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EDITORIAL

Lecanemab for mild Alzheimer disease – is there a way forward?

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Abstract

This Editorial reviews data on the efficacy and adverse effects of lecanemab amongst individuals with mild Alzheimer disease. Additionally, the recent controversy regarding the rejection by the EMA of a marketing authorization request for lecanemab, followed by its subsequent approval, is also discussed. The need for thoughtful discussions regarding the risks and benefits of this medication as well as the importance of developing Appropriate Use Recommendations and/or national guidelines for the use of lecanemab are also highlighted.

Keywords: β-Amyloid, Alzheimer disease, amyloid-related imaging abnormalities, donanemab, lecanemab, monoclonal antibody.

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Editorial

Available evidence indicates that there are approximately 57 million people worldwide living with dementia, and their number is projected to increase to about 153 million by 2050.[1] Alzheimer disease (AD) is a progressive neurodegenerative disorder that is the most common aetiology for dementia.[2] Presently, there are around 6.9 million people with AD in the USA, and their numbers are expected to increase to 13.8 million by 2060.[3] Between 2000 and 2021, deaths from AD increased by more than 140%, making it the seventh leading cause of death in the USA.[3] In 2024, the overall cost of caring for individuals with AD in the USA was $360 billion.[3]

In the USA, there are currently seven FDA-approved medications available in the market for the treatment of AD.[4] These include the acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine; the N-methyl-D-aspartate receptor antagonist memantine; a combination of donepezil and memantine; lecanemab, a monoclonal antibody that acts against the β-amyloid peptide protofibril; and donanemab, a high-affinity IgG1 monoclonal antibody that binds to the N-terminal truncated form of β-amyloid. Lecanemab had received an initial accelerated FDA approval in January 2023, followed by the traditional approval in July 2023 for the treatment of mild cognitive impairment (MCI) and mild dementia stage of AD.[5] Donanemab received FDA approval for the treatment of MCI and the mild dementia stage of AD in July 2024.[6] Aducanumab received accelerated FDA approval for the treatment of AD in June 2021;[7] however, in January 2024, the drug's manufacturer Biogen decided to discontinue further development and commercialization of the medication, stating their need to reprioritize resources for AD.[8] The FDA approval of these medications remains a landmark in the treatment of individuals with AD given that these were the first three medications to receive FDA approval for AD after almost two decades.[9]

Nevertheless, approval of both aducanumab and lecanemab by the FDA for the treatment of individuals with AD has generated significant controversy. The FDA's use of the 'accelerated approval pathway' to grant approval to aducanumab in addition to its receipt of the 'Fast Track' designation to expedite development of the drug was not well received by many experts,[10] who felt that the evidence for aducanumab benefiting individuals with AD was limited and there were major concerns raised regarding its safety amongst these individuals. Additional concerns were the medication's cost, the possible need for genetic testing prior to its infusion and the need for close monitoring of its adverse effects. Similar concerns were also raised when lecanemab received

the accelerated approval designation from the FDA for the treatment of AD.[11]

Lecanemab is a humanized IgG1 monoclonal antibody that acts against both soluble and insoluble β-amyloid peptide aggregates.[12] Although it has high affinity towards fibrils, protofibrils and oligomers, lecanemab is known to be 1,000 times more selective towards protofibrils than towards monomers.[5] Additionally, lecanemab is the first monoclonal antibody to receive full approval from the FDA for the treatment of AD.

A systematic review and meta-analysis evaluated data from five studies of lecanemab amongst individuals with AD aged between 70 years and 72 years.[13] The doses of lecanemab that were tested amongst these individuals varied between 2.5 mg/kg biweekly, 5.0 mg/kg biweekly, and 10 mg/kg biweekly to 5 mg/kg monthly and 10 mg/kg monthly. The 10 mg/kg biweekly regimen was identified as being the optimal dose for improving cognition amongst individuals with MCI and with mild dementia due to AD. This meta-analysis found that lecanemab was statistically superior to placebo on the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB; mean difference (MD) −0.45, 95% CI −0.64 to −0.2), AD Composite Score (ADCOMS; MD −0.05, 95% CI −0.07 to −0.03), AD Assessment Scale–Cognitive Subscale (ADAS-Cog; MD −1.11, 95% CI −1.64 to −0.57), and the amyloid load in PET scan (MD −60.30, 95% CI −63.41 to −57.19). The investigators noted that the most common adverse events (>10% of individuals) amongst the lecanemab group were infusion-related reactions, the presence of microhaemorrhages from haemosiderin deposits (ARIA-H), oedema (ARIA-E) and headaches when compared with the placebo group. ARIA-E was more common in *ApoE-ε4* carriers, when compared with *ApoE-ε4* homozygous participants. For the ARIA-E, there were a total of 129 events in the lecanemab group, compared with 17 events in the placebo group (risk ratio (RR) 7.97, 95% CI 4.85 to 13.10), with low heterogeneity (I^2 0%). For ARIA-H, there were a total of 165 events in the lecanemab group, compared with 93 events in the placebo group (RR 1.84, 95% CI 1.45 to 2.35), with low heterogeneity (I^2 0%). Of the nine deaths that occurred during the study period, four were thought to be possibly related to the study treatment, with some cases being due to intracerebral haemorrhage.

