Short Communication

Reducing ARIA risk in Alzheimer's disease: Real-world impact of *APOE* genotype-guided slow titration with aducanumab and lecanemab

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Abstract

We evaluated whether apolipoprotein E (*APOE*) genotype-guided slow titration of monoclonal antibodies reduced amyloid-related imaging abnormalities (ARIA) in Alzheimer's disease. We retrospectively analyzed ARIA incidence in 25 patients on aducanumab and 19 patients on lecanemab on a genotype-informed protocol in a private practice setting. ARIA-E and ARIA-H each occurred in 4% of the aducanumab group and 5% of the lecanemab group. Plaque clearance was achieved in 50% of evaluable aducanumab patients and 26.3% of lecanemab patients. Compared to clinical trial ARIA rates, our results suggest that individualized, genotype-informed titration improves safety although plaque clearance rates were less robust.

Keywords

aducanumab, Alzheimer's disease, amyloid-related imaging abnormalities, *APOE* genotype, lecanemab, monoclonal antibodies, real-world evidence, slow titration

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Introduction

Monoclonal antibodies (mAb) targeting amyloid-β (Aβ) plaques, including aducanumab and lecanemab, have shifted the treatment landscape for Alzheimer's disease (AD). However, amyloid-related imaging abnormalities (ARIA) with edema (ARIA-E) and hemorrhage (ARIA-H), remain significant safety concerns, particularly in apolipoprotein E (*APOE*) ε4 carriers, with the highest risk in ε4 homozygotes.[1–4]

While pivotal trials employed fixed titration schedules, emerging real-world evidence suggests that slow, individualized titration may mitigate ARIA risk. For example, modified dose escalation with donanemab significantly reduced ARIA incidence.[5] Here, we present outcomes from a real-world cohort treated with aducanumab and lecanemab using an *APOE* genotype-informed slow titration strategy, evaluating ARIA incidence and plaque clearance. These findings may inform clinical application of currently approved monoclonal antibodies (mAbs).

Methods

Study design and patients

We conducted a retrospective chart review at a single private practice, including patients with mild cognitive impairment with AD pathology or early symptomatic AD initiated on aducanumab (n = 25) or lecanemab (n = 19) between January 2021 and December 2023. Institutional Review Board approval was obtained prior to study initiation. Due to the retrospective nature of the study, informed consent was not required.

Inclusion criteria

- Clinical diagnosis of mild cognitive impairment (MCI) or mild dementia due to AD.

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- Confirmed amyloid positivity by PET imaging or cerebrospinal fluid biomarkers.
- Availability of *APOE* genotype.
- Minimum of six months of treatment.

Titration protocols

- Aducanumab was initiated at 1 mg/kg monthly for 3 months, then up-titrated by 1 mg/kg every 2 months (*APOE* ε4/ε4 and *APOE* ε4/-) or monthly (*APOE* -/-), with 10 mg/kg reached at about 21 and 12 months respectively.
- Lecanemab was initiated at 5 mg/kg for four biweekly infusions, then up-titrated by 1 mg/kg every 8 weeks (*APOE* ε4/ε4), 6 weeks (*APOE* ε4/-), or 4 weeks (*APOE* -/-), with 10 mg/kg reached at about 12, 10, and 7 months, respectively.
- All patients underwent standardized clinical examinations (monthly for aducanumab, bi-weekly for lecanemab) and MRI monitoring with additional imaging after each dose escalation. Titration was paused or delayed upon detection of moderate ARIA.

Outcome measures

- Incidence of ARIA-E and ARIA-H.
- Amyloid plaque clearance defined as amyloid-PET conversion to plaque-negative status.

Results

Patient characteristics are shown in Table 1. ARIA outcomes and plaque clearance are summarized in Table 2. One patient with a *PSEN1* mutation and diffuse amyloid deposition began aducanumab at age 31, three years after a positive amyloid scan. Two patients with low Mini-Mental State Examination scores due to expressive aphasia also initiated aducanumab.

Table 1. Patient characteristics.

Characteristic	Aducanumab (n = 25)	Lecanemab (n = 19)
APOE Genotype, n (%)	ε2/ε3: 1; ε3/ε3: 6; ε3/ε4: 16; ε4/ε4: 2 (ε4 carriers: 72%)	ε3/ε3: 3; ε3/ε4: 8; ε4/ε4: 8 (ε4 carriers: 84%)
Gender, n (M/F)	10/15	6/13
Age, mean (range), y	69 (31–86)	72 (57–83)
Education, mean (range), y	17.6 (12–20)	17 (12–20)
MMSE score, mean (range)	23 (9–30)	25 (18–30)

APOE: Apolipoprotein E; MMSE: Mini-Mental State Examination.
ε4 carriers were defined as patients with at least one ε4 allele (either ε3/ε4 or ε4/ε4).

Among patients receiving aducanumab, an *APOE* ε4/ε4 individual developed moderate, asymptomatic ARIA-E detected on routine imaging 468 days after starting treatment, shortly after a dose increase to 8 mg/kg. An *APOE* ε3/ε4 patient developed mild, asymptomatic ARIA-H on MRI 147 days after initiation, also following a dose increase.

