Lecanemab slows Alzheimer's disease: hope and challenges

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The search for Alzheimer's disease (AD) modifying treatments is a global medical research priority[1]. Despite dramatic findings in mouse models[2] and promising early phase human studies, successive large clinical trials of anti-amyloid immunotherapies failed to translate into clinical benefit, leading many to question the wisdom of the strategy. The publication of the phase 3 trial of lecanemab in early AD is therefore likely to be seen as an historic moment in our field—the beginning of a new era of disease-modifying therapies for AD[3,4]. It represents a more than 20-year research effort that builds on careful clinical, laboratory and trial observations[2,3].

Lecanemab is a humanised monoclonal antibody with particular affinity for large (75-300 kDa) abeta amyloid assemblies called protofibrils - intermediaries between monomers and fibrillary amyloid plaques. The trial, which involved fortnightly intravenous infusions, met its primary endpoint with a statistically robust 27% slowing of decline on the Clinical Dementia Rating Sum of Boxes (CDR-SB) score. Differences appeared by six months, while after 18 months, the lecanemab group had declined by 1.21 points compared to placebo decline of 1.66 points (difference −0.45; 95% confidence interval −0.67 to −0.23; $p<0.0001$). Lecanemab also hit many of its exploratory and biomarker outcomes and all its secondary clinical outcomes ($p<0.001$) including benefit in terms of activities of daily living in this mild AD population (37% reduction in decline). Importantly, given the devastating impact on partners and whole families, lecanemab was associated with a striking 38% less progression on a measure of "burden" on study partners.

Lecanemab produced a dramatic and rapid reduction in brain amyloid as measured by PET. By the end of the trial, the majority (~2/3rds) of lecanemab treated participants were below the level considered "amyloid-positive", and would no longer have met eligibility to enter the study.

This is not the first study to show amyloid removal, why then did this trial show clinical benefit when so many were negative or equivocal? Numerous explanations have been put forward to explain previous disappointing trial results - that the focus on amyloid was wrong or it was just too late to target amyloid once self-sustaining tau protein, inflammatory and neurodegenerative processes were established. This study provides compelling evidence that amyloid is a target worth pursuing, even in the symptomatic stages of AD. Of course, other contributing causes might be successfully targeted, and should be, and it is likely to be easier to slow the disease earlier on, but it is encouraging that it can be slowed at all at a symptomatic stage. The study also supports the concept that amyloid "levels" may need to be reduced low enough and for long enough for clinical benefits to appear[5].

A 27% slowing translates into about 5 months less decline over 18 months. The key questions are whether slowing is sustained, and whether clinical benefits are cumulative. The trial was not designed to address these questions, but some graphs of outcomes suggest a gradual widening of the gap between treatment and placebo arms over the course of the study. Longer term follow-up studies of this new disease entity, "amyloid-cleared AD", will be critical.

As with all treatments, potential benefits need to be balanced against risks at the individual level. A particular concern for all AD immunotherapy is ARIA-E (amyloid related imaging abnormalities seen on MRI) - local oedema and effusions likely related to (rapid) amyloid removal from the walls of cerebral blood vessels. The rate of ARIA-E was 12.6% of those who received lecanemab, but most (80%) did not have discernible symptoms. Overall, 2.8% of those treated developed ARIA-E and were symptomatic. Notably the risk of death during the trial was essentially identical in the treatment (0.7%) and placebo (0.8%) arms. Nonetheless, as with many biologically active therapies, great care will be needed in how patients are counselled about risks, careful monitoring, and caution in the use of concomitant treatments. The recent report of cerebral haemorrhage in an individual on lecanemab given thrombolytic therapy (tPA) for a presumed stroke is one salient example[6]. Even so, we expect many would choose to receive treatments despite the risks and the burden and frequency of administration.

Lecanemab is likely to get approval from the FDA early in 2023 under its Accelerated Approval programme. Other monoclonals (and other treatments) are due to report soon, notably phase 3 results from donanemab are expected in spring which also shows potent amyloid removal[7]. Delivering these therapies will be a massive challenge to health systems – not least because of the numbers of people likely to be eligible – even if limited to the "early" AD criteria used in trial inclusion. Even in the most advanced economies very significant new resources will be needed to diagnose early, deliver therapies, and monitor safely. There is limited capacity for diagnostic and monitoring MRI and to assess amyloid status by PET or CSF. There will be legitimate questions about equity of access within and between countries with the risk that treatments are only available to the privileged few.

Until now, with only symptomatic therapies for AD to offer, time was not of the essence in terms of diagnosis and starting treatment[8]. Now it will be. Just as services for previously "untreatable" diseases, from AIDS to cancer, have been transformed by effective but time-constrained treatments, we hope for a similar transformation for AD care. There will be many challenges to achieve this, but for millions of present and future patients globally, it is better to have these challenges and the prospects of disease slowing and retained cognition and function, rather than no prospects.

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