In a network meta-analysis, the investigators found benefits for lecanemab (MD −2.00, 95% CI −5.25 to 1.26) on the ADAS-Cog when compared with placebo.[14] The surface under the cumulative ranking (SUCRA) curve analysis for lecanemab was 67.3% on the ADAS-Cog. On CDR-SB, benefits were noted for lecanemab (MD −3.11, 95% CI −5.23 to −0.99) when compared with placebo. The SUCRA value showed that lecanemab (98.1%) was the best treatment to reduce the CDR-SB score and was associated with the maximum benefit on the CDR-SB score based on cumulative probability. However, on the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale, the investigators did not find benefits for lecanemab when compared with placebo (MD 0.47, 95% CI −0.80 to 1.73). An earlier meta-analysis had also noted similar results, where lecanemab was found to be more effective than placebo on the CDR-SB,[15] yet it was found to be significantly less acceptable and tolerable when compared with placebo.

In a paper that assessed the updated safety results from a phase III lecanemab study amongst individuals with early AD, the investigators included data from 1,795 participants from the Clarity AD (Core study) and 1,612 participants with at least one dose of lecanemab from the Core study plus the open-label extension phase.[16] In the Core plus open-label extension study, the most common adverse events in the lecanemab group (>10%) were infusion-related reactions (24.5%), followed by ARIA-H microhaemorrhages (16.0%), COVID-19 (14.7%), ARIA-E (13.6%) and headache (10.3%). ARIA-E and ARIA-H were radiographically noted to be mild to moderate. ARIA-E generally occurred within 3–6 months of treatment, was more common amongst *ApoE-ε4* carriers (16.8%) and was most common in *ApoE-ε4* homozygous participants (34.5%).

There are numerous challenges associated with individuals having AD receiving lecanemab infusions.[17] These include (1) a lack of clarity amongst patients, their caregivers, and healthcare providers on which patients are eligible for receiving lecanemab infusions, resulting in delays, and with patients requiring referral to specialized centres to access treatment; (2) limited numbers of specialized centres providing lecanemab infusions; (3) the need for genetic testing before receiving lecanemab infusions to identify individuals with *ApoE-ε4* genotype; (4) the cost of treatment, including the price of medication (US$26,500/year) plus infusion and monitoring costs; (5) time commitments for infusions including 1 hour for receiving the drug and up to 4 hours of observation period to monitor for adverse effects; and (5) the possibility of individuals from diverse racial and ethnic backgrounds being specifically excluded from receiving the treatment due to various social determinants of health.

Appropriate Use Recommendations for lecanemab state that an amyloid PET scan should be conducted prior to infusion of lecanemab to demonstrate the presence of the amyloid deposits in the brain.[18] Additionally, non-contrast MRI and diffusion-weighted imaging should be conducted to confirm whether the person is a candidate to receive lecanemab infusions by ruling out the presence of macrohaemorrhages and/or

microhaemorrhages, superficial siderosis, vasogenic oedema, or any major vascular event, including strokes. As ARIAs are the principal adverse effects of lecanemab infusions, it is recommended that MRIs should be obtained after the 5th, 7th and 14th infusions. Additionally, it is recommended to have an additional MRI scan at week 52 prior to the 26th infusion, especially amongst participants who are *ApoE-ε4* carriers and amongst individuals who had evidence for ARIAs on earlier MRI scans. Safety MRI scans are recommended for people who present with potential symptoms of ARIA, including nausea, dizziness, headache, confusion, visual changes and gait abnormalities. Serious symptoms include seizures, encephalopathy, stupor and focal neurological deficits. A vast majority (81%) of the ARIAs resolve spontaneously within 4 months. For serious symptoms, the infusions of lecanemab may need to be discontinued and the patient will need close monitoring by their team of physicians. The detection and management of adverse effects of lecanemab require specialized centres that are knowledgeable about ARIAs, have equipment, including MRI scanners, to identify and monitor the ARIAs, and have trained neurologists to manage these symptoms. As individuals who are *ApoE-ε4* carriers, especially those who are homozygotes, are at greater risk for developing ARIAs, symptomatic ARIAs and recurrent ARIAs, the Appropriate Use Recommendations state the need for *ApoE-ε* genotyping before starting therapy with lecanemab.[18] The FDA has also issued a 'black-box' or 'boxed' warning for lecanemab due to the possibility of occurrence of ARIAs amongst individuals with AD who receive these infusions.[19] They also recommend genetic testing and clear communication of risks (counselling) with the patient and their families prior to treatment initiation.

