

Effectiveness of Lecanemab on Alzheimer's Disease

Flen John Thomas, Mohammad Aamir Qayyum Sarguroh Khan*, Ramlah Atif Khan, and Sarthak Vasantkumar Patel

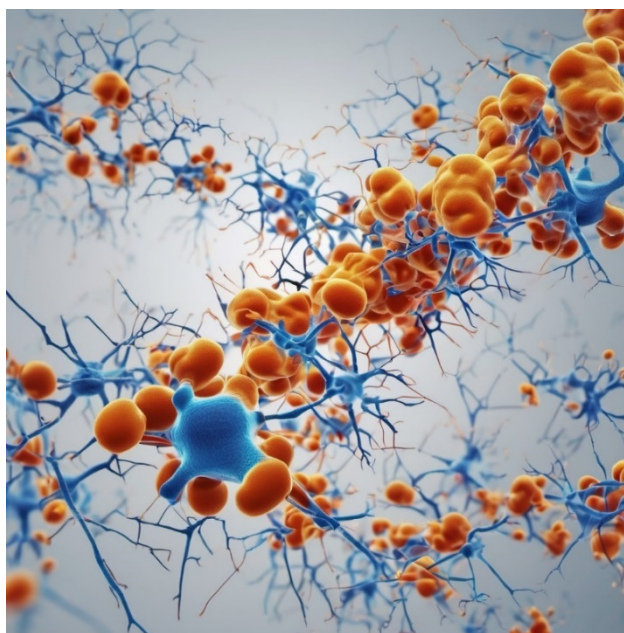
Faculty of Medicine, Ivane Javakhishvili Tbilisi State University

Submitted: October 11, 2023

Accepted: December 28, 2023

Published: January 8, 2024

Graphical Abstract



The presence of P-tau protein, a characteristic feature of Alzheimer's disease, is detected in brain parenchyma.

Abstract

Alzheimer's disease (AD) is a global public health crisis with a significant impact on individuals, families, and societies. Monoclonal antibodies have emerged as a potential disease-modifying therapy targeting amyloid- β ($A\beta$), a hallmark of AD pathology. This study offers a comprehensive overview of the efficacy and safety of lecanemab, a monoclonal antibody, focusing on its binding properties and clinical trial results. Lecanemab's unique binding profile, with a strong affinity for toxic $A\beta$ protofibrils, sets it apart from other monoclonal antibodies. Clinical trials have shown promising results, including reductions in amyloid burden, improvements in cognitive measures, and a reduction in the rate of cognitive decline. However, limitations such as small sample sizes, short-term follow-up, and the exclusion of certain patient groups must be considered. While lecanemab shows potential in slowing the progression of AD, a more extensive study is required to provide robust evidence of its efficacy, especially in diverse patient populations. Adverse effects and long-term safety also warrant further investigation. The results of this study have the potential to inform clinical guidelines and benefit healthcare professionals, caregivers, and researchers in their efforts to improve the treatment of AD. This review is a crucial step in addressing the growing challenge of AD and enhancing the well-being of affected individuals and their families.

Keywords: Alzheimer's disease, monoclonal antibodies, amyloid- β , Lecanemab, efficacy.

* Corresponding author: sargurohaamir01@gmail.com

Purpose, Rationale, and Limitations

This literature review aims to thoroughly evaluate the existing therapeutic options for Alzheimer's disease (AD) by focusing on monoclonal antibodies that target amyloid-beta (A β) plaques. This analysis assesses the effectiveness and safety of various antibodies, emphasizing distinctive features and acknowledging any constraints.

The study provides doctors and healthcare workers with information regarding the potential advantages and disadvantages of monoclonal antibody therapies in AD, assisting in clinical decisions. Moreover, it enhances the existing pool of information by pinpointing areas where research is lacking and influencing the course of future studies, ultimately aiming to advance the development of successful treatments for AD.

Comparison of monoclonal antibodies, such as subclasses of antibodies, differences in epitopes, and mechanisms of action, are beyond the scope of our literature review as we focus on the efficacy and understand the current significant knowledge available for lecanemab.

Introduction

Currently, more than 55 million people live with dementia worldwide, and there are nearly 10 million new cases every year [1]. Dementia results from various diseases and injuries that primarily or secondarily affect the brain. AD is the most common form of dementia, responsible for 60-70% of cases [1]. By 2050, 115 million people could be affected by AD, of which 10-30% would be the population aged 65 years or above. It has become a public health predicament globally, and there is a significant impact on the direct cost of AD to society [2,3].

