



Emerging disease modifying therapies for older adults with Alzheimer disease: perspectives from the EuGMS special interest group in dementia

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Alzheimer's disease [AD] affects 5% of those aged 65–74, rising to one-third of older adults aged 85 and older [1]. “Intellectual impairment” is one of Bernard Isaac's “geriatric giants” alongside incontinence, immobility and instability (falls), and dementia (the majority of which is caused by AD) is arguably the geriatric syndrome with the greatest impact on quality of life, morbidity and mortality in older adults [2]. AD is a common thread between—and a common risk factor for many of these “geriatric giants” [3, 4].

Following recent breakthroughs in AD diagnostic biomarkers and the potential for disease-modifying therapies (DMT), it is essential that as geriatricians we ensure that the implications of these breakthroughs are considered for all older adults affected by AD. This includes those with mild or early-stage impairments and those with more advanced AD, multiple long-term conditions, polypharmacy and frailty. Critically, any diagnostic and treatment advances must be incorporated alongside gerontologically attuned, person-centred care for older adults with AD.

Cholinesterase inhibitors, the mainstay of pharmacological management of AD for the past three decades, offer at best symptomatic benefit and are associated with gastrointestinal and cardiovascular side effects leading to discontinuation in up to one-third. Recent Phase-3 clinical trials demonstrating the potential efficacy of immunotherapies targeting the accumulation of fibrillar amyloid β (A β)—aducanumab, lecanemab and donanemab—are cause for cautious optimism (See Table 1) [5–7]. However, the small clinical benefits of these DMTs in early AD must be delicately balanced against potential adverse effects including amyloid-related imaging abnormalities [ARIAs] which may be severe and even fatal, infusion reactions and a significant treatment and monitoring burden (Table 1). At present, clinical experience with anti-amyloid DMTs in AD is in its infancy and largely confined to clinical trials. There are currently 21 DMTs in phase 3 trials for AD and so it is likely that more positive results for DMT in early AD are to follow in the very near future [8]. As geriatricians, it is imperative that we are pro-active in developing a literacy around the evidence supporting the potential use of DMT, but in doing so, integrate any emerging evidence alongside gerontologically informed care in older adults with all stages of AD.

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Table 1 Phase 3 trial results for emerging anti-amyloid therapies in Alzheimer's disease

	Age (Years)	Sex (Female)	AD Stage	Severity (CDR-Sb)	Duration (Months)	Efficacy (CDR-Sb)	ARIA Frequency	Symptomatic ARIA	Serious ARIA	Infusion Reactions	Ref
Aducanumab (EMERGE)* N = 1638	70.6 (SD: 7.5)	52%	MCI due to AD/mild AD [NIA-AA]	2.51	18	-0.39 [high dose]	ARIA-E: 35% ARIA-H: 20%	20% of those with ARIA	1.5%	-	[5]
Lecanemab (CLARITY-AD) N = 1795	71.4 (SD: 7.9)	51.6%	MCI due to AD/mild AD [NIA-AA]	3.2	18	-0.45 [27% slowing of decline]	ARIA-E: 12.6% ARIA-H: 21.5%	ARIA-E: 2.8% ARIA-H: 0.7%	1.1% 3 deaths due to brain swelling/ macro-haemorrhages in Open-Label Extensions	26.4%	[7, 16]
Donanemab (TRAIL-BLAZER-ALZ 2)** N = 1736	60–85	NA **	MCI due to AD/mild AD [NIA-AA]	NA **	18	29% slowing of decline	ARIA-E: 24.0% ARIA-H: 31.4%	ARIA-E: 6.1%	1.6% 2 deaths attributed to ARIA	8.7%	[6]

NA Not Available; SD Standard Deviation; MCI Mild Cognitive Impairment; AD Alzheimer Disease; CDR-Sb Clinical Dementia Rating-Sum of Boxes; ARIA amyloid-related imaging abnormalities; Ref. Reference; NIA-AA National Institute for Ageing and Alzheimer's Association Diagnostic Criteria. ARIA-E amyloid-related imaging abnormalities-edema; ARIA-H amyloid-related imaging abnormalities-haemorrhage

*Results from EMERGE were published following trial termination for futility, efficacy and safety are presented for high-dose aducanumab (low-dose did not demonstrate a significant impact of CDR-Sb)

**Data extracted from Eli Lilly Press Release 2023; full peer-reviewed published trial results are awaited

The most common primary end-point in phase 3 clinical trials for anti-amyloid DMT in AD is the Clinical Dementia Rating Scale – Sum of Boxes (CDR-Sb), which rates cognitive and functional abilities in AD and ranges from 0 to 18 (0.5–2.5 reflects questionable impairment, 3.0–4.0 very mild dementia and 4.5–9.0 mild dementia, 9.5–15.5 moderate dementia and 16.0–18.0 severe dementia) [9]. Previous data suggest that a 1.0–2.0 point increase in the CDR-Sb represents a Minimally Clinically Important Difference (MCID) [10]. Data from both CLARITY-AD (lecanemab) and EMERGE (aducanumab) trials both fall short of this MCID, calling into question their real-world clinical efficacy. At present, aducanumab and lecanemab are approved only in the United States of America for MCI due to AD and mild dementia due to AD and Appropriate Use Recommendations (AURs) have been published [11, 12] highlighting the need for clinical-biological diagnosis, availability of infusion centres, MRI monitoring, radiological and clinical expertise in the management of ARIA and infusion reactions.

