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ARTICLE

New and emerging drug therapies for Alzheimer disease

SUMMARY

Established drug therapies for Alzheimer disease (cholinesterase inhibitors and memantine) do not modify the disease course and provide only modest clinical benefit.

Biomarker measures of amyloid, tau and neurodegeneration have been integral to Alzheimer disease clinical trials for biologic drugs, for patient selection and efficacy monitoring.

At the time of writing, two monoclonal antibodies targeting the amyloid-beta protein (aducanumab and lecanemab) have been approved in the USA, and two agents (lecanemab and donanemab) are under evaluation by the Therapeutic Goods Administration in Australia.

Clinical trials have demonstrated that monoclonal antibodies are effective at removing amyloid from the brain in people with early Alzheimer disease. Cognitive benefits are statistically significant, but do not achieve the minimal clinically important difference. Amyloid-related imaging abnormalities of vasogenic oedema and microhaemorrhages occur more frequently on treatment; although these are usually asymptomatic or transient, in some people they are serious or fatal.

Targeting amyloid as a unimodal strategy is unlikely to be sufficient and future therapies may need to be multimodal, targeting multiple pathogenic pathways.

The burden of dementia is greatest in the older population where mixed dementia pathology dominates; the relationship between biomarkers, clinical phenotype and pathology attenuates; and frailty and comorbidity impact cognition. This creates challenges in identifying effective therapies for the group where dementia is most prevalent.

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Introduction

Dementia is now the second leading cause of death in Australia and the leading cause of burden of disease in people aged over 65 years.[1] Alzheimer disease is the most prevalent of the dementias. Cholinesterase inhibitors and memantine have been the only approved drug therapies for Alzheimer disease for over 20 years, and these provide modest symptomatic relief only. Recent trials showing that monoclonal antibodies can remove amyloid protein from the brain have generated optimism that disease modification may be possible, but clinically meaningful cognitive and functional benefits have not yet been demonstrated. At the time of writing, two monoclonal antibodies (aducanumab and lecanemab) have been approved in the USA by the Food and Drug Administration (FDA), and two agents (lecanemab and donanemab) are under evaluation by the Therapeutic Goods Administration in Australia.

Established drug therapies

Three cholinesterase inhibitors are approved for use in mild to moderate Alzheimer disease: donepezil, galantamine and rivastigmine. They are equally efficacious, with pooled trials demonstrating a 1.4 point improvement (on a 30-point scale) in the Mini Mental State Examination over 6 months.[2] However, the response varies significantly, with only one-third of trial participants showing a clinically measurable benefit. Adverse effects are reported in up to one-third of patients and include nausea, vomiting, diarrhoea, muscle cramps, syncope and insomnia. Postmarketing studies indicate that up to 35% of patients cease cholinesterase inhibitors because of adverse events.[3] Relative contraindications include cardiac conduction delays, bradyarrhythmias, active peptic ulcer disease and obstructive urinary disease.

Memantine, an N-methyl-D-aspartate receptor antagonist, is approved for moderate to severe Alzheimer disease. It provides a small benefit to cognition, behaviour and the ability to perform activities of daily living; there is no evidence for benefit in mild disease.[4] A reduction in agitation was identified in some but not all trials.[5]

Cost–benefit studies for cholinesterase inhibitors and memantine have failed to identify economic benefit, nor is there evidence that cholinesterase inhibitors delay transition to residential care.[6,7] Therefore,

although these drugs remain the mainstay of pharmacological management for Alzheimer disease, they fail to provide substantial symptomatic benefit and do not modify disease progression.

New and emerging therapies

Research into new therapies for Alzheimer disease has largely been dominated by the amyloid cascade hypothesis, whereby abnormal processing of the amyloid precursor protein results in pathological aggregation of the amyloid-beta protein into amyloid plaques and hyperphosphorylation of the protein tau to form neurofibrillary tangles in the brain.

Biomarker measures have been integral to patient selection and efficacy monitoring in Alzheimer disease clinical trials. Amyloid, tau and other biomarkers of neurodegeneration are measured through cerebrospinal fluid, magnetic resonance imaging (MRI) and positron emission tomography (PET) biomarker studies. Plasma biomarkers remain in development.

Anti-amyloid monoclonal antibodies

The amyloid hypothesis has driven the development of monoclonal antibodies targeting specific epitopes of the amyloid-beta protein, with close to 30 monoclonal antibodies having been tested. The vast majority of monoclonal antibodies effectively remove amyloid, but improvements in cognitive function have been limited, and trials have identified an increased risk of amyloid-related imaging abnormalities (ARIA) (see below).[8]

In 2021 and 2023 respectively, the anti-amyloid monoclonal antibodies aducanumab and lecanemab received FDA approval for the treatment of mild cognitive impairment and mild Alzheimer disease. Aducanumab was recently discontinued by its manufacturer for commercial reasons. Donanemab is currently under consideration for approval by the FDA.

