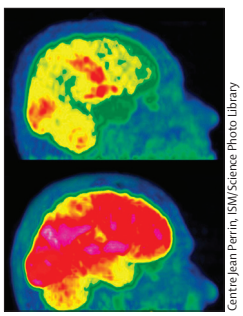
Lecanemab for Alzheimer's disease: tempering hype and hope



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The Alzheimer's disease community has become accustomed to false hope, disappointment, and controversy. With an estimated 55 million people worldwide affected by dementia, the need for an effective treatment is undeniable. But efforts to develop a drug that can modify the course of Alzheimer's disease, by using antibodies to clear amyloid-beta (Aβ) from the brain, have endured numerous setbacks over the past 20 years. Almost a decade ago, the first anti-Aβ antibodies tested in phase 3 trials, bapineuzumab and solanezumab, did not improve clinical outcomes in mild to moderate Alzheimer's disease. Hopes were dashed again in 2019 when two phase 3 trials of aducanumab—one of the next generation of anti-Aβ antibodies that specifically target Aβ aggregates—were halted early for futility. Aducanumab's resurrection and controversial approval in 2021 by the US Food and Drug Administration (FDA) under its accelerated approval programme, which allows early approval of drugs in areas of unmet need based on a positive change on a surrogate endpoint—in this case amyloid reduction in the brain—sparked furore among the research community.

Against this backdrop, on Nov 29, results of the eagerly awaited CLARITY AD study of lecanemab—an antibody targeting larger Aβ oligomers, or protofibrils—were presented at the Clinical Trials on Alzheimer's Disease conference in San Francisco, USA, and published concurrently. Anticipation had been mounting since the announcement 2 months earlier, via a press release, of positive top-line results. In the trial, 1795 people with mild cognitive impairment or early Alzheimer's disease, plus evidence of amyloid on a PET scan or by CSF testing, were randomly assigned to receive 10 mg lecanemab via intravenous infusion every 2 weeks, or matched placebo. 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—an absolute difference of 0·45 points (change from baseline 1·21 for lecanemab *vs* 1·66 with placebo, p<0·001). All key secondary endpoints were met. Incidence of amyloid-related imaging abnormalities (ARIA), an adverse event associated with anti-Aβ antibodies and which manifests as oedema or microhaemorrhages, occurred in 21% of the lecanemab group; most cases were asymptomatic and detected incidentally. However, reports of a second death in the ongoing open-label extension phase of the study—possibly linked to co-administration of the thrombolytic drug alteplase—have heightened concerns about lecanemab's safety in patients taking blood-thinning drugs. An initial decision on the drug's approval by the FDA is expected by Jan 6, 2023, and from the European Medicines Agency later in 2023.

After such a long and fruitless wait for a successful therapy for Alzheimer's disease, a phase 3 trial showing efficacy on clinical outcomes is welcome news. However, a 0·45-point difference on the CDR-SB, an 18-point scale, might not be clinically meaningful. A 2019 study suggested that the minimal clinically important difference for the CDR-SB was 0·98 for people with mild cognitive impairment and presumed Alzheimer's aetiology, and 1·63 for those with mild Alzheimer's disease. Furthermore, development of ARIA—seen in one in five patients taking lecanemab—could potentially lead to unmasking, introducing bias.

Given these concerns, whether lecanemab is the game changer that some have suggested remains to be seen. Ongoing trials are assessing the efficacy of subcutaneous administration and whether lecanemab can prevent onset of dementia in patients with amyloid pathology but no clinical symptoms. However, the immediate impact of lecanemab should not be overstated. A decision is yet to be made on cost but it is likely to be prohibitive for low-income and middle-income countries—where most people with dementia live. Many health systems lack the infrastructure to enable widespread roll-out of lecanemab: the availability of PET imaging to determine treatment eligibility is patchy, memory clinics will need the personnel to facilitate bi-weekly intravenous drug infusions, and the capacity for regular MRI scanning to detect ARIA will need to be scaled up. The results on lecanemab might well pave the way for much needed treatments for Alzheimer's disease. But for now, the key public health message for Alzheimer's disease remains that laid out in the 2020 *Lancet* Commission on dementia prevention, intervention, and care: target the modifiable risk factors for dementia—such as hypertension, smoking, diabetes, and obesity—to maintain brain health across the lifespan. ■ *The Lancet*

For more on **the first anti-Aβ antibody trials** see *N Engl J Med* 2014; **370:** 322–33 and *N Engl J Med* 2014; **370:** 311–21

For more on **aducanumab** see **World Report** *Lancet* 2022; **399:** 1585

For the **lecanemab trial** see *N Engl J Med* 2022; published online Nov 29. https://www.nejm.org/doi/full/10.1056/NEJMoa2212948

For more on **patient deaths** see https://www.statnews.com/2022/10/28/patient-death-lecanemab-alzheimers-trial and https://www.science.org/content/article/second-death-linked-potential-antibody-treatment-alzheimer-s-disease

For more on **minimal clinically important differences** see *Alzheimers Dement* 2019; **5:** 354–63

For **The *Lancet* Commission on dementia** see **The Lancet Commissions** *Lancet* 2020; **396:** 413–46