Assessing preparedness for Alzheimer disease-modifying therapies in Australasian health care systems

Therapeutic advancement is well underway, and the medical community needs to keep pace

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doi: 10.5694/mja2.51880

In June 2021, the United States Food and Drug Administration (FDA) announced the accelerated approval of aducanumab for the treatment of Alzheimer disease.[1] This decision, against the FDA's own expert committee, was made on the basis that it lowered brain amyloid levels (an indirect surrogate biomarker) rather than on direct clinical benefit. This was highly controversial: two phase 3 studies were halted early due to a futility analysis,[2] the decision was based on *post hoc* analyses, and the pricing of aducanumab (USD$56 000 per annum) was very high. Aducanumab was then limited to patients with early disease and the price was reduced. The associated costs of drug infusion, positron emission tomography (PET), and safety monitoring including magnetic resonance imaging (MRI) scans rendered the total cost prohibitive, resulting in the Centers for Medicare and Medicaid Services limiting payment to patients in clinical trials and registries.[3] Biogen lodged an application to the Australian Therapeutic Goods Administration in June 2021 but later withdrew it in June 2022.

A further potential disease-modifying therapy (DMT), lecanemab, was approved by the FDA for the treatment of early Alzheimer disease in January 2023, with accompanying media releases on both the licensing company's commitment to safety and appropriate pricing.[4,5] An application for approval has been lodged in Australia.

These therapies are costly and not without risk. Three deaths have been reported related to treatment with lecanemab.[6] Patients receiving DMT require frequent monitoring with MRI brain scans (four or more per year), as there is a high rate of clinically significant amyloid-related imaging abnormalities (ARIA), both brain oedema (ARIA-E) and macro- and microhaemorrhages (ARIA-H). Although most cases of ARIA are asymptomatic, close monitoring with MRI is mandated.[7] So far, these therapies have been associated with increased brain volume loss (ie, increased brain atrophy). In addition, they require fortnightly or monthly intravenous infusions, and infusion reactions are common.[2,4]

There are an estimated 487 500 persons living with all forms of dementia in Australia, at least half of whom have Alzheimer disease.[8] Are we ready for DMTs in Australasia? In this article, we consider the readiness of the dementia community, highlight gaps in our health care systems, and provide recommendations for increasing workforce capacity and capability.

Evaluating a disease-modifying therapy for Alzheimer disease

The accepted criteria for gauging the clinical meaningfulness of any treatment include:

- the treatment should be biologically plausible;
- there should be a dose response with clinically meaningful benefit;
- the effect size should be large enough to be at least clinically detectable;
- there should be convergence of measures within a trial; and
- there should be reproducibility between trials.

We note that aducanumab meets only the first (and weakest) of these criteria: it uncontestably removes cortical fibrillar amyloid.[2,9,10] Lecanemab was strongly positive for its primary (change from baseline to 18 months on the Clinical Dementia Rating Scale Sum of Boxes [CDR-SOB], –0.45) and secondary endpoints (change in amyloid burden on PET, –59.1 centiloids),[4] but note that a one- to two-point change on the CDR-SOB is regarded as a minimally clinically important difference.[11]

Preparedness of the Australasian medical community for a dementia disease-modifying therapy

These debates have prompted much introspection from clinicians involved in the care of people with dementia, especially regarding DMT readiness and workforce capacity.[9] The introduction of an effective dementia therapy would likely require important changes in the delivery of dementia care.

We propose that dementia DMTs approval should incorporate consideration of the ramifications beyond the issue of drug efficacy. At present, patients receiving any Alzheimer disease monoclonal antibody therapy require an Alzheimer disease diagnosis validation by amyloid PET or cerebrospinal fluid (CSF) Alzheimer disease biomarker testing[12] — neither of which are available on universal health care in Australia and New Zealand. The socio-economic implications of any potential approved therapy are a major consideration.[13] We note that prior health economic analyses for aducanumab had negligible clinical benefit or improvement in health outcomes at considerable cost,[14] which may be different for lecanemab.[5]

Models of care

Supportive care is the current gold standard of dementia medical treatment, including symptomatic treatments and non-pharmacological therapies. It is fortunate that a multidisciplinary team model is accepted practice in dementia care,[15] but dementia care delivery models will require significant modification. Physicians will need upskilling in the diagnosis and treatment of cognitive disorders. Neurologists, geriatricians, and psychiatrists are well poised for this upskilling, working with general practitioners, neuropsychologists, and other health clinicians. A large sector of dementia clinicians will require structured education in molecular diagnostics. Patients will need rapid access to cognitive clinicians, neuropsychologists, neuroradiologists, advanced neuroimaging, and CSF and blood biomarker capabilities.

Diagnostic and monitoring infrastructure

Early diagnosis of specific dementia subtypes is finally on the horizon.[16,17] Clinical phenotypes do not always match underlying molecular pathology in dementias,[18] and obtaining a molecular diagnosis has been shown to definitively change management.[19] Blood biomarkers look to be available in the next five years. Furthermore, abnormal biomarkers alone raise significant management issues, including treatment of asymptomatic patients (amyloid not causing cognitive decline) and of patients excluded from trials (eg, those with multiple microhaemorrhages). Moreover, the optimal duration of treatment is not currently known.

