogenesis.[11] Additionally, recent discoveries regarding the pathogenesis and treatment of AD[12] revealed that the brain contains accumulated amyloid and misfolded tau proteins which led to adaptive immune response. These discoveries may open up new treatment options for this disease, including active and passive anti-amyloid immunotherapies that clear brain amyloid deposits.[13] Aducanumab, lecanemab, gantenerumab, solanezumab, and bapineuzumab are only a few anti-amyloid mAbs being researched as a possible treatment for AD.[13] These mAbs distinguish epitopes according to the precise portion and conformations of amyloid, and they differ in their selectivity for polymorphic variants.[14] To reduce

the amount and toxicity of amyloid in the brain, mAbs target amyloid through the different metabolic cascades, removing or preventing the misfolded amyloid.[13] These mAbs identify epitopes according to the amyloid, and they differ in their selectivity for polymorphic variants.[13] Clinical trial results to date seem to support the amyloid theory in the development of AD. However, there were numerous randomized control trial failures in the use of mAbs, leaving open the question of how amyloid-targeting medications may be developed in the future. This study collected the updated clinical investigations of mAbs in AD patients and then assessed the feasibility and efficacy of the immunotherapies with mAbs in AD.

Methods

We used Google Scholar, PubMed, and ClinicalTrials.gov on June 15, 2023, with the combinations of the succeeding keywords such as "monoclonal antibody", "Solanezumab", "Aducanumab", "Alzheimer's", "Lecanemab", "BIIB037", "sporadic", "mild cognitive impairment", and "passive immunotherapy".

Results

By injecting amyloid antigens (active immunization) or anti-amyloid antibodies into the brain of AD patients, immunotherapeutic methods help amyloid be cleared from the brain of AD.[13] Passive anti-amyloid antibody vaccination can improve the clearance of amyloid from the brain and plasma, resulting in a reduction in amyloid burden.[15]

Late-phase trials with most mAbs have yielded disappointing results so far. Notwithstanding the dispute, aducanumab's phase III research indicated somewhat encouraging results,[16] which supports the idea of continuing to explore the anti-amyloid mAbs for the management of AD. Some of the drugs described in this study that help lower brain amyloid levels are still being tested in clinical studies.[17]

Unlike monomers or insoluble fibrils, soluble amyloid-beta protofibrils have been found to be more hazardous to neurons, and lecanemab is a humanized monoclonal antibody that attaches to them with high affinity.[18] In a Bayesian analysis of the 12-month alteration in score from a dose-finding phase 2b trial containing 854 individuals with initial AD, lecanemab, and placebo failed to significantly differ from each other (primary endpoint).[19] Lecanemab, however, was associated with less clinical decline than placebo on several measures, and investigations on 1.5-year-old individuals demonstrated time/dose-dependent amyloid clearance with the medication.[20] Lecanemab was found to be effective when prescribed intravenously (10 mg/kg every two weeks) of amyloid-related imaging abnormalities (ARIAs).[21] Moreover, lecanemab was tested for safety and effectiveness in patients with early AD as part of a phase 3 experiment known as clarity AD.[22] Lecanemab decreased amyloid indicators in early AD, moderately slowed

cognitive and functional decline compared to placebo after 18 months; however, it was also led to negative side effects.[23] Accordingly, lecanemab's efficiency and safety in the treatment of early AD call for longer trials.

Via peptide aggregation separation and fibrillar amyloid clearance, the completely human amyloid immunoglobulin G1 antibody gantenerumab is intended to improve the clearance of amyloid plaques in the neural tissue.[24] The human immunoglobulin G1 backbone stimulates microglial phagocytosis of aggregated amyloid via the Fc gamma receptor.[25] Gantenerumab's capability to attach to amyloid in ex vivo plaques was demonstrated by electron microscopy, and binding to amyloid in the brains of AD patients was exhibited by immunofluorescence staining.[25] Postmortem analysis of AD brain tissue reveals that phagocytosis by the Fc gamma receptor and microglia, after degradation of lysosomes, removes fluorescent-labeled gantenerumab linked to amyloid plaques.[26] The affinity of gantenerumab is highest for aggregated forms of amyloid and soluble oligomers. According to preliminary findings, binding to oligomers takes place and reduces their toxicity.[27] According to the above-mentioned evidence, gantenerumab inhibits the growth of aggregated amyloid and activates microglial phagocytosis, exerting two significant impacts on aggregated amyloid.[25] The effect of gantenerumab AD pathology and neurodegeneration is on amyloid, comprising time/dose-dependant diminutions in total tau levels in cerebrospinal fluid phosphorylated tau and reducing the neurofilament light chain and neurogranin[28,29] (Figure 1).