In 1984, Dr. George Glenner and Dr. Caine Wong identified A β as the major component of the clumps of protein found in cerebral vasculature and brain cortex in patients with AD [4]. Later, in 1991, John Hardy and David Allsopp described the A β hypothesis [5]. They described the mutation that takes place in the A β precursor protein (APP) gene on chromosome 21, which leads to a mismatch between the catabolism and anabolism of the A β protein, resulting in the deposition of an abnormal fibrous protein called senile plaques and neurofibrillary tangle because of abnormal phosphorylation

and ultimately the neuronal death. The catabolism is mediated by apolipoprotein (ApoE), as it plays a crucial role in the clearance and aggregation of A β [6]. ApoE is a crucial cholesterol carrier in the brain, supporting lipid transport and injury repair. Genetic variations in the ApoE gene are the primary determinants of AD risk. The ϵ 4 allele increases the risk of AD, while the ϵ 3 allele is common and has a typical risk, and the ϵ 2 allele decreases the risk. The ApoE ϵ 4 allele is also linked to higher risks of cerebral amyloid angiopathy and age-related cognitive decline in normal aging. ApoEs play a role in delivering lipids to cells and binding to cell-surface receptors and the A β peptide. The interaction with A β is believed to trigger toxic events leading to synaptic dysfunction and neurodegeneration in AD. Different ApoE isoforms have distinct roles in regulating A β aggregation, clearance, and functions in brain lipid transport, glucose metabolism, neuronal signaling, neuroinflammation, and mitochondrial function [7]. The discovery of the presenilin gene in 1995 provided further backing to the amyloid hypothesis, as these genes were linked to the early onset of Inherited AD and are involved in producing A β [8].

Until the year 2002, AD could only be diagnosed with a postmortem examination of brain tissues. The development of Positron emission tomography scans using amyloid-specific tracers allowed for better visualization and quantification of A β deposits in the brains of individuals with AD [4].

The A β peptide, derived from the transmembrane β -APP, exists in two major variants: A β 40 and A β 42. A β 40 is more abundant in cerebrospinal fluid (CSF), while A β 42 is longer, less soluble, and prone to aggregation, forming oligomers, fibrils, and insoluble plaques in the brain. The CSF A β 42/40 ratio and total tau and hyperphosphorylated tau (p-tau) provide a more accurate prediction of AD pathology than individual markers [9].

As we know, AD is characterized by two classic pathological lesions, which are the senile amyloid plaques and neurofibrillary tangles [10]. The monoclonal antibodies target the A β in various forms: monomers, oligomers, protofibrils, and insoluble fibrils in plaques [11]. Among the previously mentioned forms of amyloid, the most toxic are the protofibrils and oligomers [12].

Methodology

The methodology involved a focused literature review, emphasizing AD, A β , and disease-modifying therapies. Specific objectives centered on anti-A β monoclonal antibodies, especially lecanemab. Selection criteria were used to collect relevant studies and trials. Five original studies and one review were considered. Data included study design, sample size, outcomes, and effectiveness. The comparative analysis assessed lecanemab's impact. The data evaluated the efficacy and cognitive outcomes. The review summarized lessons learned and suggested future research. It provided a brief conclusion with evidence-based recommendations. Proper citation and referencing were maintained throughout. The review was edited and structured for submission, adhering to ethical guidelines.

Background

Currently, there is no cure for AD. Therefore, there is an urgent need to find effective treatments that can slow or halt disease progression and improve patient outcomes. Despite the rising prevalence and impending burden of AD around the globe, currently there are only 7 drugs that the Food and Drug Administration (FDA) has approved for clinical practice of which 4 drugs (cholinesterase inhibitors: donepezil [Aricept®], rivastigmine [Exelon®], galantamine [Razadyne®]; glutamate regulators: memantine [Namenda®]) belong to the group of that provide with symptomatic relief in the cognitive domain and brexpiprazole (Rexulti®) an atypical antipsychotic. Of the 2 monoclonal antibodies that provide the disease-modifying treatment that can slow the progression of the disease, lecanemab was granted traditional approval, and aducanumab was granted accelerated approval [13,14]. Currently, FDA-approved drugs have been summarized in Figure 1. At present, there are no therapeutic solutions available that target the ApoE. Developing drugs that target or enhance catabolism could provide better therapeutic results.

The discovery of the protofibril-binding monoclonal antibody lecanemab is groundbreaking compared to other disease-modifying drugs (aducanumab) [15]. As lecanemab was sped through the clinical trials, the long-term effects

of the treatment have not been studied thoroughly, and this review would allow a better evaluation of the efficacy. Also, it must be noted that, to date, the results of clinical trials have been based on the amyloid hypothesis of AD. No study has been conducted to evaluate the effectiveness of lecanemab against the already existing monoclonal antibody treatment. This review would help us identify the impact of dementia and the challenges that will likely be met during AD treatment.

