Lecanemab: the game changer in the ongoing fight to treat Alzheimer’s disease?

Qi Qin\textsuperscript{a}, Yi Tang\textsuperscript{b}

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia (Jia \textit{et al.}, 2020). With an estimated 60 million people worldwide affected by dementia, researchers have intensified efforts to develop effective AD treatments. Over the past decades, significant advances have been made in the formulation of AD therapeutic strategies. To date, 143 agents are undergoing 172 clinical trials as potential treatments for AD (Cummings \textit{et al.}, 2022). These agents are divided into cognitive enhancers, drugs targeting neuropsychiatric symptoms and disease-modifying therapies. However, most of these clinical trials failed due to no significant differences between the drug and placebo.

Currently, the United States Food and Drug Administration (FDA) has only approved six drugs for the treatment of AD: three acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine), memantine, aducanumab and lecanemab (Vaz \textit{et al.}, 2022). Among them, acetylcholinesterase inhibitors and memantine provide temporal resolution of symptoms but do not target AD pathological features—amyloid-beta (Aβ) plaques and tau neurofibrillary tangles. Against this background, on January 06, 2023, the FDA approved Leqembi (lecanemab-irmb) via the Accelerated Approval pathway for early AD treatment. Lecanemab is the second disease-modifying medication approved for AD treatment after aducanumab approval. Both aducanumab and lecanemab are monoclonal antibodies specifically targeting brain aggregated Aβ (Tolar \textit{et al.}, 2020). These medications represent an essential advancement in the ongoing fight against AD, but whether lecanemab is a game changer in this endeavor remains to be clarified.

Lecanemab is a humanized IgG1 monoclonal antibody with a high binding affinity to soluble Aβ oligomers and Aβ protofibrils (Soderberg \textit{et al.}, 2022). In experimental animal models, lecanemab not only reduced Aβ aggregates but also prevented Aβ deposition (Tucker \textit{et al.}, 2015). In a phase 1 study, the lecanemab antibody was well tolerated with dose-proportional exposure (Soderberg \textit{et al.}, 2022). Based on these findings, a phase 2b trial was conducted to assess the efficacy of lecanemab in 609 patients with early AD (mild cognitive impairment due to AD and mild AD dementia) (Swanson \textit{et al.}, 2021). They found that biweekly intravenous administration of 10 mg/kg lecanemab was the optimal dose, with a 9.9% incidence of amyloid-related imaging abnormalities (ARIA) with edema or effusions. After 18 months of treatment, lecanemab showed a dose- and time-dependent reduction in brain amyloid accompanied by an improvement in neuropsychological decline. These effects were verified by the reduction in amyloid PET and CSF biomarker analysis. This phase 2b data accelerated the approval of lecanemab and provided support for the design of phase 3 trial (Clarity AD, NCT03887455).
Clarity AD was an 18-month, multicenter, double-blind, placebo-controlled trial that aimed to explore the safety and efficacy of lecanemab in treating patients with early AD (van Dyck et al., 2023). A total of 1795 participants who underwent amyloid PET scans or CSF testing were randomly assigned to receive 10-mg/kg biweekly lecanemab via intravenous infusion. The change from baseline at 18 months in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score, designed as the primary endpoint, was 1.21 for the lecanemab and 1.66 for the placebo. The secondary clinical endpoints showed a similar trend as the immediate endpoint. However, lecanemab resulted in infusion-related reactions in 26.4% of participants and ARIA with edema or effusions in 12.6%, which was higher compared with findings in the phase 2b trial. Furthermore, a phase 3 trial revealed that lecanemab reduced amyloid deposition in early AD and resulted in moderately lower cognition decline, but adverse events accompanied with it.

Although the phase III Clarity AD clinical trial showed good clinical benefits for patients with early AD, several questions remained regarding the true efficacy, clinical relevance, safety, and accessibility of lecanemab. As for efficacy, after 18 months of treatment, lecanemab significantly reduced the CDR-SB score by 0.45 points compared with the placebo. Another study recommended that the minimum clinically significant difference of CDR-SB in early AD patients should exceed 0.98 (Dhadda et al., 2022). A 0.45-point difference might not be clinically meaningful. However, the clinical validation of AD drugs is mainly based on whether they can effectively slow clinical deterioration. The average change in CDR-SB from baseline was only 1.66 points. Still, the difference between the treatment and placebo groups and placebo groups gradually increased over time after the 6-month time-point. This point indicates the clinical significance of 0.45 points.

