Lancet Neurology Insight - Preparing for disease modifying treatment for Alzheimer's disease

Christopher R. S. Belder[1,2,3], Jonathan M. Schott[1], Nick C. Fox[1,3]

1 Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, University College London, London, UK
2 Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia
3 UK Dementia Research Institute at UCL, UCL Queen Square Institute of Neurology, University College London, London, UK

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The long-awaited era of disease modifying treatment (DMT) for Alzheimer's disease (AD) has finally arrived and will substantially impact how the disease is perceived and managed. Disease-modifying treatments pose challenges for equitable clinical delivery and patient support.

Numerous DMTs for AD are in development; the closest to widespread clinical implementation are lecanemab and donanemab – intravenous monoclonal antibody therapies that robustly remove brain β-amyloid plaques and can slow cognitive and functional decline (1-3). Lecanemab was granted United States Food and Drug Administration (FDA) accelerated approval in January 2023 with a decision on traditional approval expected by July 2023; marketing authorisation applications have been made to the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom. For donanemab, initial FDA accelerated approval based on phase 2 trial results was declined in January 2023 but a further application has been announced based on the phase 3 trial (results announced May 2023 but yet unpublished) (3). Lecanemab and donanemab have side-effects, notably amyloid-related imaging abnormalities (ARIA) in 21.5% and 38.9% of patients, respectively (1, 2). While usually asymptomatic and transient, ARIA requires close monitoring. The clinical implementation of these drugs will, at least initially, likely follow the design of the clinical trials (Table 1).

Table 1 – Overview of Lecanemab and Donanemab trial design

	Lecanemab[a]	**Donanemab[b]**
Entry criteria	Diagnosis of MCI or mild AD MMSE ≥22 Study partner Screening MRI scan Amyloid positivity (PET or CSF)	Diagnosis of MCI or mild AD MMSE 20-28 Study partner Screening MRI scan Amyloid positivity (PET) Tau PET
Drug delivery	Two-weekly intravenous infusion	Monthly intravenous infusion
Monitoring	Clinical assessment every 3 months MRI – at week 9, and every 3 months for first 6 months of	Clinical assessment every 3 months MRI – at week 4 and 12, and every 3 months for first 12 months of

	treatment, then every 6 months until completion If ARIA detected, MRI performed every 30 days until resolved	treatment, then every 6 months until completion If ARIA detected, MRI repeated every 4-6 weeks until resolved Amyloid-PET performed week 24, 52 and 76
Duration of dosing	Throughout the study	Stopped once amyloid-PET negative

[a] Based on Clarity-AD, 18 month placebo-controlled trial of n=1795 (1, 4). [b] Based on TRAILBLAZER-ALZ phase 2, 18 month placebo-controlled trial of n=257 and announced but yet unpublished TRAILBLAZER-ALZ 2 phase 3, 18 month placebo-controlled trial of n=1736 (2, 3, 5).

Healthcare system readiness

No national healthcare system is ready to deliver DMTs to more than a fraction of patients who might be eligible. The UK is not alone in having fragmented dementia services which are inadequately resourced, staffed, and mainly community based. New multi-disciplinary teams and facilities will be needed to provide therapies safely. Delivery of DMTs will require an accurate, molecular diagnosis of AD. Yet in the UK, only about 60% of people with dementia receive even a clinical diagnosis of 'dementia' (6). Despite National Institute for Heath and Care Excellence (NICE) guidance recommending structural imaging unless dementia is well established and the subtype is clear (7), there is very wide variation in imaging use between centres, and in an audit of NHS England memory services, only 26% of those scanned had an MRI (with substantial variation between centres) (8). Less than 2% of patients have molecular confirmation of AD using CSF (included in NICE guidance) or amyloid-PET (which is not). There are currently no NICE guidelines for the investigation and management of mild cognitive impairment (MCI), a key target group for treatment (9).

The advent of DMTs provides an opportunity for change. Licencing of immune modulators and thrombolysis led to radical changes in treatment paradigms for multiple sclerosis and stroke respectively, including the development of new pathways, rapid assessment units, and upscaling of multidisciplinary teams and nurse specialists. These changes improved outcomes for *all* patients, not just those eligible for the specific treatment, and provided the infrastructure to allow for the rapid adoption of newer treatments as they became available.

What changes are needed?

The availability of DMTs for AD will bring an influx of patients into clinical services – those with AD, those with other dementias, and individuals concerned about their cognition or risk. Clear referral criteria and equitable pathways from primary care to specialist services will be required – access must not be limited to those living near major centres, and minority groups and individuals living alone must not be disadvantaged. Much as the slogan "time is brain" was adopted in stroke, the advent of DMT means that the consequences of diagnostic delay are greater – if progression can be slowed, then initiating treatment as early as possible in the disease course will result in maximal benefit; if the evidence supports treatment only for those with mild AD, then patients may progress past the point of eligibility whilst awaiting appointments or diagnostic tests. There will be a need for careful communication and expectation management – the vast majority of patients will

not fulfil eligibility criteria for DMTs either due to advanced disease, MCI/dementia due to non-AD pathology or the presence of neurologic or systemic comorbidities (e.g. cerebrovascular disease, microbleeds); alternative care pathways will be needed for these patients. For those concerned about risk, this provides an opportunity to promote dementia prevention via modifiable risk factors (10).