Road to Development of Monoclonal Antibodies

César Milstein and Georges J.F. Köhler, in 1975, first developed the monoclonal antibodies and were awarded the Nobel Prize for the same. The first monoclonal antibody was AN-1792, which involved immunizing patients with synthetic A β to stimulate an immune response and the production of antibodies against A β . However, the trial had to be abruptly stopped as patients developed aseptic meningoencephalitis [16].

The next clinical trial during the development was the ApoE ϵ 4 carrier and non-carrier study, a phase 3 clinical trial testing the efficacy of bapineuzumab. The trial failed to demonstrate any statistically significant difference in efficacy between the placebo and bapineuzumab group and no effect of bapineuzumab on amyloid load or cerebrospinal fluid phosphorylated tau [17].

Doody et al., 2014 conducted two phase 3 trials, EXPEDITION 1 and EXPEDITION 2, enrolling more than 2000 patients diagnosed with mild-to-moderate AD. The main results focused on the alterations in cognitive and functional scores observed across 18 months. Both trials failed to show any substantial enhancement with solanezumab compared to the placebo. The disparities in cognitive and functional scores did not demonstrate statistical significance. The safety investigation revealed similar amyloid-related imaging abnormalities between solanezumab and placebo. Ultimately, solanezumab failed to demonstrate any cognitive or functional advantages in those suffering from AD [18].

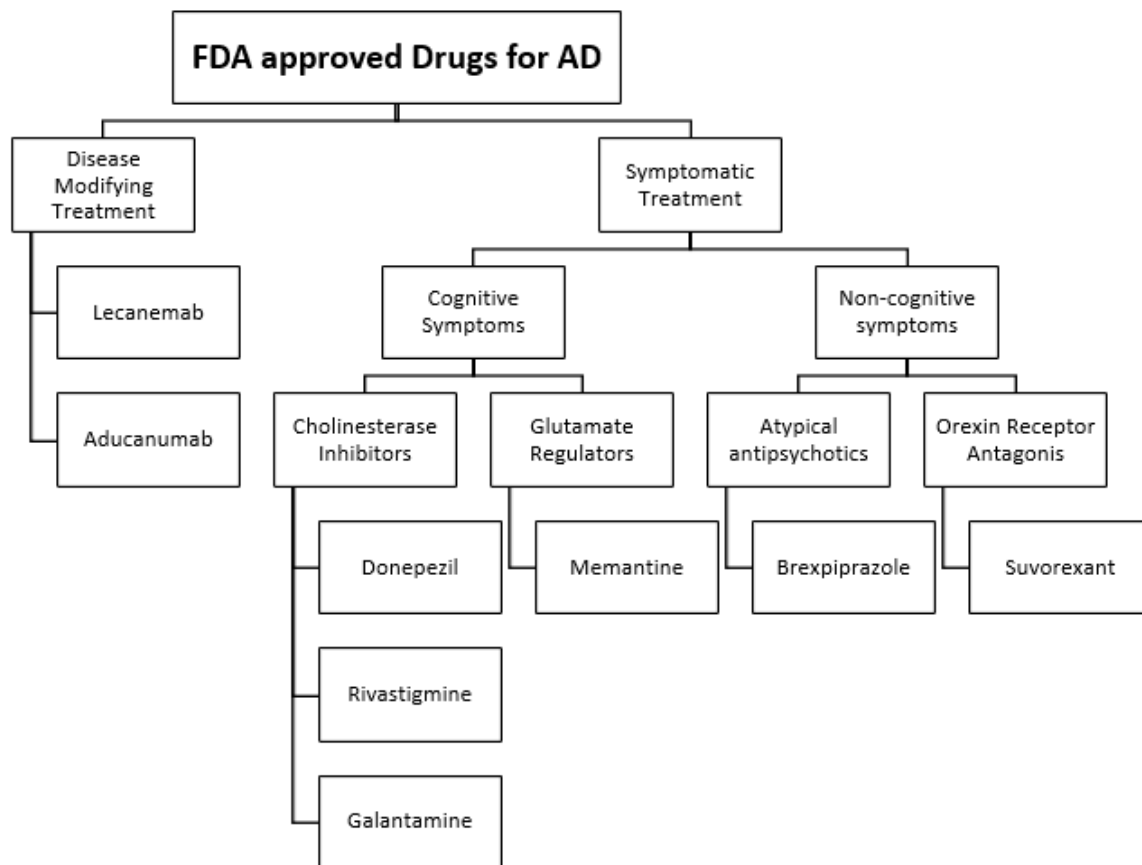


Figure 1. US Food and Drug Administration-approved drugs for the treatment of Alzheimer's Disease.