Human immunoglobulin 1 (IgG1) mAb aducanumab can only target aggregated amyloid such as neuritic amyloid plaques and high molecular weight, but it does not target amyloid monomers.[13] Furthermore, aducanumab exhibits a preference for parenchymal versus vascular amyloid in the brain.[30] Anti-amyloid mAb therapies in AD in vivo models have been highly effective in reducing brain damage and enhancing cognitive abilities through microglial activation and amyloid aggregation prevention.[31] It has been demonstrated that aducanumab has a definite therapeutic effect and completely eradicates amyloid from mouse brain tissue. Transgenic (tg) mice's brains can absorb aducanumab,
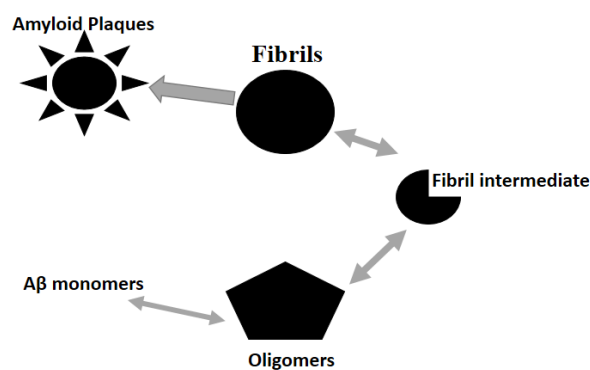
Figure 1. The Amyloid Theory Includes the Aβ Soluble Monomer/Oligomer Aggregation in Insoluble Amyloid Plaques and Fibrils

which binds to parenchymal amyloid and inhibits both soluble and insoluble amyloids.[32] Old tgAPPPS1-21 mice (an experimental model for AD) were given weekly doses of aducanumab (10 mg/kg) for four months, and the results demonstrated that aducanumab clearly reduces amyloid cytotoxicity and improves phagocytosis and cell survival.[13]

The injection of aducanumab combined with an ultrasound animal model of AD can improve cognition because ultrasound scans with intravenously administered microbubbles provisionally breach the blood-brain barrier, allowing aducanumab's access to the brain and increasing brain levels of aducanumab.[33] Aducanumab could reduce amyloid plaque in a concentration-dependent way in Tg2576 mice as an AD model but not in 22-month-old animals, showing that it was more successful at preventing amyloid aggregation than at removing the pre-existing amyloid plaques.[30,34] However, after receiving aducanumab medication, these mice did not exhibit any improvement in their cognition or behavior.[30]

The US Food and Drug Administration (FDA) authorized aducanumab as the first disease-modifying therapy for AD in June 2021.[35] Mild dementia and cognitive impairment were treated with aducanumab, and the positive advance in the synthesis of aducanumab is regarded as groundbreaking progress in the treatment of AD.[36] Aducanumab slows cognitive decline in mild or prodromal AD as judged by the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating-Sum of Boxes (CDR-SB) scores by binding to amyloid plaques and the amyloid-β oligomer and inducing amyloid clearance.[13]

