

RESEARCH ARTICLE

Regional amyloid-PET clearance dynamics and anti-A β monoclonal antibody therapy: a preliminary real-world study

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Abstract

INTRODUCTION: Amyloid positron emission tomography (PET) is the reference biomarker for treatment target engagement in anti-amyloid beta (A β) therapies in early symptomatic Alzheimer's disease (AD), yet global metrics may mask a regional heterogeneity of amyloid clearance.

METHODS: We report real-world longitudinal amyloid-PET data from 26 patients treated with lecanemab or donanemab for 6 months. Global Centiloids and regional standardized uptake value ratios (SUVRs) were quantified at baseline and 6 months and examined according to treatment, clinical diagnosis, and clinical stage.

RESULTS: Amyloid removal was regionally heterogeneous. Patients with mild cognitive impairment showed greater cortical amyloid reduction than those with mild dementia, while early- and late-onset AD exhibited comparable clearance. Frontal, anterior cingulate, and parietal regions showed the largest SUVR reductions, whereas the occipital cortex and temporal mesial cortex were consistently spared, including in patients reaching global amyloid-PET negativity.

DISCUSSION: Early amyloid clearance following anti-amyloid treatment is regionally heterogeneous and incompletely captured by global PET measures.

KEYWORDS

Alzheimer's disease, amyloid positron emission tomography, anti-amyloid therapy, target engagement

Highlights

- Amyloid-PET shows regional heterogeneity after 6 months of anti-amyloid therapy.

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- MCI shows greater amyloid reduction than mild dementia at 6 months.
- Global PET negativity may mask persistent regional amyloid uptake.
- Occipital cortex often retains amyloid despite global PET negativity.

1 | BACKGROUND

The approval of lecanemab and donanemab has introduced disease-modifying therapies for early symptomatic Alzheimer's disease (AD), with amyloid positron emission tomography (PET) playing a central role in demonstrating the reduction of fibrillar amyloid beta ($A\beta$) burden.^{1,2} Both anti- $A\beta$ monoclonal antibodies produce marked reductions in amyloid-PET signal accompanied by modest but significant clinical benefit, establishing longitudinal amyloid-PET as the reference biomarker of pharmacodynamic response to anti- $A\beta$ therapy.¹⁻³

A recent framework proposed by the Alzheimer's Association introduces treatment-related amyloid clearance (TRAC) to standardize interpretation of amyloid-PET changes after anti- $A\beta$ therapy. "Full TRAC" indicates that post-treatment amyloid levels fall below a predefined PET positivity threshold, while "partial TRAC" denotes substantial reduction that remains above that cutoff.⁴

However, major uncertainties remain. Current practice defines treatment success using global amyloid burden (e.g., Centiloid [CL] values), but thresholds vary across trials and global metrics often exclude certain brain regions (e.g., occipital cortex or striatum).⁵ Therefore, residual amyloid deposits might persist regionally even when global PET measures indicate "negativity."⁴

This issue is clinically relevant in routine practice. Donanemab discontinuation has been operationalized using predefined global CL thresholds,^{1,6} whereas for lecanemab no PET-based criteria currently inform treatment modification, continuation, or interpretation of sub-optimal response.^{7,8} At the same time, the extent to which amyloid removal varies across brain regions, clinical stages, and AD phenotypes during early treatment remains incompletely characterized outside clinical trials.⁴

Building on this rationale, we describe real-world amyloid-PET data from a cohort of patients treated with lecanemab or donanemab, focusing on how both global and regional standardized uptake value ratios (SUVRs) change after 6 months of therapy. We assessed patterns of amyloid reduction by treatment, clinical stage, and AD phenotype and described regional amyloid-PET findings after achievement of global amyloid negativity.

2 | METHODS

2.1 | PARTICIPANTS

A total of 56 anti- $A\beta$ treatment courses (lecanemab or donanemab) were initiated between September 2024 and March 2026 at the Cen-

ter for Alzheimer's and Related Diseases (CARD), IRCCS San Raffaele Hospital, Milan, Italy. This included four patients who were switched from lecanemab to donanemab during follow-up. At the time of data lock, 26 treatment courses (25 unique patients) had completed the 6-month follow-up PET assessment and were eligible for analysis. Among the four patients who switched therapy, only one had completed both treatment courses with corresponding longitudinal PET evaluations and therefore contributed two treatment episodes to the analyzed dataset.