Ostrowitzki et al., 2022 examined the effects of crenezumab, a humanized monoclonal antibody specifically targeting A β oligomers, in persons with prodromal to moderate AD. The safety and efficacy of crenezumab were assessed in two phase 3 trials, namely CREAD and CREAD2, which included more than 7000 people. The evaluation spanned 100 weeks. The main result of the CREAD research, which measured the change in Clinical Dementia Rating-Sum of Boxes (CDR-SB) score from the beginning to week 105, did not reveal a notable distinction between the placebo and crenezumab groups. The safety investigation did not identify any new signals, and cases of amyloid-related imaging abnormalities with edema were infrequent and of low severity. No significant alterations in AD biomarkers were detected. Both studies were terminated after an interim analysis revealed that CREAD was improbable to achieve the primary objective. Although crenezumab was well-tolerated, it did not effectively decrease the clinical deterioration in persons with early AD [19].

In discussing the previously conducted clinical trials, we finally reached the monoclonal antibodies, which are presently under accelerated approval by the FDA. Aducanumab, another monoclonal antibody designed for humans specifically targeting A β , was assessed in two large-scale Phase-3 trials, EMERGE and ENGAGE, to treat early-stage AD. Despite the original suspension of both studies due to futility analysis, further examination using a more extensive dataset uncovered contrasting results. The high-dose aducanumab group in the EMERGE study showed a significant improvement in the major measure, the Clinical Dementia Rating-Sum-of-Boxes (CDR-SB), compared to the placebo group. However, the ENGAGE study did not achieve its primary (CDR-SB) or secondary (Mini Mental State Examination and ADAS-Cog13) goals. Subsequent analyses of biomarkers (PET-SUVr for amyloid and tau; CSF-A β , p-tau, and t-tau) revealed that the intended target was effectively engaged, and there was a decrease in indicators of AD pathogenesis that was dependent on the dosage in

both trials. Typical adverse outcomes included edema caused by amyloid-related imaging abnormalities. The data demonstrate the inconsistency in the effectiveness of aducanumab across different trials, highlighting the difficulties in creating successful therapies for AD [20].

Role of Lecanemab in AD

Söderberg L, Johannesson M, Nygren P, et al. [15] used inhibition ELISA, immunodepletion, and surface plasmon resonance to characterize the binding properties of lecanemab, aducanumab, and gantenerumab to different A β species. A β exists in various species, including monomers, oligomers, protofibrils, and insoluble fibrils in plaques. Oligomers and protofibrils are toxic, and removing these aggregates might represent an effective treatment for AD. All three monoclonal antibodies bound the monomer with low affinity. However, lecanemab and aducanumab showed weak binding to the monomer, and gantenerumab showed slightly stronger binding. Lecanemab is notable for its 10-fold stronger binding to protofibrils compared to fibrils. This contrasts aducanumab and gantenerumab, which preferred binding to fibrils over protofibrils. The results demonstrated distinct binding profiles of lecanemab, aducanumab, and gantenerumab, which could explain these antibodies' clinical efficacy and side effects.

Swanson CJ, Zhang Y, Dhadda S, et al. [21] conducted a randomized, double-blind clinical trial to compare three doses of lecanemab with placebo across two regimens in early Alzheimer's disease, mild cognitive impairment due to AD and mild AD — a total of 854 randomized subjects received treatment (609 lecanemab, 245 placebo). The primary endpoint was to analyze the 12-month change in Alzheimer's Disease Composite Score (ADCOMS) for the ED90 dose using Bayesian analysis. It aimed for an 80% probability of at least a 25% reduction in clinical decline compared to a placebo. The secondary endpoint included 18-month analyses of brain amyloid reduction, changes in clinical measures, i.e., ADCOMS, CDR-SB (Clinical Dementia Rating-Sum-of-Boxes), ADAS-Cog14 (Alzheimer's Disease Assessment Scale-Cognitive Subscale), alterations in CSF biomarkers, and total hippocampal volume using MRI.

The above study was further complemented by Dhadda S, Kanekiyo M, Li D, et al. [22], who conducted a sensitivity analysis of study 201. The results showed a positive lecanemab treatment outcome on both the primary endpoint (change from baseline in the Alzheimer's Disease Composite Score (ADCOMS) at 12 months with Bayesian analyses) and secondary endpoint (ADCOMS at 18 months and Clinical Dementia Rating-Sum-of-Boxes (CDR-SB) and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog14) at 18 months) with all statistical models taken into consideration.