Future extension studies examining the benefits seen over a 18-month plateau or continuing with extended treatment may be crucial in determining whether these DMTs should be more widely used. In TRAILBLAZER ALZ-2, the inclusion of individuals with more advanced disease (greater tau burden) yielded a lower percentage change in comparison to an intermediate tau burden [6], hinting that DMTs may be less effective at more advanced stages of AD. Whilst the real-world clinical impact of these DMTs on key gerontological syndromes and quality-of-life is currently not clear, there is early data from CLARITY-AD to suggest that Lecanemab was associated with significantly less decline on exploratory Quality-of-Life outcomes (both patient and caregiver-rated) at 18-months [13]. For geriatricians, it is imperative that future studies include outcomes relevant to older adults with AD including further data on health-related quality-of-life, impact on falls, continence and physical frailty [14]. Despite trial participants being younger, better educated with less medical comorbidities than real-world patients, a significant number of older adults presenting to memory services may potentially be eligible for treatment with these DMTs [15].

The potential efficacy of DMTs in AD must be considered alongside the risk of ARIA (Table 1). Even though the majority of ARIA were asymptomatic, occurred early in treatment course and spontaneously resolved, serious ARIA occurred in 1.1–1.6% (Table 1). Serious ARIA may result in hospitalisation to manage complications such as seizures. A small number of fatalities have also been reported in the open-label extensions of Lecanemab and with Donanemab, Eli Lilly reported 2 fatalities attributable to ARIA [6, 16]. The nature of these rare adverse events remains a concern, especially in the context of questionable real-world efficacy of DMT.

Detection and management of ARIA involves a more intensive MRI scanning schedule which like infusion reactions, may have led to functional unblinding in phase 3 trials [16]. The CDR-Sb includes subjective reports from patients/caregivers and unblinding may influence subjective impression of changes. A further concern in clinical trial data is brain volume loss in individuals treated with anti-amyloid therapies which is of unclear clinical significance [16, 17]. It is imperative that those treated with DMT are enrolled in prospective registries so that the real-world impact of these adverse effects can be further elucidated.

Anti-amyloid DMTs are not licenced in Europe, but if future DMTs follow with more convincing efficacy, one of the key entry points to availing of these medications is an accurate and timely clinical-biological diagnosis of AD. Even though demonstration of AD pathological change is well-established clinically (depleted A β -42/elevated p-tau in cerebrospinal fluid or positive amyloid/tau positron emission tomography), biomarkers may lose utility with advanced age (typically not used > 80 years) and interpretation is complicated by the frequent occurrence of co-pathology in older adults—where “pure” AD is the exception rather than the rule [18]. In potentially moving towards a more biologically based diagnosis, there will likely be a significant increase in the number of individuals referred to and diagnosed with AD in memory services, necessitating geriatricians to develop an understanding of both the use and implications of clinical-biological definitions of AD. Critically, this must be accompanied by an increase in the number, multi-disciplinary resource allocation and re-configuration of memory services in their current form. This must not come at the expense of resource allocation for older adults with more advanced AD ineligible for potential DMT. It is important to remember that AD is significantly underdiagnosed and increased sophistication in clinical-biological diagnosis for older adults potentially eligible for DMT must be incorporated alongside initiatives to increase accurate and timely diagnosis on a global scale.

A critical concern in the potential use of DMT in dementia refers to the requirement for biomarker confirmation for diagnosis, regular intravenous infusions once/twice per month (requiring infusion suites, clinical staff experienced in the delivery of these medications and management of potential infusion reactions), regular MRI scanning and expertise in the management of ARIA and their potentially severe complications [11, 12]. Given that many older adults with AD do not even receive an MRI at time of diagnosis, substantial changes would be required to deliver DMTs at a population level including increasing neuroimaging availability, radiologists trained in interpreting their interpretation and clear pathways to identify and manage potential ARIA.

Should the evidence in favour of the use of DMTs in older adults with AD become more convincing, geriatricians will

play a crucial role in advocating that equitable resources be made available for both better diagnostics for AD, as well as health and social care resources to support those living with established disease. If DMT were to be used in older adults AD, it should only be considered as part of a broad evidence-based treatment approach including addressing modifiable risk factors based on individual risk profiles in older adults. As with most conditions in later-life, AD responds best to a multi-modal and multi-disciplinary treatment plan. This includes maintaining and enhancing proactive brain-health approaches, addressing vascular risk factors, diet and exercise and the use of cognitive stimulation where appropriate [19].

In summary, the advent of DMT in AD is a welcome development but the real-world benefit of these medications for older adults is yet to be determined. For geriatricians, AD significantly contributes to later-life rates of institutionalisation, frailty, falls, continence issues and other geriatric syndromes associated with diminished quality of life. We must consider the potential effect of any potential DMT on these important outcomes and advocate for their inclusion in clinical trials alongside traditional gold-standard dementia severity assessments. As geriatricians, there must be a delicate balance between advocating for timely access to any potential DMT which may benefit older adults with AD and advocacy for continued and enhanced supportive care pathways for older adults with more advanced AD or more significant levels of frailty who may not be eligible for new DMT. Whilst the needle has indeed been moved by the potential emergence of DMT, we must ensure that older adults with more severe AD are not left behind and cautiously evaluate the real-world clinical impact of potential DMT on gerontologically-focussed outcomes which are important to older adults, their caregivers and clinicians alike.

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