Lecanemab for Alzheimer’s disease

New trial reports little to celebrate for patients and carers

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The detailed results of a phase 3 randomised controlled trial of lecanemab, 1 the latest monoclonal antibody drug for Alzheimer’s disease, prompted fervent media coverage heralding a new era of disease modifying treatments. Such treatment has been long hoped for, for differing reasons, by patients, clinicians, researchers, governments, and drug companies. However, the null effects on cognition of other anti-amyloid agents, 2, 3 the tiny effect on cognition reported for lecanemab, and concerns about safety 4 mean that perspective is needed. Hyperbolic rhetoric gives patients and their families false hope, which clinicians must address, and pre-empt regulatory decision making.

Unlike previous trials of anti-amyloid immunotherapy, the lecanemab trial found a statistically significant result, indicating that the reported difference between placebo and treatment groups in average rate of cognitive decline was unlikely to be due to chance. The prevailing narrative is that this trial “succeeded” where others have “failed.” In reality, lecanemab, like other anti-amyloid agents, successfully cleared amyloid from the brain. This clearance had no discernible effect on cognition in some trials, a very small and non-significant effect in other trials, 2, 3 and a very small significant effect in the latest trial. The overall trial evidence tells us that successful amyloid clearance in adults with early Alzheimer’s disease has either no effect or a tiny effect on cognitive decline. 2, 3

Clinically meaningful?

Though statistically significant, the reduction in cognitive decline reported for lecanemab does not necessarily reflect a meaningful improvement for patients or their families. Previous attempts to quantify the minimum clinically important difference in the trial’s primary outcome measure—the Clinical Dementia Rating (CDR) sum of boxes score (range 0-18)—suggested that minimum changes of 0.98 in mild cognitive impairment and 1.63 in mild Alzheimer’s disease are meaningful. 5 After 18 months of treatment with lecanemab, differences of 0.35 and 0.62 for those with mild cognitive impairment and mild Alzheimer’s disease, respectively, fell well short, representing only around a third of what a minimum clinically important difference might look like.

Trial participants were highly selected (70% of those screened for inclusion were ineligible) with an average age of 71. The trial’s extensive exclusion criteria limit any likely real world benefit for most people with, or at risk of, dementia. Dementia develops mostly in older adults with multimorbidity and a complex mix of pathologies, of which amyloid pathology is just one. 6, 7

Safety concerns

As with other anti-amyloid agents, 6 lecanemab comes with substantial safety concerns. During the trial, 12.6% (113/898) of participants treated with lecanemab developed brain oedema detectable by imaging (placebo group 1.7%), 22% of whom were symptomatic. A further 17.3% (placebo 9%) experienced brain haemorrhage, almost always asymptomatic, though the long term effects are unknown; and 6.9% (placebo 2.9%) experienced adverse events severe enough to discontinue the trial. Numbers of deaths in both groups were comparable during the main trial (lecanemab 6/898, placebo 7/897), but more information is needed about two deaths reported during the trial’s open label extension. Both participants had brain haemorrhage, possibly associated with taking lecanemab alongside anticoagulants or thrombolysis. 6

An additional concern is the possibility of “unblinding,” when a patient, family member, or clinician correctly deduces the treatment arm. This is particularly problematic when outcome measures are derived from patient or informant report. Although sensitivity analyses suggested that potential unblinding from cerebral oedema or haemorrhage did not influence results, no similar analysis was reported for the more common infusion related reactions (26.4% for lecanemab v 7.4% for placebo), raising the possibility of bias.

Looking ahead

As with aducanumab, 8 another monoclonal antibody, lecanemab if licensed is likely to cost tens of thousands of pounds a year for each patient. 10 In addition, health systems would need to provide positron emission tomography scans or lumbar puncture to determine eligibility, fortnightly infusions of the drug indefinitely, and repeated magnetic resonance imaging to monitor for adverse events, all of which is far beyond the capacity of most countries, even those with well resourced healthcare systems.

Controversially, the US Food and Drug Agency licensed aducanumab through its accelerated approval process in 2021, 8 and this precedent suggests that lecanemab may also be approved in the US. The European Medicines Agency requires demonstration of minimum clinically important difference, 11 so approval in Europe seems less likely. Before appraising aducanumab, the National Institute for Health and Care Excellence (NICE) in the UK requested data on outcomes important to patients and carers, such as behavioural symptoms and time...
to institutionalisation. Neither is available for lecanemab. Pressure for approval and clinical use is likely to be fierce. Viewed objectively, however, lecanemab is not the hoped for “game changer.” Rather, it is further evidence that anti-amyloid therapies do not produce clinically meaningful benefits for people with Alzheimer’s disease. Weighed against the scale and severity of adverse events and substantial practical barriers to widespread use, lecanemab is unlikely to represent a favourable risk-benefit balance for patients or value for money for health systems.

Instead, we need meaningful policy action on reducing the dementia risk, diversification of disease modification targets, and better funding for implementation of non-pharmacological interventions with proved benefits for people living with dementia.

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