The study conducted by van Dyck CH, Swanson CJ, Aisen P, et al. [23] was an 18-month, double-blind, phase 3 trial involving individuals aged 50 to 90 with early AD, who showed evidence of amyloid in their brain through PET scans or cerebrospinal fluid tests. They were randomly assigned to receive either lecanemab (10 mg per kilogram of body weight every 2 weeks) or a placebo. The primary goal was to measure the change in their Clinical Dementia Rating-Sum of Boxes (CDR-SB) score at 18 months. Key secondary goals included changes in amyloid levels on PET scans, scores on cognitive tests (ADAS-cog14), a composite Alzheimer's Disease Assessment Score (ADCOMS), and daily living activities (ADCS-MCI-ADL). The mean CDR-SB score at baseline was approximately 3.2 in both groups.

McDade E, Cummings JL, Dhadda S, et al. [24] conducted an OLE (Open-Label Extension) of study 201, which was a double-blind, randomized, placebo-controlled study of 856 patients randomized to one of five dose regimens or placebo initiated to allow patients to receive open-label lecanemab 10 mg/kg once in two weeks for up to 24 months with a gap period of mean 24 months.

Mingchao Shi, Fengna Chu, Feiqi Zhu, et al. [25] reviewed and summarized recent studies on the therapeutic effects and clinical trial results of anti-A β monoclonal antibodies (MABs) in patients with AD. Specifically, they focused on discussing the impact of aducanumab and lecanemab on AD pathology and clinical profiles. The review suggested evidence for immunotherapy with anti-A β MABs in AD.

Table 1. Comprehensive Overview of Studies on Lecanemab in Alzheimer's Disease

Ref.	Study Design	Results and Findings	Safety and Tolerability Findings
[15]	In vitro characterization of lecanemab, aducanumab, and gantenerumab binding to different A β species.	Lecanemab showed 10-fold stronger binding to A β protofibrils compared to fibrils. Distinct binding profiles may explain clinical efficacy and side effects.	No specific safety and tolerability findings were reported in the study.
[21]	A randomized, double-blind clinical trial comparing three doses of lecanemab with placebo in early AD.	10 mg/kg biweekly at 12 months missed the 80% threshold on ADCOMS. At 18 months, lecanemab reduced brain amyloid, with positive support from CSF biomarkers. ADCOMS, ADAS-Cog 14, and CDR-SB favored lecanemab over placebo.	Well-tolerated, with a 9.9% incidence of amyloid-related imaging issues at the 10 mg/kg dose.
[22]	Sensitivity analysis of Study 201.	Positive outcomes for lecanemab on both primary (ADCOMS at 12 months) and secondary endpoints (ADCOMS, CDR-SB, ADAS-Cog14 at 18 months) in Bayesian analyses.	No specific safety and tolerability findings were reported in the provided text.
[23]	18-month, double-blind, phase 3 trial involving individuals aged 50 to 90 with early AD.	Lecanemab reduced cognitive decline (CDR-SB) by 27% compared with placebo. Greater reductions in brain amyloid burden with lecanemab. All key secondary endpoints were met.	Infusion-related reactions were recorded in approximately 1/4th of the participants. Amyloid-related imaging abnormalities were reported.
[24]	OLE of Study 201.	Lecanemab at 10 mg/kg biweekly showed dose-dependent reductions in brain amyloid levels. Treatment benefits persisted for an average of 24 months during the gap.	No specific safety and tolerability findings were reported in the provided text.
[25]	Review summarizing recent studies on anti-A β monoclonal antibodies (mabs) in patients with AD.	Aducanumab and lecanemab showed relatively sound effects in declining brain A β levels and improving cognitive impairment.	No specific safety and tolerability findings were reported in the provided text.

Results

Lecanemab showed the most pronounced preference for soluble A β protofibrils (toxic) versus monomeric and fibrillar forms of A β in comparison to the other two A β antibodies (aducanumab and gantenerumab) investigated in the study. Lecanemab's preferential and strong binding to A β protofibrils may explain the difference in clinical efficacy compared to aducanumab and gantenerumab [15].