Greater access to diagnostic tests will be required, and demand for MRI will be a major bottle-neck. It is likely that more scanners will be required, and more efficient use of existing scanners will be needed including the development of shorter, focussed protocols; expert neuroradiological support will be required for scan interpretation and detection of ARIA. In due course blood-based biomarkers may be used to provide evidence for AD pathology – plasma p-tau217 is already an entry-criteria for the TRAILBLAZER-ALZ3 study (11) – but for now this will likely rely on amyloid-PET or CSF examination. These modalities have advantages and disadvantages in terms of cost, access and acceptability. Pragmatically, their use may be based initially on the approach used in the trials. Upscaling access to CSF testing may be more cost-effective than PET (12) and could provide evidence for both amyloid and tau pathology; this requires increased lumbar puncture capacity with trained nursing or medical staff, and increased laboratory staff and equipment for analysis and interpretation. Expansion of amyloid-PET requires increased tracer availability, access to PET imaging centres, nuclear medicine physicians, and reimbursement/approvals. While significant challenges, they are not insurmountable: protocols are in place to train clinical nurse specialists to perform LPs (13), and wide access to FDG-PET for cancer diagnosis and monitoring demonstrates that PET scanning using 18F tracers is feasible at scale.

In the donanemab trials, flortaucipir tau-PET was required to determine that individuals had intermediate levels of tau pathology. Flortaucipir is FDA approved but not reimbursed, and is not available in many countries. It is unclear whether this could be replaced by CSF examination, plasma biomarkers or even by careful clinical staging; this will require further work to determine the appropriate cut-points for inclusion/exclusion.

Administration

The number of individuals potentially eligible for intravenous infusions on a two-weekly or monthly basis will dwarf those receiving similar treatment for other neurological disorders. Infrastructure including infusion suites, pharmacy, and staff will need to be expanded or built in sites that allow convenient access for patients and carers. Again, as shown by the radical pathway shifts put in place to deliver thrombolysis/thrombectomy for stroke, this is not insurmountable. In due course it may be possible to move to home treatment delivery (some trials have already successfully implemented this (4)); there will be obvious benefits should effective subcutaneously administered drugs become available.

Monitoring and safety

Akin to experience with multiple sclerosis and stroke, the move from low efficacy, low risk treatments to disease modifying treatments requires management of rare but potentially life-threatening side effects. APOE-ε4 positivity is a major risk factor for ARIA. It is likely that genetic testing will be needed to facilitate discussions of treatment risk. Given the potential implications for family members, involvement of genetic counsellors may be needed.

While certain factors – APOE-ε4 status, the presence of microbleeds, and anticoagulation/thrombolysis – help predict risk and problems typically emerge soon after treatment initiation, it is not yet possible to determine who will develop ARIA or who is at risk of serious outcomes. Many patients with ARIA can be re-dosed safely after a period off treatment. Current protocols mandate frequent MRI which requires scanning and reporting infrastructure; as more real-world experience is gained these protocols are likely to be tailored and more focussed, and it may be that blood based biomarkers for ARIA will be developed. Symptoms of ARIA can be non-specific including blurred vision, headaches, unsteadiness, or can include focal deficits such as dysphasia; there will be a need for clear management guidelines, careful patient and carer education, and increased awareness amongst a wide range of healthcare professionals to ensure appropriate recognition and investigation of these patients, and that potentially harmful treatments (e.g. thrombolysis) are avoided (14).

Stopping criteria

A major and as yet unanswered question for healthcare delivery and cost is when these medications should be stopped – and how. It is not yet known if rendering a patient 'amyloid negative' is sufficient, noting that in the trials of donanemab dosing was stopped once amyloid-PET levels dropped below a pre-specified level (2). If after a period of remission amyloid re-accumulates, it is unclear if re-dosing is required. Some patients will not achieve amyloid clearance or will continue to progress clinically and so treatment may no longer be appropriate, or the burden of frequent intravenous medications and monitoring will outweigh the potential benefit. Careful communication with patients and caregivers will be needed. While initial approvals are likely to follow clinical trial protocols and similar clinical and molecular monitoring will likely be required, there will be major advantages in moving from PET/CSF to blood-based biomarkers when these are shown to be effective. The longer-term outcomes and safety of these treatments are unknown, and will need to be ascertained through post-market surveillance registries such as ALZ-NET, an Alzheimer's Association initiated registry for patients receiving FDA approved DMTs for AD in the USA (15).

Conclusion

The challenges involved in preparing for timely and equitable delivery of AD DMTs are significant. It is likely that new treatments will first be introduced in specialist centres, but as experience is gained, we will need to move to deliver treatments to all those who are eligible. The costs will be substantial, and innovative funding models akin to the industry/governmental risk-sharing scheme used to deliver early MS drugs in the UK may be required (16). Political will is vital and it is gratifying that the UK government has signalled this as a priority through the Dame Barbara Windsor Dementia Mission. Effecting change will require cooperation between all stakeholders, including clinicians, industry, charities, governments, patients, and carers. While undoubtedly a major challenge, this is also an unprecedented opportunity to fundamentally change the way dementia is perceived, improve pathways and care for all patients, slow or perhaps halt the disease in some, and pave the way to deliver the next generation of therapies as they become available.

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