Lecanemab: A Hopeful Alzheimer's Disease Treatment

Annals of Neurosciences
31(2) 83–85, 2024

DOI: 10.1177/09727531231189925
journals.sagepub.com/home/aon

Zaib Un Nisa Mughal[1], Bisma Ahmed[1], Fatima Amin[1], Aiman Sadiq[1] and Burhanuddin Sohail Rangwala[1]

Introduction

A clinical condition known as dementia is characterized by a continuous decrease in at least two cognitive capacities, such as memory, verbal ability, executive function, spatial ability, personality, and behavior, which impairs the capacity to perform essential and daily tasks. The majority of dementia diagnoses, up to 80%, are due to Alzheimer's disease (AD), making it by far the most frequent cause of dementia.[1] The indicators of AD are amyloid-peptide plaques and neural tangles, which can be seen postmortem or in vivo using biomarkers.[2] Clinical signs of AD include amyloid-beta (Aβ) peptide-containing age-related extracellular plaques and hyperphosphorylated tau protein-containing neurofibrillary tangles intracellularly, cerebral amyloid angiopathy brought on by Aβ deposition on vessel walls, and neuronal death. Critical AD therapy approaches involve lowering Aβ production and removing the buildup of Aβ and hyperphosphorylated tau in the brain. Despite significant advancements in etiology and clinical treatment over the past few decades, it is still unclear what causes AD to start and grow.[3]

Main Text

The most typical AD symptom in an elderly person is a set of subtle, developing memory issues mostly focused on episodic memory. The patient might meet the amnestic-moderate cognitive impairment (MCI) requirements at this point. Then, difficulties with topography, multitasking, and self-confidence loss are frequently observed. Dementia caused by AD can now be identified in a patient when cognitive impairments grow more severe and pervasive and begin to interfere with daily activities. Growing reliance is the norm, and as the condition progresses, behavioral changes, decreased mobility, convulsions, and hallucinations may appear. The average time from presentation to death is 8.5 years.[4]

Only four medications have currently been given the Food and Drug Administration's (FDA) approval for treating AD symptoms. Galantamine, rivastigmine, and donepezil are three of the acetylcholinesterase enzyme (ACHE) inhibitors, and memantine is one of them, which inhibits N-methyl-D-aspartate receptor activity. BACE-1 inhibitors, RAGE inhibitors, PPAR-agonists, and 5HT6 antagonists are some classic treatments for AD. There are many potential mechanisms for Aβ immunotherapy. T-cells are stimulated by active vaccination to generate signaling cytokines that activate B cells. Other immunotherapies include the passive administration of monoclonal antibodies (mAb), such as bapineuzumab, solanezumab, gantenerumab, crenezumab, and tanezumab. Immunotherapies can have serious side effects, such as amyloid-related imaging abnormalities (ARIA), microhemorrhage, and hemosiderosis. Aducanumab is a molecule that attaches to the N-terminus of A3-6. More data is needed to confirm Biogen's Aducanumab results. Immunotherapies are the majority of anti-Tau drugs in clinical trials. To date, phase II has been reached for four anti-tau mAb (Gosuranemab, Tilavonemab, Semorinemab, and Zagotenemab) and one anti-tau vaccination (AADvac1).[5,6]

Lecanemab is a mAb medication that is used to treat Aβ plaques, or more specifically, as an Aβ-targeting antibody to lessen their accumulation. On January 6, 2023, the FDA approved a novel drug, Lecanemab (marketed as Leqembi), with the intention of treating AD. When used in the early stages of the disease, Lecanemab has the potential to slow the patient's cognitive decline. Treatment with Lecanemab minimizes amyloid deposition and improves clinical degradation, according to other studies, such as a randomized, double-blind trial of 854 participants (lecanemab, 609; placebo, 245) with mild dementia, mild cognitive impairment, and AD at the onset. Lecanemab was compared to a placebo in three doses across two regimens using a Bayesian

[1]Department of Medicine, Jinnah Sindh Medical University, Karachi, Sindh, Pakistan

Corresponding author:
Burhanuddin Sohail Rangwala, Department of Medicine, Jinnah Sindh Medical University, Karachi, Sindh 75510, Pakistan.
E-mail: brangwala70@gmail.com

matched-response randomization strategy, according to Swanson et al. The AD Composite Score showed that 64% of participants performed well after receiving the 90% effective dosage of 10 mg/kg twice a week for a period of 12 months, compared to 25% of those who received a placebo. Following 18 months of administration of 10 mg/kg lecanemab twice weekly, there was a decline in brain amyloid proteins.[7]

In March 2019, Biogen applied for clearance based on a *post-hoc* evaluation of the maximum dosage of the drug following the premature termination of two identical trials for the drug due to futility. However, the findings from the other trial's analyses revealed no advantage. One of those evaluations showed that the maximum dose—10 mg/kg—had a statistically substantial positive effect on a number of outcome factors. The majority of these cases were asymptomatic or had minor symptoms, but 1% of them had severe side effects. In 41% of patients, there were imaging defects associated with amyloid, like edema or microhemorrhages (ARIA-E or ARIA-H).[8]

Eisai received the rights to create BAN2401 as a medicinal antibody, and in order to do so, the company partnered with Biogen in March 2014. In this effort, Eisai has support from Biogen. Preclinical data using postmortem brain slices from Down syndrome patients was used to corroborate the findings of ongoing clinical trials for AD.