In the study by Swanson CJ, Zhang Y, Dhadda S, et al. [21], they found that after 12 months, the 10 mg/kg dose of lecanemab every other week showed a 64% chance of being 25% better than a placebo on ADCOMS, but it missed the 80% threshold. By 18 months, lecanemab reduced brain amyloid and had positive support from CSF biomarkers. ADCOMS, ADAS-Cog 14, and CDR-SB favored lecanemab over placebo at 18 months. Lecanemab was well-tolerated, with a 9.9% incidence of amyloid-related imaging issues at

the 10 mg/kg dose. This was further reinforced by another study's result conducted by Dhadda S, Kanekiyo M, Li D, et al. [22], which showed lecanemab had a 29.7% slower decline than placebo for ADCOMS at 18 months.

Van Dyck CH, Swanson CJ, Aisen P, et al. [23] found that after 18 months of treatment, lecanemab reduced cognitive decline, as measured by the Clinical Dementia Rating-Sum of Boxes (CDR-SB), which quantifies symptom severity across a range of cognitive and functional domains, by 27% compared with placebo—showing a significant difference. In a sub-study involving 698 participants, greater reductions in brain amyloid burden with lecanemab than with placebo was noticed. All key secondary endpoints (as previously mentioned) were assessed to be met. Infusion-related reactions of lecanemab were recorded in approximately 1/4th of the participants, and amyloid-related imaging abnormalities with edema or effusions were also reported.

During the core study conducted by McDade E, Cummings JL, Dhadda S, et al. [24], lecanemab at 10 mg/kg biweekly showed dose-dependent reductions in brain amyloid levels, measured using PET scans, along with corresponding changes in plasma biomarkers and slowdown in cognitive decline at the 12- and 18-month marks. Clinical progression rates during the treatment gap were similar between lecanemab and placebo groups, and the treatment benefits persisted for an average of 24 months. Notably, plasma A β 42/40 ratio and p-tau181 levels returned to pre-randomization levels faster than amyloid PET during this gap. In the OLE, biweekly lecanemab at 10 mg/kg also led to dose-dependent reductions in amyloid PET levels, improvements in the plasma A β 42/40 ratio, and reductions in plasma p-tau181. Moreover, monoclonal antibodies have been proven to be relatively safe in humans, and some of them were proven to have mild-to-moderate effects on declining brain A β levels and improving cognitive impairment. Among them, aducanumab and lecanemab have relatively good effects [25].

Discussion

Lecanemab, a monoclonal antibody designed for treating AD, stands out due to its unique binding profile and strong affinity for toxic A β protofibrils, distinguishing it from other antibodies targeting AD pathology. Encouraging results from clinical trials demonstrate reductions in amyloid burden, cognitive improvements, and a slowdown in the rate of cognitive decline, positioning lecanemab as a potential disease-modifying therapy.

Despite its promise, there are notable considerations. Clinical trials often have limitations, such as small sample sizes and short-term follow-up, impacting the generalizability of results. Additionally, lecanemab is associated with adverse effects, including amyloid-related imaging abnormalities, raising safety concerns. The long-term safety of lecanemab remains uncertain due to expedited approval processes. Moreover, the exclusive focus on reducing beta-amyloid accumulation raises questions about its efficacy in significantly alleviating AD symptoms. Comparative effectiveness studies and the inclusion of diverse patient groups are crucial for a comprehensive understanding of lecanemab's role in AD treatment.

The efficacy of treatment in patients diagnosed with early AD still needs extensive study to show a significant decrease in the progression of symptoms, with beta-amyloid reduction as the primary endpoint and cognitive decline as the secondary endpoint. The strict exclusion criteria in clinical trials present challenges in applying results to patients with comorbidities or diverse demographic backgrounds. Furthermore, the limited discussion of adverse effects associated with lecanemab is essential for a comprehensive evaluation of its safety profile. Addressing these limitations and conducting further research will be crucial to gaining a more comprehensive understanding of the potential of lecanemab and similar treatments in AD management.

Conclusion

The thorough examination of Lecanemab's ability to bind, its effectiveness in clinical settings, and its safety record offers a positive outlook on its potential contribution to the therapy of Alzheimer's disease (AD). Overall, although Lecanemab demonstrates potential in specifically targeting A β protofibrils and producing favorable clinical results, more investigation and a comprehensive evaluation of its safety and long-term efficacy are essential for determining its function in treating Alzheimer's disease. The discourse surrounding Lecanemab highlights the necessity of a well-rounded comprehension of its advantages and possible obstacles to guarantee informed decision-making in treating Alzheimer's disease.

Glossary

Tau: microtubule-associated protein (MAP) that helps stabilize microtubules in neurons.

A β : amyloid β is a naturally occurring byproduct of the metabolism of cells that comes from the APP. It is harmful when it builds up in the brain.

AD: Alzheimer's disease is a degenerative disease that may cause loss of the capacity to respond to the environment and carry on a conversation, starting with minor memory loss.