A valid question that is often raised when discussing the benefits of medications like lecanemab is whether there are any meaningful clinical benefits to using these drugs amongst individuals with AD. In their review, Jin and Noble opined that the results show that lecanemab reduces cognitive decline by 27% and provides an approximate 6-month delay in disease progression.[20] Although modest, these figures should be evaluated in the context of the realities of conducting long-term pharmacotherapeutic trials in chronic diseases and the need for developing a standard expectation for meaningful outcomes for these diseases, against which all future trial responses can be evaluated.[20] These medications may represent a breakthrough in AD treatment and care.

One study estimated the potential value-based price of lecanemab plus standard of care (SoC) when compared with SoC alone using a broad range of willingness-to-pay thresholds in the USA.[21] The authors found that lecanemab plus SoC was predicted to result in a gain of 0.61 quality-adjusted life-years (societal, 0.64) and a decrease of US$8,707 in total non-treatment costs (societal, US$11,214) when compared with SoC alone amongst individuals with early AD. For a willingness-to-pay threshold from US$50,000 to US$200,000 per quality-adjusted life-year gained, the potential annual value-based price of lecanemab was estimated to range from US$9,249 (societal, US$10,400) to US$35,605 (societal, US$38,053).

The decision by the US Centers for Medicare & Medicaid Services to provide coverage for lecanemab amongst individuals with AD is a welcome step in the right direction.[22] To receive Medicare coverage, individuals will need to be (1) enrolled in Medicare, (2) diagnosed with MCI or mild dementia due to AD and have documented evidence of β-amyloid plaque on the brain, and (3) have a physician who participates in a qualifying registry, with an appropriate clinical team and follow-up care being available. Despite the above coverage by the US Centers for Medicare & Medicaid Services in the USA and it is license in the UK, the National Institute for Health and Care Excellence (NICE) has recommended that lecanemab should not be made available on the National Health Service.[23] The NICE Independent Committee felt that the overall cost of the treatment, when combined with its relatively small clinical benefits, indicated that it was not a cost-effective treatment for the National Health Service to consider.[23]

The news in July 2024 that the EMA had rejected a marketing authorization request for lecanemab was seen as a setback for the marketing of the drug.[24] The EMA's Committee for Medicinal Products for Human Use (CHMP) recommended not granting a marketing authorization for lecanemab,[25] stating that the "observed effect of lecanemab on delaying cognitive decline did not counterbalance the risk of serious side events associated with the medicine, in particular the frequent occurrence of amyloid-related imaging abnormalities (ARIA)". However, after re-examining its initial opinion, in November 2024, the CHMP recommended granting a marketing authorization to lecanemab for the treatment of MCI or mild dementia due to AD (early AD) amongst individuals who have only one or no copy of *ApoE-ε4*, as these individuals are less likely to experience ARIA.[26] The CHMP concluded that, in the restricted population that was assessed in the re-examination, the benefits of lecanemab in slowing down progression of symptoms of the AD outweighed its risks.

Lecanemab is currently approved in the USA, Japan, China, South Korea, Hong Kong, Israel, United Arab Emirates and the UK.[27] It is presently being marketed in the USA, Japan and China. The Therapeutic Goods Administration of Australia had made an initial decision not to register lecanemab for the treatment of patients with MCI due to AD and mild AD dementia.[27] Eisai Co., Ltd., the

manufacturer of lecanemab, has decided to request a reconsideration of this decision under Section 60 of the Therapeutic Goods Act of Australia.[27]

Although many additional steps are still needed before lecanemab can be made available for routine use amongst individuals with mild AD, the development of Appropriate Use Recommendations and/or national guidelines may help with alleviating this situation as patients and caregivers of these individuals are desperately looking for anything that can assist with improving cognition, function and quality of life amongst individuals with AD.[18,28]

