

# Monoclonal antibodies for early Alzheimer disease: a long road to discovery and marketing approval, a short timeline for health systems to organise services

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Disease-modifying drugs are now available for the treatment of early Alzheimer disease (AD). These agents belong to the class of monoclonal antibodies (mAbs) and target amyloid- $\beta_{1-42}$  in different molecular epitopes and aggregation states [1]. In the United States, two anti-amyloid drugs are available on the market following approval by the Food and Drug Administration (FDA): lecanemab, approved in 2023, and donanemab, approved in 2024. Earlier, in 2022, another mAb, aducanumab, was available in the US before being withdrawn in 2024. Since then, other countries have aligned with the FDA's decision and licensed these anti-amyloid mAbs for clinical use in patients with mild cognitive impairment and mild dementia due to AD.

After extensive debate at the European Medicine Agency (EMA), lecanemab was eventually approved by the European Commission on 15 April 2025. Donanemab received

a positive recommendation in July 2025 and marketing authorisation on 25 September 2025.

The main concerns of the regulatory authorities relate to the modest clinical benefit demonstrated in clinical trials and the risk of side effects, notably amyloid related imaging abnormalities (ARIA), which can present as asymptomatic or symptomatic brain oedema/effusion (ARIA-E) and haemorrhages (ARIA-H) on magnetic resonance imaging (MRI). Both lecanemab and donanemab showed similar effect size in slowing disease progression (a reduction in disease progression on the CDR-SB scale of 27% with lecanemab and 29% with donanemab) [2, 3]. In the donanemab trial, a greater response (35% change) was observed in patients with low/medium tau-related neuropathological changes [3]. A 30% reduction in the slope trajectory translates in approximately a 5-month delay in expected cognitive and functional decline.

In clinical trials, ARIA-related side effects were detected in 21.5% of patients treated with lecanemab (vs. 9.5% with placebo) and 36.8% of those treated with donanemab (vs. 14.9% with placebo), and these were mostly asymptomatic [2, 3]. However, more recent data using a modified dose titration regimen for donanemab, with a lower starting dose, have shown a significant reduction in ARIA events, even in *APOE*  $\epsilon 4$  carriers who are at higher risk of ARIA [4].

Following the EMA approval of the first anti-amyloid mAb, the Italian Drug Regulatory Agency (AIFA) will need to develop recommendations for patient inclusion criteria, protocols for drug administration and side effects monitoring, and the overall patient journey. Additionally, AIFA will need to define standards for the reorganization of dedicated healthcare services. Guidelines for appropriate use recommendations (AUR) are already available in the literature for both lecanemab [5, 6] and donanemab [7], and can serve as a baseline framework to be adapted to the context of the Italian healthcare system.

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The work of the Italian Authorities should be guided by the optimization of the risk/benefit ratio, aiming to maximize clinical benefit and minimize the risk of ARIA. To maximize clinical benefit, accurate selection of patients with a higher probability of response to treatment is needed, i.e., those at an early disease stage and with biological evidence of AD pathology and absent or minimal co-pathology such as small vessel disease or Lewy body disease. To minimize the risk of side effects, a careful assessment of clinical, neuroimaging, and genetic factors predisposing to ARIA should be performed before treatment. After initiation, patients should be closely monitored clinically and radiologically for early detection of ARIA and prompt dosing modification (Fig. 1).

In this context, several issues require in-depth consideration and are not fully addressed in the published guidelines [5–7]. A panel of dementia experts affiliated with SINDem (The Italian Neurological Society for Dementia) has identified crucial themes in the patient journey and the need for health service reorganization to ensure efficient care for patients eligible for these treatments.

To optimize the diagnostic process, several clinical issues deserve consideration.

Inclusion/exclusion criteria:

- What is the minimum dataset (i.e., type of cognitive assessment; blood-based biomarkers; MRI;) that should be

used for case finding of suitable candidates, and which specialist should be primarily involved?