ADAS-Cog/11: 11-item Alzheimer's Disease Assessment Scale-Cognitive subscale is among the most widely used assessments to gauge cognitive function in clinical trials and research investigations for novel medications and other therapies. Compared to the Mini-Mental State Exam, it is more comprehensive and focuses mostly on memory and language.

ApoE: apolipoprotein E transfers lipids between the body's tissues and cells.

CDR-SOB: Clinical Dementia Rating-Sum of Boxes; Memory, Orientation, Judgement and problem-solving, Community Affairs, Home and Hobbies, and Personal Care are the six areas of cognitive and functional performance relevant to Alzheimer's disease and related dementias. These categories are measured on a 5-point scale.

CSF: cerebrospinal fluid is a plasma ultrafiltrate found in the brain's ventricles as well as the sub-arachnoid spaces of the spine and skull. It carries out essential tasks such as protecting the brain, eliminating waste, and supplying nutrition.

MMSE: Mini-Mental State Examination: This is a series of 11 questions that medical practitioners frequently use to screen for cognitive impairment, which is defined as issues with thinking, speaking, understanding, and remembering.

SUVr is the standardized uptake value ratio, the ratio of the standardized uptake value data from two distinct regions (a target and a reference region) inside the same PET scan.

Conflict of interest

The authors declare no conflict of interest. For a signed statement, please contact the journal office at editor@precisionnanomedicine.com.

Data Availability Statement

The data used in the current study are available from the corresponding author upon reasonable request.

Quote this article as Thomas FJ, Khan MAQS, Khan RA, and Patel SV, Effectiveness of Lecanemab on Alzheimer's Disease, *Precis. Nanomed.* 2023, 7(1):1211-1220, <https://doi.org/10.332/001c.92098>

COPYRIGHT NOTICE ©The Author(s) 2024. This article is distributed under the terms of the [Creative Commons Attribution 4.0 International License](https://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. World Health Organization, Dementia, Newsroom <https://www.who.int/news-room/fact-sheets/detail/dementia>, Accessed: 1/25/2023

2. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer's disease. *Nat Rev Dis Primers*. 2015; 1:15056. Published 2015 Oct 15.
3. Povova J, Ambroz P, Bar M, et al. Epidemiological of and risk factors for Alzheimer's disease: a review. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2012;156(2):108-114
4. Bacskai, B. J., Klunk, W. E., Mathis, C. A., & Hyman, B. T. (2002). Imaging amyloid-beta deposits in vivo. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism*, 22(9), 1035–1041. <https://doi.org/10.1097/00004647-200209000-00001>
5. Hardy, J., & Allsop, D. (1991). Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends in pharmacological sciences*, 12(10), 383–388. [https://doi.org/10.1016/0165-6147\(91\)90609-v](https://doi.org/10.1016/0165-6147(91)90609-v)
6. Wisniewski, T., & Drummond, E. (2020, May 1). APOE-amyloid interaction: Therapeutic targets. *Neurobiology of Disease*. <https://doi.org/10.1016/j.nbd.2020.104784>
7. Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy [published correction appears in *Nat Rev Neurol*. 2013. doi: 10.1038/nrneurol.2013.32. Liu, Chia-Chan [corrected to Liu, Chia-Chen]]. *Nat Rev Neurol*. 2013;9(2):106-118. doi:10.1038/nrneurol.2012.263
8. Campion, D., Flaman, J. M., Brice, A., Hannequin, D., Dubois, B., Martin, C., Moreau, V., Charbonnier, F., Didierjean, O., & Tardieu, S. (1995). Mutations of the presenilin I gene in families with early-onset Alzheimer's disease. *Human molecular genetics*, 4(12), 2373–2377. <https://doi.org/10.1093/hmg/4.12.2373>
9. Andersen E, Casteigne B, Chapman W, et al. Diagnostic biomarkers in Alzheimer's disease. Biomarkers in Neuropsychiatry. doi:10.1016/j.bionps.2021.100041
10. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med*. 2011;1(1): a006189.
11. Walsh DM, Lomakin A, Benedek GB, Condron MM, Teplow DB. Amyloid beta-protein fibrillogenesis. Detection of a protofibrillar intermediate. *J Biol Chem*. 1997;272(35):22364-22372.
12. Johansson AS, Berglind-Dehlin F, Karlsson G, Edwards K, Gellerfors P, Lannfelt L. Physiochemical characterization of the Alzheimer's disease-related peptides A beta 1-42Arctic and A beta 1-42wt. *FEBS J*. 2006;273(12):2618-2630.
13. Monoclonal Antibodies for Alzheimer's Resources. (n.d.). <https://www.aan.com/tools-resources/monoclonal-antibodies-alzheimers>
14. How Is Alzheimer's Disease Treated? (n.d.). National Institute on Aging. <https://www.nia.nih.gov/health/alzheimers-treatment/how-alzheimers-disease-treated#mild>
15. Söderberg L, Johannesson M, Nygren P, et al. Lecanemab, Aducanumab, and Gantenerumab - Binding Profiles to Different Forms of Amyloid-Beta Might Explain Efficacy and Side Effects in Clinical Trials for Alzheimer's Disease [published online ahead of print, 2022 Oct 17]. *Neurotherapeutics*.
16. Gilman, S., Koller, M., Black, R. S., Jenkins, L., Griffith, S. G., Fox, N. C., Eisner, L., Kirby, L., Rovira, M. B., Forette, F., Orgogozo, J. M., & AN1792(QS-21)-201 Study Team (2005). Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. *Neurology*, 64(9), 1553–1562. <https://doi.org/10.1212/01.WNL.0000159740.16984.3C>
17. Vandenberghe, R., Rinne, J. O., Boada, M., Katayama, S., Scheltens, P., Vellas, B., Tuchman, M., Gass, A., Fiebach, J. B., Hill, D., Lobello, K., Li, D., McRae, T., Lucas, P., Evans, I., Booth, K., Luscan, G., Wyman, B. T., Hua, L., Yang, L., ... Bapineuzumab 3000 and 3001 Clinical Study Investigators (2016). Bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, phase 3 trials. *Alzheimer's research & therapy*, 8(1), 18. <https://doi.org/10.1186/s13195-016-0189-7>
18. Doody, R. R. S., Thomas, R. R. G. R., Farlow, M. R., Iwatsubo, T., Vellas, B., Joffe, S., Kieburtz, K., Raman, R., Sun, X., Aisen, P. S., Siemers, E., Liu-Seifert, H., & Mohs, R. C. (2014, January 23). Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease. *The New England Journal of Medicine*. <https://doi.org/10.1056/nejmoa1312889>