There are still some unanswered clinical questions regarding the use of lecanemab amongst individuals with AD, including the lack of clinical trials of lecanemab amongst individuals with multimorbidity and amongst individuals who have mixed neuropathology in the brain. Additionally, there are no controlled trials that have compared the efficacy of lecanemab with other medications for AD, irrespective of their mechanisms of action.[29] Furthermore, there is some concern that the use of monoclonal antibodies amongst individuals with AD can result in progressive loss of cerebral and hippocampal volumes and with ventricular enlargement. The mechanism for these changes has not yet been identified, and their clinical significance is unclear. The benefits and risks of using lecanemab amongst individuals with early-onset AD also need further clarification.[30]

Based on available evidence, it appears that lecanemab may have small, yet beneficial effects amongst individuals with MCI and mild dementia due to AD, and these benefits may outweigh risks, especially amongst individuals who do not have the *ApoE-ε4* allele or are heterozygous. The debate regarding the drug's cost *versus* benefits is set to continue into the foreseeable future as both sides of the argument have valid points that need to be considered thoughtfully. The availability of data from multiple high-quality longer-term (>18 months) trials, especially amongst individuals from diverse racial and ethnic backgrounds, may help resolve some of these important points of contention. Additionally, the development of easier modes of administration of the drug (subcutaneous), the use of ultra-fast MRI sequencing for monitoring brain-related adverse events, and making this medication available for use, especially amongst individuals with early-onset AD may further alleviate the situation.[31] Furthermore, minimizing any type of financial waste with the use of this medication may assist with it being made available to those populations who require this medication the most.[32]

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References

1. Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet.* 2024;404(10452):572–628. https://doi.org/10.1016/S0140-6736(24)01296-0
2. Abdul Manap AS, Almadodi R, Sultana S, et al. Alzheimer's disease: a review on the current trends of the effective diagnosis and therapeutics. *Front Aging Neurosci.* 2024;6:1429211. https://doi.org/10.3389/fnagi.2024.1429211
3. Alzheimer's Association Report. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2024;20(5):3708–3821. https://doi.org/10.1002/alz.13809
4. Qi X, Nizamutdinov D, Yi SS, et al. Disease modifying monoclonal antibodies and symptomatic pharmacological treatment for Alzheimer's disease. *Biomedicines.* 2024;12(11):2636. https://doi.org/10.3390/biomedicines12112636
5. Yoon CH, Groff C, Criss O. Lecanemab: a second in class therapy for the management of early Alzheimer's disease. *Innov Pharm.* 2024;15(1):10.24926/iip.v15i1.5787. https://doi.org/10.24926/iip.v15i1.5787
6. Harris E. FDA green-lights second Alzheimer drug, Donanemab. *JAMA.* 2024;332(7):524. https://doi.org/10.1001/jama.2024.13386
7. Heidebrink JL, Paulson HL. Lessons learned from approval of Aducanumab for Alzheimer's disease. *Annu Rev Med.* 2024;75:99–111. https://doi.org/10.1146/annurev-med-051022-043645
8. Biogen to realign resources for Alzheimer's disease franchise. https://investors.biogen.com/news-releases/news-release-details/biogen-realign-resources-alzheimers-disease-franchise. Accessed December 7, 2024.
9. Diniz BS. Immunotherapy in Alzheimer's disease: from the bench to the bedside. *Am J Geriatr Psychiatry.* 2024;32(5):584–585. https://doi.org/10.1016/j.jagp.2024.01.013
10. Tampi RR, Forester BP, Agronin M. Aducanumab: evidence from clinical trial data and controversies. *Drugs Context.* 2021;10:2021-7-3. https://doi.org/10.7573/dic.2021-7-3
11. Burke JF, Kerber KA, Langa KM, et al. Lecanemab: looking before we leap. *Neurology.* 2023;101(15):661–665. https://doi.org/10.1212/WNL.0000000000207505
12. Levien TL, Baker DE. Lecanemab. *Hosp Pharm.* 2024;59(5):519–528. https://doi.org/10.1177/00185787231185869
13. Arroyo-Pacheco N, Sarmiento-Blanco S, Vergara-Cadavid G, et al. Monoclonal therapy with lecanemab in the treatment of mild Alzheimer's disease: a systematic review and meta-analysis. *Ageing Res Rev.* 2025;104:102620. https://doi.org/10.1016/j.arr.2024.102620
14. Cao W, Zhu B, Liu Z, et al. Comparison of the efficacy of updated drugs for the treatment on the improvement of cognitive function in patients with Alzheimer's disease: a systematic review and network meta-analysis. *Neuroscience.* 2024;565:29–39. https://doi.org/10.1016/j.neuroscience.2024.11.029
15. Terao I, Kodama W. Comparative efficacy, tolerability and acceptability of donanemab, lecanemab, aducanumab and lithium on cognitive function in mild cognitive impairment and Alzheimer's disease: a systematic review and network meta-analysis. *Ageing Res Rev.* 2024;94:102203. https://doi.org/10.1016/j.arr.2024.102203
16. Honig LS, Sabbagh MN, van Dyck CH, et al. Updated safety results from phase 3 lecanemab study in early Alzheimer's disease. *Alzheimers Res Ther.* 2024;16(1):105. https://doi.org/10.1186/s13195-024-01441-8
17. Beshir SA, Hussain N, Menon VB, et al. Advancements and challenges in Antiamyloid therapy for Alzheimer's disease: a comprehensive review. *Int J Alzheimers Dis.* 2024;2024:2052142. https://doi.org/10.1155/2024/2052142
18. Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: appropriate use recommendations. *J Prev Alzheimers Dis.* 2023;10(3):362–377. https://doi.org/10.14283/jpad.2023.30

