CRITICAL REVIEW

Anti-Amyloid Immunotherapy in Early Alzheimer's Disease: Clinical Efficacy, Amyloid-Related Imaging Abnormalities, and the Translational Gap Between Biomarker and Functional Outcomes

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ABSTRACT

Anti-amyloid immunotherapy has emerged as the first disease-modifying therapeutic strategy in Alzheimer's disease (AD) to achieve regulatory approval, following decades of failed clinical trials. Lecanemab (Leqembi®) and donanemab have demonstrated statistically significant slowing of clinical decline in early symptomatic AD populations — yet the magnitude of benefit, the clinical meaningfulness of observed differences, the risk of amyloid-related imaging abnormalities (ARIA), and the challenge of identifying appropriate candidates for these costly and logistically demanding therapies have generated substantial scientific and policy debate. This critical review evaluates the phase III trial evidence for lecanemab (CLARITY AD) and donanemab (TRAILBLAZER-ALZ 2) through the lens of effect size interpretation, ARIA risk stratification, APOE ε4 genotype considerations, real-world implementation challenges, and the broader question of whether amyloid clearance is a sufficiently complete therapeutic target given the multifactorial nature of AD pathology. We conclude by proposing a precision medicine framework for appropriate candidate selection that integrates amyloid PET or CSF biomarker status, APOE genotyping, cognitive staging, and ARIA risk assessment.

Keywords: *Alzheimer's disease, lecanemab, donanemab, anti-amyloid immunotherapy, ARIA, APOE ε4, amyloid PET, disease-modifying therapy, mild cognitive impairment, tau PET*

1. INTRODUCTION

Alzheimer's disease afflicts an estimated 55 million people globally and remains one of the greatest unmet medical needs of the twenty-first century. The amyloid cascade hypothesis — positing that the pathological accumulation of amyloid-β (Aβ) peptide in the brain is the seminal event driving downstream tau pathology, neuroinflammation, synaptic dysfunction, and neurodegeneration — has guided drug development strategies for three decades, despite a prolonged series of phase III trial failures that generated widespread skepticism about the hypothesis itself.

The FDA's accelerated approval of aducanumab in 2021 — later withdrawn by its manufacturer — and the subsequent traditional approvals of lecanemab (January 2023) and donanemab (July 2024) have reinvigorated amyloid-targeting strategies while simultaneously intensifying scrutiny of the benefit-risk profile of this therapeutic class. Unlike earlier failed agents, lecanemab and donanemab target soluble amyloid protofibrils and plaque-bound amyloid, respectively — mechanistic distinctions that may explain their superior efficacy over earlier monoclonal antibodies targeting primarily monomeric Aβ.

The central challenge facing clinicians, payers, and policymakers is interpreting the clinical meaningfulness of statistically significant but numerically modest slowing of decline on composite endpoints. Simultaneously, the risk of ARIA — encompassing ARIA-E (edema/effusions) and ARIA-H (microhemorrhages/hemosiderosis) — particularly in APOE ε4 homozygotes, demands careful pre-treatment risk stratification. This critical review provides a balanced, evidence-based analysis of the current anti-amyloid immunotherapy landscape.

2. CLINICAL TRIAL EVIDENCE

2.1 CLARITY AD — Lecanemab

The CLARITY AD trial enrolled 1,795 participants with early AD (mild cognitive impairment due to AD or mild AD dementia with confirmed amyloid pathology by PET or CSF biomarkers) randomized to lecanemab 10 mg/kg biweekly or placebo. Over 18 months, lecanemab treatment resulted in a 27% reduction in the rate of cognitive decline as measured by the Clinical Dementia Rating Sum of Boxes (CDR-SB). The absolute difference was 0.45 CDR-SB points (95% CI: 0.67–0.23; p<0.001) in favor of lecanemab. Secondary endpoints including the ADAS-Cog14, ADCS-MCI-ADL, and ADCOMS all showed nominally significant improvements. Amyloid PET showed near-complete clearance in approximately 70% of lecanemab-treated participants by 18 months.

2.2 TRAILBLAZER-ALZ 2 — Donanemab

The TRAILBLAZER-ALZ 2 trial enrolled 1,736 participants with early symptomatic AD stratified by tau PET burden (low/medium vs. high tau). In the combined low/medium tau population — representing the more intact neurological reserve phenotype — donanemab demonstrated a 35% slowing of decline on the integrated Alzheimer's Disease Rating Scale (iADRS) versus placebo. Notably, donanemab was administered until amyloid plaque clearance was confirmed on PET (or for a maximum of 72 weeks), with subsequent placebo substitution in completers — a discontinuation design with important durability implications. Amyloid clearance was achieved in approximately 84% of donanemab-treated participants within 76 weeks.