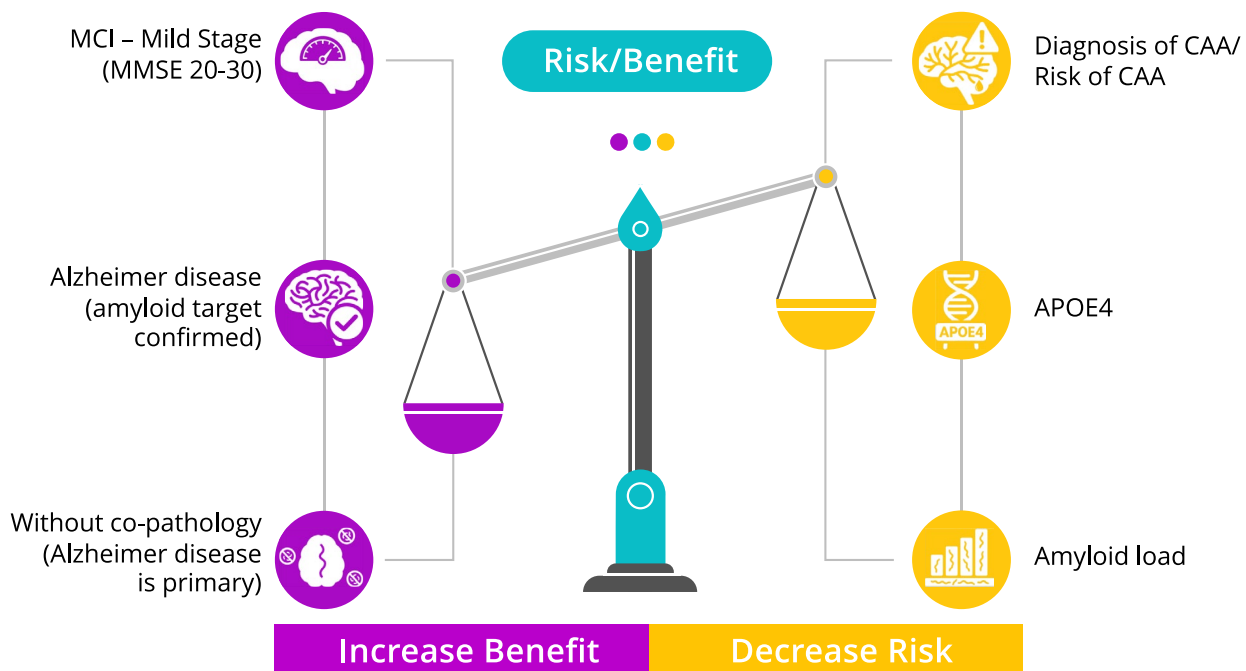
- Should a chronological upper age limit be established, and patient's frailty be considered an integrative variable?
- In the evaluation of patients with MCI due to AD, risk factors algorithm of progression should influence the clinician's decision-making process?
- Apart from patients with typical hippocampal amnesic syndrome, should other atypical AD variants be considered (e.g., those with a high probability of AD-related neuropathology as the primary cause, such as posterior cortical atrophy and logopenic aphasia, or nonfluent aphasia and corticobasal syndrome)?
- Which medical conditions and medications (in addition to anticoagulants) should constitute exclusion criteria for anti-amyloid mAbs?

Establishing a biological diagnosis:

- Which is the most cost-effective investigational pathway for a biological diagnosis?
- If CSF is considered the first-line investigation and amyloid-PET a second choice, how would this sequence be implemented in memory clinics without expertise or access to personnel who can perform lumbar punctures?

### Eligible Subjects: Precise Selection

### Reduced Prognostic Risk Factors For ARIA



**Fig. 1** The image shows the conditions related to the improvement of benefit (list on the left) and decrease of the risks (list on the right) to optimize the risk/benefit balance with the use of anti-amyloid monoclonal antibodies for mild Alzheimer disease

- When amyloid PET is used, will quantification of brain amyloid burden using centiloids or other metrics be necessary for a biological diagnosis, other than monitoring of response to therapy, or will visual assessment with validated criteria be sufficient?
- Should approved blood-based biomarkers (e.g., pTau<sub>217</sub>/Aβ<sub>1–42</sub> ratio) be considered as first-line screening if approved by EMA/AIFA, as recently suggested by the FDA?

To minimize risk of ARIA, the following issues should be considered.