19. Mahase E. Alzheimer's disease: Lecanemab gets full FDA approval and black box safety warning. *BMJ*. 2023;382:1580. https://doi.org/10.1136/bmj.p1580
20. Jin M, Noble JM. What's in it for me? contextualizing the potential clinical impacts of Lecanemab, Donanemab, and other anti-β-amyloid monoclonal antibodies in early Alzheimer's disease. *eNeuro.* 2024;11(9):ENEURO.0088-24.2024. https://doi.org/10.1523/ENEURO.0088-24.2024
21. Tahami Monfared AA, Tafazzoli A, et al. The potential economic value of Lecanemab in patients with early Alzheimer's disease using simulation modeling. *Neurol Ther.* 2022;11(3):1285–1307. https://doi.org/10.1007/s40120-022-00373-5
22. Centers for Medicare and Medicaid Services. Statement: Broader Medicare Coverage of Leqembi available following FDA traditional approval. https://www.cms.gov/newsroom/press-releases/statement-broader-medicare-coverage-leqembi-available-following-fda-traditional-approval. Accessed December 14, 2024.
23. Kmietowicz Z, Mahase E. Lecanemab: benefits of Alzheimer's drug are "just too small" to justify cost, says NICE. *BMJ.* 2024;386:q1853. https://doi.org/10.1136/bmj.q1853
24. Mahase E. Lecanemab: European drug agency rejects Alzheimer's drug amid debate over efficacy and safety. *BMJ.* 2024;386:q1692. https://doi.org/10.1136/bmj.q1692
25. European Medicines Agency. Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 22–25 July 2024. https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-22-25-july-2024#negative-recommendation-on-new-medicine-68843. Accessed December 15, 2024.
26. European Medicines Agency. Leqembi recommended for treatment of early Alzheimer's disease. https://www.ema.europa.eu/en/news/leqembi-recommended-treatment-early-alzheimers-disease. Accessed December 15, 2024.
27. Update on regulatory review of Lecanemab for early Alzheimer's disease in Australia. https://www.eisai.com/news/2024/news202476.html. Accessed January 23, 2025.
28. Park KH, Kim GH, Kim CH, et al. Lecanemab: appropriate use recommendations by Korean Dementia Association. *Dement Neurocogn Disord.* 2024;23(4):165–187. https://doi.org/10.12779/dnd.2024.23.4.165
29. Nadeau SE. Lecanemab questions. *Neurology.* 2024;102(7):e209320. https://doi.org/10.1212/WNL.0000000000209320
30. Iwatsubo T. Editorial: clinical implementation of Lecanemab: challenges, questions and solutions. *J Prev Alzheimers Dis*. 2023;10(3):353–355. https://doi.org/10.14283/jpad.2023.41
31. The Lancet. Divisions over lecanemab: keeping an open mind. *Lancet.* 2024;404(10458):1077. https://doi.org/10.1016/S0140-6736(24)02075-0
32. Zhou FF, Tseng CH, Leng M, et al. Reducing wasteful spending on discarded Lecanemab in the US medicare program. *JAMA Intern Med.* 2024;184(12):1477–1479. https://doi.org/10.1001/jamainternmed.2024.5292