Aducanumab and lecanemab

Aducanumab was approved by the FDA on the basis of reduction in brain amyloid in 76-week clinical trials (EMERGE and ENGAGE).[9] The primary outcome, an 18-point integrated scale of cognition and function, the Clinical Dementia Rating-Sum of Boxes (CDR-SOB), failed to identify any improvement at low dose, while at high dose there was a statistically significant difference.

The 76-week lecanemab trial (CLARITY AD) found a statistically significant reduction in the CDR-SOB, with reduced brain amyloid burden.[10]

Of note, neither aducanumab or lecanemab achieved the minimal clinically important difference (MCID) in cognitive or functional endpoints. The MCID refers to the smallest change in cognitive or functional endpoints that constitutes a clinically meaningful treatment effect. The MCID for the CDR-SOB endpoint is a reduction of 0.98 points in people with mild cognitive impairment and 1.63 points in people with Alzheimer disease.[11] In the high-dose aducanumab group the mean reduction in CDR-SOB was 0.39 (95% confidence interval [CI] 0.09 to 0.69) while lecanemab achieved a mean reduction of 0.45 (95% CI 0.23 to 0.67).[9,10] That is, although the differences were statistically significant, they did not achieve a level that is viewed as clinically meaningful. While a degree of controversy surrounds the defining of clinically meaningful endpoints, particularly from the perspective of patients and carers, alternative approaches remain unvalidated.

Donanemab

In a 76-week phase 3 clinical trial of donanemab (TRAILBLAZER-ALZ 2), there was a significant difference in the primary outcome measure, the integrated Alzheimer's disease rating scale (iADRS), which is a 144-point scale incorporating cognition and function.[12] Significant reduction in brain amyloid was demonstrated. However, the change in the iADRS of 2.92 (95% CI 1.51 to 4.33) did not achieve the MCID of 5 points for mild cognitive impairment and 9 for Alzheimer disease. In contrast to aducanumab and lecanemab, where therapy continued unless contraindicated, donanemab was switched to placebo when levels of brain PET amyloid reduced below a designated threshold, with the mean time for this being 47 weeks.

Therefore, for the 3 monoclonal antibodies at the forefront of approval, brain amyloid was effectively removed but measures of cognitive and functional improvement did not achieve MCIDs.

Amyloid-related imaging abnormalities (ARIA)

ARIA are detected on MRI, necessitating regular monitoring scans. There are two subtypes of ARIA, which often co-occur: ARIA-E (vasogenic oedema) and ARIA-H (microhaemorrhage). ARIA occurred in 42 to 44% of patients who received high-dose aducanumab, compared with 9% who received placebo.[9] In the lecanemab trial, ARIA occurred in 21.5% of treated patients versus 9.5% with placebo.[10] ARIA occurred in 36.8% of donanemab-treated patients versus 14.9% in the placebo arm.[12]

The majority of ARIA are asymptomatic or mild with symptoms including headache, delirium and gait disturbance. Continuation or temporary suspension of the monoclonal antibody, with MRI monitoring, is recommended in mild or asymptomatic

cases. However, severe ARIA are life-threatening, necessitating withdrawal of the monoclonal antibody and commencement of immunosuppressive therapy.

Risk of ARIA is associated with increased age, higher monoclonal antibody dose, and apolipoprotein E ε4 homozygosity (the strongest genetic risk factor for sporadic Alzheimer disease).[8]

Will treating earlier with anti-amyloid monoclonal antibodies be more effective?

The TRAILBLAZER-ALZ 2 donanemab trial stratified patients according to biomarker tau load, and identified that those with low or medium tau levels had a better response, suggesting that treating earlier was more efficacious. Trials are in development for lecanemab and donanemab in participants with positive Alzheimer biomarkers and intact cognition.

In 2 recently published papers looking at preclinical Alzheimer disease and mild cognitive impairment, solanezumab attenuated accumulation of amyloid in a 240-week trial but had no impact on cognition,[13] while gantenerumab effectively reduced amyloid but did not impact cognitive decline over 116 weeks.[14] Therefore, although amyloid removal was effective in prodromal disease, there was no impact on cognition. An alternative, more optimistic view is that there may be a delayed benefit of amyloid removal in prodromal disease but, in the absence of supporting data, benefits are not confirmed.

Other unanswered questions about amyloid removal

Where amyloid removal is confirmed, there is a concurrent reduction in brain volume and an increase in ventricular size, termed pseudoatrophy.[15] While postulated to reflect amyloid removal, the relevance and long-term effects of reduction in brain size are unknown.[16]

The potential impact of ARIA on natural progression of Alzheimer disease is unknown, with one study demonstrating that microbleeds, though often asymptomatic, resulted in faster decline.[17]

Further unanswered questions include the rate and impact of amyloid re-accumulation and changes in symptom trajectory beyond the duration of trials. Post-trial data with 3-year follow-up is anticipated and will assist in identifying whether there is a delayed benefit of amyloid removal.