Two patients who remained plaque-positive on aducanumab were switched to lecanemab once it became available and are included in the lecanemab analysis. One of these patients (*APOE* ε3/ε4), developed mild ARIA-E 71 days after switching. Another patient, not previously on aducanumab (*APOE* ε4/ε4), developed asymptomatic mild ARIA-H 401 days after starting lecanemab.

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

Discussion

Our findings demonstrate that *APOE* genotype-guided slow titration strategies significantly reduce ARIA incidence although plaque clearance was not as robust and may take longer to achieve. Compared with pivotal trial data—where ARIA incidence in *APOE* ε4 carriers reached 35–40%—our observed rates were substantially lower (4–5%).[1,3,4,6] In our cohort, 72% of aducanumab-treated patients and 84% of lecanemab-treated patients were *APOE* ε4 carriers.

Recent work with donanemab also supports this approach: modified slower dose titration reduced ARIA-E from 24% to 14%, and from 57% to 19% in ε4 homozygotes, without compromising plaque clearance.[5]

In our cohort, aducanumab plaque clearance rates (50%) were consistent with EMERGE and ENGAGE trial benchmarks (~30–40% amyloid reduction at 18 months).[4] Lecanemab plaque clearance (26%) was lower than the 68% plaque-negativity rate reported in the CLARITY trial.[3] However, we did not measure percentage reductions in amyloid burden, and our patients may have started with higher baseline levels, limiting plaque negativity despite possible signal reduction.

Notably, some patients cleared plaque at doses as low as 6 mg/kg on aducanumab, consistent with trial data.[7] ARIA onset was delayed (median ~300 days) supporting the safety of slow escalation.

The biological rationale for slow titration is grounded in Aβ clearance mechanisms. Solubilized Aβ is cleared via several pathways: transport across the blood-brain barrier (BBB) into vascular smooth muscle cells, along perivascular routes to the glymphatic system or through neuronal, glial or enzymatic degradation.[8]

Rapid solubilization may overwhelm these systems, promoting vascular amyloid deposition, inflammation and BBB disruption, ultimately leading to ARIA-E and ARIA-H.

Table 2. Summary of outcomes (ARIA incidence and plaque clearance).

Treatment Group	N	ARIA-E (%)	ARIA-H (%)	Plaque Clearance (%)	Median Time to ARIA	Median Time to Clearance (months)
Aducanumab	25	1 (4%)	1 (4%)	50% (8/16)	308 days	12–18 months
Lecanemab	19	1 (5%)	1 (5%)	26.3% (5/19)	236 days	12–14 months

ARIA-E: amyloid-related imaging abnormalities–edema; ARIA-H: amyloid-related imaging abnormalities–hemorrhage.

APOE proteins facilitate Aβ clearance, but the ε4 isoform is less effective, making ε4 carriers particularly vulnerable to ARIA with mAb therapy.[8]

A slower titration likely reduces the sudden load of solubilized Aβ, giving clearance pathways time to adapt and possibly allowing the BBB to repair itself. In a prior study of 20 AD patients (19/20 ε4 carriers), none developed ARIA during slow-titrated, low-dose aducanumab over 8 months, the period of highest ARIA risk.[9]

Our observations also align with studies like ICEBERG (2024), which suggest that vascular amyloid (cerebral amyloid angiopathy, or CAA) and microvascular fragility—not simply parenchymal plaques—may drive ARIA risk.[10] CAA affects ~80% of AD patients and weakens vascular integrity, leading to hemorrhagic and ischemic lesions8.

Thus, mitigating ARIA may require accommodating the vascular amyloid burden alongside plaque clearance goals.

Our study limitations include retrospective design, limited sample size, and potential imaging variability. Notably, amyloid clearance rates were modest (26–50%) compared to nearly 70–80% clearance rates reported in pivotal trials, possibly reflecting shorter follow-up durations and patient heterogeneity. Additionally, because this was a clinical study, quantitative measures of amyloid burden, such as centiloid values, were unavailable. Nevertheless, these real-world observations support further prospective validation.

Conclusions

As monoclonal antibody use becomes more widespread, strategies to mitigate ARIA will be critical. *APOE* genotype-guided slow dose titration appears effective at reducing ARIA risk although plaque clearance was reduced and may require a longer treatment course.

Especially in *APOE* ε4 carriers, slow titration may better accommodate concurrent CAA and allow BBB stabilization, decreasing both ARIA-E and ARIA-H incidence.

Future research should focus on algorithm-driven titration schedules personalized to genetic risk, co-morbidities such as CAA, baseline amyloid burden, and emerging plasma biomarkers (e.g., p-tau217) to further enhance safety and efficacy.

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Ethical considerations

The Institutional Review Board approved the study and waived the requirement for approval. (BRANY File # 25-12-034-1701), Investigator Initiated Protocol N1005; BRANY | 1981 Marcus Avenue, Suite 210, Lake Success, NY 11042 | 516.470.6900 T | 516-470-6903 F | www.brany.com.

Consent to participate

The requirement for informed consent to participate has been waived by the Institutional Review Board.

Author contributions

Nicholas Mervosh: Data curation; Formal analysis; Project administration.

Nadir Bilici: Data curation; Formal analysis; Project administration.

Thomas Wisniewski: Writing – review & editing.

Gayatri Devi: Conceptualization; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

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Declaration of conflicting interests

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Data availability statement

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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