Discussion

Aducanumab medication produced positive results in a phase Ib double-blind, randomized, and placebo-controlled study, and it was found to be beneficial for AD-related mild cognitive impairment (MCI) or mild AD dementia.[13] As a result, phase III clinical studies for aducanumab were initiated in 2015.[37] According to a study containing 196 patients with AD, amyloid plaques reduced and gradually decreased in clinical parameters

in moderate or prodromal AD using aducanumab.[13] Aducanumab also showed considerable efficacy on clinical and biomarker results, a favorable safety and tolerability outline.[38] The negative effect of removing amyloid, known as ARIAs, was dose-dependent in the group receiving aducanumab. Being the most solid genetic risk factor for delayed AD, APOE4 carriers experienced ARIAs more frequently than non-carriers,[39] which was a key safety result and should support the additional use of aducanumab for AD treatment.[40] Recent notable findings from a phase III trial using aducanumab showed the drug's small but highest efficacy, providing crucial amyloid confirmation as a therapeutic target.[41]

In phase Ib, IV, and III studies, aducanumab has been found to be an effective treatment for reducing amyloid plaques which is likely related to the dose and length of treatment.[42] The investigations of 803 patients (Emerge) and 945 patients (Engage) in the 2018 trial were different, and the results were not always consistent.[13] These studies revealed that aducanumab was applied positively in the Emerge group and negatively in the Engage group.[13,43]

Fortunately, several follow-up studies involving the Emerge and Engage groups revealed that aducanumab-treated individuals in the Engage group have a modest drop in the CDR-SB parallel to the Emerge group alterations (Table 1).[13] Although inconsistent results were observed in these investigations regarding cognitive outcomes, the trials demonstrated exceptional dose-dependent amyloid elimination in both treatments (Table 1).[13]

Conclusions

Since 2005, 101 trials examining mAbs in cases with MCI or AD have been registered, and data are accessible from 50 trials comprising about 18 000 people.[48] The results of a recent meta-analysis revealed that there is still uncertainty regarding the risk-benefit sketch of mAbs. Clarifying how amyloid affects cognitive decline, supplying information on treatment response rates, and accounting for small clinically significant differences should be the main goals of future research.

Clarifying whether eliminating the amyloid burden has an impact on the development of cognitive decline should be the main goal of mAb research, along with

Table 1. Clinical Trials of a Immunotherapy for the Treatment of AD

Type of Agent	Period	Main Efficiency Measures	Other Results	References
Bapineuzumab,	78	DAD ADASCog11	DS, NTB, CDR-SB	Vandenberghe et al[44]
Aducanumab,	78	CDR-SB	ADCS-ADL-MC, MMSE, ADAS-Cog	Emerge study[45]
Aducanumab,	78	CDR-SB	ADCS-ADL-MCI, MMSE, ADAS-Cog	Emerge study [45]
Aducanumab,	78	CDR-SB	ADCS-ADL-MCI, MMSE, ADAS-Cog	Engage study[45]
Aducanumab,	78	CDR-SB	ADCS-ADL-MC, MMSE, ADAS-Cog	Engage study[45]
Crenezumab	100	CDR-SB	ADCS- iADL, ADCS-ADL, ADAS-Cog, CDR-GS, MMSE	CREAD1 study [46]
Crenezumab	100	CDR-SB	iADL, ADCS- ADCS-ADL, ADAS-Cog, CDR-GS, MMSE	CREAD2 study [47]

Note. A: Amyloid; AD: Alzheimer's disease; DAD: Disability assessment for dementia; ADAS-Cog: Alzheimer's disease assessment scale-Cognitive subscale; DS: Dependence scale; NTB: Neuropsychological test battery; CDR-SB: Clinical dementia rating-Sum of boxes; ADCS-ADL: Alzheimer's Disease Cooperative Study–Activities of Daily Living; MCI: Mild cognitive impairment; MMSE: Mini-mental state examination; CDR-GS: Clinical dementia rate-Global score; FAQ: Functional activities questionnaire; MMSE: Mini-mental state examination.

providing information on treatment response rates that take the minimal clinically important difference into account. This is especially important given that the target demographic is trending toward those who are at an earlier stage of the disease on the premise that eliminating plaques from a brain that is still largely intact can have a greater clinical impact. Since the implementation of mAbs is still connected with a significantly increased risk of ARIA, even in the most recently developed ones, research on these medications should also concentrate on evaluating the potential long-term effects of ARIA events and looking into potential elements envisaging their commencement.

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The authors declare that there is no conflict of interests.

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