These studies demonstrated that lecanemab attaches to Aβ deposits under these circumstances. Researchers are currently working on developing a hexavalent antibody based on mAb158 in an attempt to increase the binding strength specifically to Aβ protofibrils.[9]

A parallel-group, 18-month, multicenter, double-blind, placebo-controlled study called Clarity AD included people with early-stage AD. Lecanemab (10 mg/kg every 2 weeks) or a placebo was given intravenously to eligible subjects in a 1:1 ratio. Randomization was stratified by clinical subgroup (mild cognitive deficits caused by AD or mild dementia linked to AD based on the criteria listed below), the presence or absence of concurrently prescribed, FDA-approved medicines (e.g., ACHE inhibitors, memantine, or both) for AD symptoms at the initial state, apolipoprotein E4 (ApoE) carriers or noncarriers, and geographic location. In addition to the plasma biomarker blood test, trial participants had the choice to participate in three different studies that looked at changes over time in amyloid burden in the brain as identified by positron-emission tomography (PET), brain tau pathophysiological characteristics as determined by PET, and biomarkers of AD in the cerebrospinal fluid (CSF).[10]

Conclusion

In conclusion, the available data demonstrate that Lecanemab lowers Aβ plaques, has a high selectivity for Aβ protofibrils, and prevents Aβ deposition in the brain. In clinical trials, it effectively reduced brain amyloid plaques when compared to a placebo, but it was also accompanied by certain negative side effects. Lecanemab is being researched as a promising therapy for AD, but further research is required to determine its effectiveness.

Abbreviations

MCI, Moderate cognitive impairment; FDA, Food and Drug Administration; ACHE, acetylcholinesterase enzyme; NMDA, N-methyl-D-aspartate; mAb, monoclonal antibodies; ARIA, amyloid-related imaging abnormalities; AD, Alzheimer' disease; ApoE, apolipoprotein E; PET, positron-emission tomography; CSF, cerebrospinal fluid.

Authors' Contributions

The conceptualization was done by ZUNM and BSR. The literature and drafting of the manuscript were conducted by ZUNM, BA, FA and AS. The editing and supervision were performed by BSR. All authors have read and agreed to the final version of the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author received no financial support for the research, authorship and/or publication of this article.

ORCID iD

Burhanuddin Sohail Rangwala https://orcid.org/0009-0008-5812-9049

References

1.Crous-Bou M, Minguillón C, Gramunt N, et al. Alzheimer's disease prevention: From risk factors to early intervention. *Alzheimer's Res Ther* 2017; 9: 1–9.

2. Jack Jr CR, Bennett DA, Blennow K, et al. NIA-AA research framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018; 14(4): 535–562.

3.Chételat G. Multimodal neuroimaging in Alzheimer's disease: Early diagnosis, physiopathological mechanisms, and impact of lifestyle. *J Alzheimer's Dis* 2018; 64(s1): S199–S211.

4. Jost BC and Grossberg GT. The natural history of Alzheimer's disease: A brain bank study. *J Am Geriatr Soc* 1995; 43(11): 1248–1255.
5. Vaz M and Silvestre S. Alzheimer's disease: Recent treatment strategies. *Eur J Pharmacol* 2020; 887: 173554.
6. Khan S, Barve KH and Kumar MS. Recent advancements in pathogenesis, diagnostics and treatment of Alzheimer's disease. *Curr Neuropharmacol* 2020; 18(11): 1106–1125.
7. Ailioaie LM, Ailioaie C and Litscher G. Photobiomodulation in Alzheimer's disease—A complementary method to state-of-the-art pharmaceutical formulations and nanomedicine? *Pharmaceutics* 2023; 15(3): 916.
8. Collins TR. Neurologists react to Lecanemab news with swirl of excitement, caution. *Neurology Today* 2022; 22(21): 5–6.
9. Alkhamis ZZ and Alfalasi SA. A new hope in Alzheimer's treatment; Lecanemab. *Int Neuropsychiatr Dis J* 2023; 19(1): 40–45.
10. Van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med* 2023; 388(1): 9–21.