Guidelines for the detection and diagnosis of ARIA have been developed[12] but will need honing and updating. Reporting will be needed by a radiology workforce skilled in the diagnosis of ARIA and managed by clinicians skilled in the care of people with brain oedema and haemorrhage. New Medicare codes may need to be generated for the purposes of these treatments.

Precision medicine to determine disease risk and therapy response is likely to expand. Apolipoprotein E (*APOE*) genotypes are already known to have an impact on the safety and response to some anti-amyloid monoclonal antibody treatments.[7] *APOE ε4* carriers are more likely to have ARIA and to have faster Alzheimer disease progression than other *APOE* allele carriers, potentially affecting response and risk. *APOE* allele tests are not reimbursed in Australia and New Zealand, with some patients also concerned about the consequences of genetic testing for health or life insurance.[20] Genetic counselling before testing may be required in some states and territories.

Treatment administration infrastructure

Most current Alzheimer disease therapies in late phase 3 development require two to four weekly intravenous infusions.[2,4] Multiple sclerosis, another common neurological disease, could serve as a model for rapid implementation. The treatment of multiple sclerosis in the past two decades has transformed care and prognosis, requiring considerable restructure to health care provision. Conservative estimates of demand for an intravenous Alzheimer disease treatment would represent a fivefold increase in patients compared with multiple sclerosis. Infusion therapies are now part of the armamentarium for the treatment of many other chronic diseases but increased ancillary staffing will be needed to manage the complexities of scheduling the biweekly infusions, the scans, and the complications arising.

Personnel: increasing the dementia-care medical workforce, supporting cross-disciplinary training

In Australia and New Zealand, dementia is largely treated in the primary care sector and diagnosed in multidisciplinary memory clinics. Victoria has a network of geriatrician-staffed Cognitive, Dementia and Memory Services. Specialist public cognitive neurology services are rare and, historically, the diagnosis of dementia has relied heavily on the private rooms of physicians and psychiatrists. Only 15% of Australian patients receive a diagnosis of dementia in a memory clinic, with most patients diagnosed in hospital settings.[21]

There have been informal cognitive neurology Fellowships in Australia for more than ten years, but the first position accredited by the Australian and New Zealand Association of Neurologists was approved in 2015. This has been oversubscribed since then, with a waiting list of three years and requests from multiple subspecialty advanced trainees suggesting there is great demand for this expertise.

Recommendations

We need to increase diagnostic capacity by:

- developing a comprehensive curriculum for cognitive health and dementia to be delivered by all accredited medical schools;
- prioritising dementia training by relevant medical colleges, especially of physicians, psychiatrists and general practitioners;
- increasing the capacity for molecular imaging and CSF analysis of pathological proteins while awaiting validation of dementia syndrome-specific plasma biomarkers; and
- increasing dementia training and education for allied health clinicians, especially neuropsychologists, social workers, nurses, and speech and occupational therapists to support their critical roles.

Furthermore, we need to increase management capacity through:

- identifying appropriate workspaces for the delivery of infusion therapies, perhaps modelled on those used in multiple sclerosis;
- providing training and accreditation of a broad clinician workforce experienced in dementia trials and treatment;
- educating radiologists for the detection and monitoring of ARIA; and

- supporting opportunities for cross-disciplinary clinical training, formal subspecialty accreditation, and minimum standards for continuing professional development.

Lastly, we need to monitor treatment response, safety, and socio-economic value via:

- performing full health economic evaluations, including post-marketing analyses;
- requiring pharmaceutical company participation in phase 4 clinical trials; and
- updating and evaluating the criteria for clinically meaningful responses in dementia syndromes.

Conclusion

We are sensitive to the lack of an approved DMT for Australasian patients with Alzheimer disease, and to the fact that dementia advocacy groups have applauded the accelerated FDA approval of aducanumab and lecanemab in the United States. These are the first of many new dementia pathology-specific DMTs. Other Alzheimer disease DMTs are in phase 3 trials, with results of further phase 3 trials expected at the end of 2023 (eg, ClinicalTrials.gov NCT04437511, NCT04388254, and NCT04592874). Therapeutic advancement is well underway, and the medical community needs to keep pace.

Acknowledgements: We thank the members of the Australasian Cognitive Neurology Association who contributed to discussion and consultation for this article.

Open access: Open access publishing facilitated by Monash University, as part of the Wiley - Monash University agreement via the Council of Australian University Librarians.

Competing interests: Amy Brodtmann has received fees for consultancy on the Biogen Australia, Roche Australia and Eisai Australia Scientific Advisory Boards. Bruce Brew reports speaker fees from AbbVie, Janssen and Viiv; consultancy fees for Eisai Australia Scientific Advisory Board; and speaker fees and grants from Biogen. Peter Panegyres has received consultancy fees from Biogen. David Darby has been on the Scientific Advisory Board for Biogen in the development of aducanumab, and has been an investigator for the Biogen ENGAGE and EMBARK trials. David Darby was an investigator for Roche trials of gantenerumab.

Provenance: Not commissioned; externally peer reviewed. ■

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