Challenges with anti-amyloid monoclonal antibodies

There will be challenges in delivering anti-amyloid monoclonal antibodies. Studies suggest that less than 10% of patients with confirmed mild cognitive impairment or Alzheimer disease will be eligible for monoclonal antibody therapy,[18] with the youngest and least comorbid likely to be most appropriate. Those where MRI is contraindicated will be excluded, as will those with significant comorbidities, other immune conditions, a history of seizures or stroke, and bleeding disorders or use of anticoagulants given the risk of ARIA-H. In those who pass initial medical screening, MRI scans to ensure that ARIA are not present and PET scans to confirm biomarker-based eligibility will be required. The complexity of screening, staffing and infrastructure required to enable monoclonal antibody therapy has significant capacity implications with a concurrent need for counselling and care of those ineligible.

There is lower response to monoclonal antibody therapies in the setting of apolipoprotein E ε4 homozygosity,[8] and increased risk of ARIA. Therefore, apolipoprotein E genotyping will be required to risk-stratify and predict response in people assessed as eligible for treatment and without contraindications.

Lecanemab and donanemab are administered by intravenous infusion, at 2- and 4-weekly intervals respectively. This creates substantial patient and carer burden. Infrastructure requirements are significant, including skilled infusion services and ongoing access to MRI and amyloid and tau PET imaging to monitor response and adverse effects. In the event of symptoms suggestive of ARIA, additional MRI scans beyond recommended monitoring scans will be required.

Multidisciplinary teams of expert clinicians, nurses, radiologists and nuclear medicine physicians will be needed to assess, prescribe, administer and manage monoclonal antibodies, restricting their use to tertiary facilities thereby exacerbating existing inequities of socioeconomic status, cultural background and rural–urban divide.

While the development of subcutaneously administered monoclonal antibodies and plasma-based biomarkers may alleviate some of these inequities, workforce and infrastructure needs will remain.

Economic studies have predicted significant strain on the health dollar in the setting of unfavourable cost-effectiveness of amyloid monoclonal antibody therapies.[19,20] The economic question will need to be asked as to how essential services to facilitate safe community living can be afforded for the vast majority who will be ineligible for monoclonal antibodies or for those who continue to decline cognitively and functionally despite receiving a monoclonal antibody.

Future directions

Current scientific consensus is that amyloid-based strategies are unlikely to be sufficient for managing Alzheimer disease, and multiple pathogenic pathways

will need to be addressed. The location and volume of tau correlates with clinical phenotype and severity;[21] however, trials of monoclonal antibodies targeting tau have been discontinued because of lack of efficacy, or they are in their early stages.[22] Other processes such as inflammation, vascular disease and metabolic pathways are recognised as key in pathogenesis. Tyrosine kinase inhibitors targeting inflammatory cells have shown mixed results and have been limited by the absence of biomarker measures.[23] Trials of metformin, semaglutide, insulin and empagliflozin are in progress, targeting insulin signalling, insulin resistance, and metabolic and inflammatory pathways.[24]

One of the major challenges is the epidemiology of dementia. In Australia, 43% of people with dementia are aged over 85 years.[1] Pathological series confirm a high prevalence of mixed dementia pathology in this age group, with Alzheimer disease being only one of many pathologies present.[25] With advancing age, the correlation between biomarkers, clinical phenotype and pathology attenuates making both interpretation and monitoring of biomarkers more challenging.[26] Frailty increases with age, and the burden of neuropathology required for dementia to develop is less in the setting of frailty.[27] Comorbidities correlate with age and predict biomarker positivity,[28] with poorly controlled comorbidities predicting faster cognitive decline.[29] Therefore, in the age group where the burden of dementia is greatest, single-disease therapies are unlikely to result in a 'cure', and focusing on comorbidities and frailty may be equally or more efficacious.

Is prevention the answer?

The Lancet Commission 2020 report identified 12 life-course risk factors for dementia, with modification of these socioeconomic, lifestyle and environmental risk factors calculated as having the potential to prevent or delay up to 40% of dementias.[30] However, the data are from observational studies and provide limited evidence that risk factor modification will produce the calculated reduction in dementia. Despite this, implementation of preventative strategies is supported, as they will enhance population health and not induce harm.

Conclusion

While trials of anti-amyloid monoclonal antibodies have generated much excitement regarding a potential cure for Alzheimer disease, the removal of amyloid has not translated to clinically meaningful cognitive or functional benefits. Trials of Alzheimer disease therapies targeting multiple pathogenic pathways are in progress, acknowledging that multimodal therapies may be required. Until disease-modifying therapies are effective and broadly available, multidisciplinary care remains the mainstay of dementia management, including carer and patient education, post-diagnostic care, optimisation of comorbidities, and implementation of services. <

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Conflicts of interest: none declared

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