19. Ostrowitzki, S., Bittner, T., Sink, K. M., Mackey, H., Rabe, C., Honig, L. S., Cassetta, E., Woodward, M., Boada, M., van Dyck, C. H., Grimmer, T., Selkoe, D. J., Schneider, A., Blondeau, K., Hu, N., Quartino, A., Clayton, D., Dolton, M., Dang, Y., Ostaszewski, B., ... Doody, R. S. (2022). Evaluating the Safety and Efficacy of Crenezumab vs Placebo in Adults with Early Alzheimer Disease: Two Phase 3 Randomized Placebo-Controlled Trials. *JAMA neurology*, 79(11), 1113–1121. <https://doi.org/10.1001/jamaneurol.2022.2909>
20. Budd Haeberlein, S., Aisen, P. S., Barkhof, F., Chalkias, S., Chen, T., Cohen, S., Dent, G., Hansson, O., Harrison, K., von Hehn, C., Iwatsubo, T., Mallinckrodt, C., Mummery, C. J., Muralidharan, K. K., Nestorov, I., Nisenbaum, L., Rajagovindan, R., Skordos, L., Tian, Y., van Dyck, C. H., ... Sandrock, A. (2022). Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. *The journal of prevention of Alzheimer's disease*, 9(2), 197–210. <https://doi.org/10.14283/jpad.2022.30>
21. Swanson CJ, Zhang Y, Dhadda S, 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 [published correction appears in *Alzheimers Res Ther*. 2022 May 21;14(1):70]. *Alzheimers Res Ther*. 2021;13(1):80.
22. Dhadda S, Kanekiyo M, Li D, et al. Consistency of efficacy results across various clinical measures and statistical methods in the lecanemab phase 2 trial of early Alzheimer's disease. *Alzheimers Res Ther*. 2022;14(1):182.
23. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med*. 2023;388(1):9-21
24. McDade E, Cummings JL, Dhadda S, et al. Lecanemab in patients with early Alzheimer's disease: detailed results on biomarker, cognitive, and clinical effects from the randomized and open-label extension of the phase 2 proof-of-concept study. *Alzheimers Res Ther*. 2022;14(1):191.
25. Shi M, Chu F, Zhu F, Zhu J. Impact of Anti-amyloid- β Monoclonal Antibodies on the Pathology and Clinical Profile of Alzheimer's Disease: A Focus on Aducanumab and Lecanemab. *Front Aging Neurosci*. 2022;14:870517. Published 2022 Apr 12. doi:10.3389/fnagi.2022.870517