According to the clinical relevance in Clarity AD, it was found that ApoEε4 homozygous patients showed an unexpectedly slow decline after lecanemab treatment. ApoEε4 homozygous is only a small AD subgroup. Except for the CDR-SB, the homozygous group showed favorable results following lecanemab treatment in other assessments, such as ADAS-cog and ADCS MCI-ADL. Given the facts mentioned above, longer trials and larger samples are warranted to determine the efficacy of lecanemab in the ApoEε4 homozygous subgroup. Currently, open-label trials of lecanemab are ongoing to provide further efficacy data, including a 5-year phase 2 long-term trial (NCT01767311) and a 4-year phase 3 long-term trial (NCT03887455) for patients with early AD.

The debates about the efficacy of lecanemab are also paired with safety questions. The most common side effects of lecanemab were infusion-related reactions (26.4%), ARIA hemorrhages (ARIA-H; 17.3%) and ARIA with edema or effusions (ARIA-E; 12.6%). The symptoms of infusion-related reactions were relatively mild and could be prevented with nonsteroidal anti-inflammatory drugs, glucocorticoids, or antihistamines. Generally, ARIA did not show any symptoms and resolved over time, but some patients showed symptoms such as headache, dizziness, and seizures (Tahami Monfared et al., 2022). All cases with serious ARIA and hemorrhages involved patients receiving anticoagulant medication at the time. It was suspected that lecanemab weakened blood vessels in the brain as it attacked the amyloid plaques, which might have worsened the bleeding. These safety issues suggest that full informed consent and effective safety management are required when applying lecanemab. Patients who may benefit from this drug should be identified to avoid its application to high-risk patients with severe adverse reactions.

Another concern is the accessibility of lecanemab. It was likely to be priced at $26500 per patient per year, which may be difficult for patients in low-income and developing countries. Therefore, some hospitals may restrict the administration of lecanemab to patients due to coverage negotiation issues. The availability of MRI and PET imaging to detect ARIA and determine the lecanemab treatment qualification may also be limiting factors. Many health systems lack the infrastructure to facilitate the widespread application of lecanemab.

Despite these concerns in AD treatment and the existing knowledge gaps in AD pathology, anti-Aβ antibodies have progressed. Several anti-Aβ antibodies, such as aducanumab, bapineuzumab, gantenerumab, solanezumab, and lecanemab, have been developed and undergone clinical trials. Although results from most clinical trials have not been promising, these anti-Aβ antibodies may be an alternative therapeutic option. These antibodies have been proven to be relatively safe in humans. Among them, aducanumab and gantenerumab partially target Aβ oligomers, whereas solanezumab and lecanemab aim to clear insoluble Aβ plaques. Aducanumab
Lecanemab: the game changer in the ongoing fight...

and lecanemab have been demonstrated to exert mild-to-moderate effects in reducing brain Aβ levels and ameliorating cognitive impairment.

In light of the findings discussed here, it is still uncertain whether lecanemab is the game changer in the ongoing fight against Alzheimer’s disease. Longer clinical trials are needed to determine the efficacy and safety of lecanemab in AD patients and accelerate its approval for clinical application. Just like Tacrine, the first cholinesterase inhibitor was associated with significant adverse effects. It is expected to be a potential treatment for AD patients and promotes the development of better cholinesterase inhibitors in the future.

**Conflict of Interest Disclosures**

All authors have no actual or potential competing interests to declare.

**Funding**

This work was supported in part by the National Natural Science Foundation of China (82220108009, 81970996, 82201568), National Key R&D Program of China (2022YFC3602600), STI2030-Major Projects (2021ZD0201801), Young Elite Scientists Sponsorship Program by CAST (2021QNRC001), Projects (2021ZD0201801), Young Elite Scientists of China (2022YFC3602600), STI2030-Major Projects (2021ZD0201801), Young Elite Scientists Sponsorship Program by CAST (2021QNRC001), Beijing Nova Program (Z211100002121051).

**REFERENCES**