Parameter	Lecanemab (CLARITY AD)	Donanemab (TRAILBLAZER-ALZ 2)
N enrolled	1,795	1,736
Primary endpoint	CDR-SB change at 18 months	iADRS change at 76 weeks
Relative slowing of decline	27% (p<0.001)	35% (p<0.001, low/med tau)
Absolute difference	−0.45 CDR-SB points	−3.25 iADRS points
ARIA-E (symptomatic)	2.8%	6.1%
ARIA-H (any grade)	17.3%	31.4%
Fatal ARIA events	3 (0.3%)	3 (0.3%)
Amyloid clearance (PET)	~70% at 18 months	~84% at 76 weeks

Table 1. Head-to-head comparison of key trial parameters for lecanemab and donanemab.

3. INTERPRETING CLINICAL MEANINGFULNESS

The question of whether a 27–35% relative slowing of cognitive decline translates into clinically perceptible benefit for patients and caregivers remains actively debated. The minimum clinically important difference (MCID) for the CDR-SB has been estimated at 0.5–1.0 points over 18 months

in the mild AD population — placing the observed 0.45-point benefit marginally below commonly cited MCID thresholds. Proponents argue that even sub-MCID slowing is meaningful at a population level and that longer-term trials would amplify observed differences. Critics contend that expensive, risky therapies requiring frequent infusions and MRI monitoring must demonstrate benefit that patients and caregivers can actually perceive to justify widespread adoption.

Patient-reported and caregiver-reported outcome analyses from CLARITY AD subgroup data suggest that the treatment effect is more readily detectable in mild AD dementia patients (as opposed to MCI-AD) and in those who achieve robust amyloid clearance — supporting a precision approach to patient selection rather than broad population-level treatment. Extended open-label follow-up data, now available for lecanemab, suggest that the benefit-placebo gap continues to widen beyond the 18-month double-blind period, providing more optimistic projections for long-term clinical impact.

4. ARIA: RISK STRATIFICATION AND MANAGEMENT

ARIA represents the primary safety concern of anti-amyloid immunotherapy. ARIA-E (cerebral edema and sulcal effusions) typically manifests within the first 12 weeks of treatment, while ARIA-H (microhemorrhages and hemosiderosis) may accumulate throughout the treatment course. The vast majority of ARIA events are radiographically detected and asymptomatic; however, symptomatic ARIA — particularly when severe — carries risk of lasting neurological deficits and, in rare cases, fatal outcomes.

APOE ε4 genotype is the dominant risk factor: APOE ε4 homozygotes carry a cumulative ARIA-E rate of approximately 45% with lecanemab (vs. ~10% in ε4 non-carriers), representing a 4.5-fold increased risk that substantially alters the benefit-risk calculus for this genotype subgroup. Current clinical practice recommendations include baseline MRI within 1 year of treatment initiation, treatment hold for symptomatic or radiographically severe ARIA, and enhanced MRI surveillance at weeks 4, 8, 12, and 26.

APOE Genotype	ARIA-E Rate (%)	ARIA-H Rate (%)	Clinical Guidance
ε4/ε4 (homozygous)	~45%	~40%	Discuss risk carefully; consider relative contraindication
ε3/ε4 (heterozygous)	~20%	~20%	Proceed with enhanced monitoring protocol
ε3/ε3 or ε2 carrier	~10%	~12%	Standard monitoring; most favorable profile

Table 2. ARIA risk stratification by APOE ε4 genotype for lecanemab-treated patients.

5. PRECISION MEDICINE CANDIDATE SELECTION FRAMEWORK

Based on the totality of available evidence, we propose the following candidate selection framework for anti-amyloid immunotherapy: (1) Biomarker-confirmed AD pathology — amyloid PET or CSF Aβ42/40 ratio plus tau biomarker positivity is mandatory; clinical diagnosis alone is insufficient. (2) Early symptomatic stage — MCI due to AD or mild AD dementia (CDR 0.5–1.0); trial data do not support use in asymptomatic or moderate-to-severe AD. (3) APOE ε4 genotyping — essential for informed consent and risk communication; homozygous ε4 carriers require individualized benefit-risk discussion. (4) Absence of high ARIA-risk features — prior macrohemorrhage, anticoagulant use, and uncontrolled hypertension are relative or absolute

contraindications. (5) Cognitive reserve assessment — patients with higher baseline cognitive reserve (education, cognitive engagement history) appear to sustain functional benefit longer.

6. CONCLUSIONS

Anti-amyloid immunotherapy has crossed a pivotal clinical threshold, with lecanemab and donanemab representing the first pharmacological interventions to meaningfully slow the trajectory of Alzheimer's disease — a monumental scientific achievement. The clinical meaningfulness of these effects, while modest in absolute terms, is real and supported by convergent biomarker, functional, and emerging real-world evidence. A precision medicine approach — rigorously applying biomarker-confirmed amyloid pathology, APOE ε4 genotyping, and clinical staging criteria to patient selection — is essential to maximize the benefit-risk profile. Amyloid clearance alone is unlikely to be a complete therapeutic strategy; combination approaches incorporating tau-targeting agents, neuroinflammation modulators, and neuroprotective strategies will define the next decade of AD drug development.

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