Evaluation of ARIA risk:

- To what extent does detection of cortical siderosis and microbleeds differ between GE and SWI sequences, or between 1.5 T and 3 T MRI scanners?
- Should specific centres be selected for centralised MRI evaluation to align with the new Boston criteria for cerebral amyloid angiopathy and vascular burden assessment?
- Do patients who meet eligibility MRI criteria have an increased risk of ARIA (and how much) even if they have a low burden of CAA or cerebrovascular disease and (e.g., 1–3 microbleeds or a Fazekas scale score of 2)?
- Could an ARIA risk card, including clinical, radiological, and genetic features (e.g., *APOE* ε4 heterozygosity, arterial hypertension, cerebrovascular load, number of microbleeds, and amyloid load), be helpful in the management of treatment infusion?
- If patients with *APOE* ε4 heterozygosity are eligible, should the schedule of monitoring and follow-up be adjusted for these patients (e.g., the use of 3 T MRI scanners and SWI sequences to increase sensitivity to ARIA)?

How to manage ARIA side effects and mimickers:

- Given the higher risk of acute symptoms due to ARIA in patients on anti-amyloid drugs, is it necessary to implement a dedicated neuroimaging protocol to assess patients presenting at ER services with sudden focal onset symptoms, and if so, should those patients be referred directly to a hub centre of the stroke network?
- What is the best acute management treatment for stroke in these patients?
- What should be done if oral anticoagulation is suddenly required?

The greatest challenge will be adapting the organization of current memory services to the changes required by this

new paradigm of diagnostic and monitoring workup, scaling from a large number of potential candidates to the small percentage of patients (around 10%) expected to be eligible for this treatment. For case finding and first-level screening, a major game-changer could be the use of blood-based biomarkers to identify or exclude candidates for further investigations to reach a biological diagnosis. In May 2025, a diagnostic test based on detection of plasma pTau<sub>217</sub> and Aβ<sub>1–42</sub> received FDA approval as an aid for AD diagnosis. Most validation studies suggest their use as screening tools, with two cut-offs providing an effective strategy to reduce the number of patients requiring CSF or amyloid PET assessment [8]. Moreover, the informative value of biological staging extends to the prognostic likelihood of rate of progression in symptomatic patients with AD [9]. This information, in association with clinical-demographic variables [10], can inform the clinician's decision making when evaluating the risk/benefit ratio in the real-world scenario of the memory clinics. In addition to this point, there is also a timely need for novel biomarkers to predict ARIA and to overcome the current limitations of MRI markers.

In the near future, the organization of dementia services would benefit from improved networking among health-care professionals and from the contribution of different specialists (clinicians, neuroradiologists, nuclear medicine physicians, biologists, geneticists, neuropsychologists). The application of virtual consultations could facilitate more efficient interactions. Interdisciplinary case discussion meetings will be essential for collective decisions about eligibility and patient management. Tele-consulting for neuro-image assessment could strengthen collaborations between local neuroradiologists and specialists at infusion centres, enabling a rapid exchange of information in cases of acute or subacute ARIA-like symptoms. There is a significant risk of inequity and limited access to treatments for certain subpopulations or regions, making it essential to implement a network to optimise referrals. The use of remote cognitive assessment may be useful to mitigate the negative impact of limited access to early diagnosis.

After two years of experience in the US and in other few Countries, recent published data on the use of anti-amyloid mAbs in real-world settings may inform clinicians on the best approach to management of these treatments and regulatory Authorities on the needs for the organization of dedicated health services [11]. A reorganization of health services for dementia is therefore mandatory in the context of a publicly-funded health system, such as the one available in Italy. There are urgent needs to be addressed before the widespread commercialization of mAbs. These include: 1) defining and preparing services capable of drug delivery to selected eligible patients; 2) implementing new modes of interdisciplinary streamlined communication; 3)

establishing a Pharmacovigilance Risk Assessment Committee to implement a patient register as well as post-authorization studies of safety and efficacy.

In conclusion, the availability of monoclonal antibodies marks a significant advance in the treatment of early Alzheimer's disease. While the introduction of these therapies poses important challenges for the Italian healthcare system, we believe that, with careful patient selection, rigorous monitoring, and appropriate organizational changes, these treatments can be implemented safely and effectively. The SINDem group strongly endorses the timely and responsible adoption of anti-amyloid monoclonal antibodies for eligible patients with Alzheimer's disease in Italy, and supports the development of clear, evidence-based protocols to ensure equitable access and optimal patient outcomes.

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## Declarations

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