All patients underwent comprehensive neurological and neuropsychological assessments at baseline and at 6-month follow-up, together with baseline and protocol-specified ARIA-monitoring 1.5T brain MRI. Baseline and 6-month follow-up amyloid-PET scans were obtained for all patients. Eligibility and contraindications followed European Medicines Agency (EMA)-approved indications for the respective agents. Clinical and demographic characteristics of the cohort are summarized in Table 1.

2.2 | Amyloid PET

Twenty-four patients underwent amyloid-PET on a PET/computed tomography (CT) scanner (GE Healthcare) and two on a PET/MRI scanner (GE Healthcare) for quantitative CL assessment.⁵ Either [^{18}F]Florbetaben ($n = 12$) (Neuraceq, Life Molecular Imaging) or [^{18}F]Flutemetamol ($n = 14$) (Vizamyl, GE Healthcare) was used following standard acquisition protocols. Within each patient, the same tracer and scanner were consistently used at baseline and follow-up to ensure longitudinal comparability. Image preprocessing and amyloid quantification were performed using the Combinostics cNeuro® cPET platform (Combinostics Oy, Tampere, Finland), which applies a standardized, multiatlas-based parcellation (Figure 1). Global amyloid burden was expressed in CL⁵ using validated tracer-specific calibration models for [^{18}F]florbetaben and [^{18}F]flutemetamol. CL values were used as the primary global metric for amyloid quantification and classification of amyloid-PET negativity, in line with trial-derived and framework-based definitions.^{1,2,4,6,9,10} In addition to global CL values, SUVRs were calculated for descriptive global and regional analyses using the whole cerebellum as the reference region, in line with validated tracer-specific calibration models provided by the platform. Regional SUVRs included the following predefined areas: anterior cingulate, prefrontal, temporal mesial, temporal lateral, parietal, occipital, sensorimotor, precuneus, and caudate. Composite SUVRs were also obtained, averaging SUVR of anterior and posterior cingulate, orbital, frontal, temporal, and parietal cortices.¹¹ Three experienced nuclear

RESEARCH IN CONTEXT

1. **Systematic review:** The authors conducted a targeted PubMed search integrated with meeting abstracts and presentations. Pivotal clinical trials and appropriate use recommendations for lecanemab and donanemab established global CL reduction as the reference biomarker of pharmacodynamic response to anti-amyloid therapies. However, in routine practice amyloid-PET is rarely repeated at 6 months, and real-world descriptions of very early amyloid clearance – particularly at the regional level – are lacking.
2. **Interpretation:** We provide real-world evidence that amyloid changes are detectable and regionally heterogeneous after 6 months of therapy. Reliance on global metrics to define PET negativity may mask persistent regional amyloid uptake, underscoring the importance of a comprehensive, regionally informed interpretation of follow-up scans rather than exclusive dependence on global CL thresholds.
3. **Future directions:** Prospective studies should determine whether early regional clearance at 6 months predicts long-term clinical response and whether interim amyloid-PET can inform individualized treatment decisions.

medicine physicians (A.M.S.G., A.P., G.P.) blindly reviewed baseline and longitudinal scans for visual reading.

2.3 | Statistical analysis

Continuous variables were summarized as mean (standard deviation) or median (interquartile range) and categorical variables as counts (%). Between-group comparisons at baseline were performed using Wilcoxon rank-sum or Fisher's exact tests, as appropriate.

Longitudinal amyloid change was quantified as the difference between 6-month and baseline values (Δ CL, Δ SUVR). Longitudinal clinical changes were also quantified as the difference between 6-month and baseline values (Δ MMSE and Δ CDR-SB), although analyses of clinical outcomes were considered exploratory. Group differences in global and regional amyloid change were assessed using ANCOVA models, adjusting for PET tracer and monoclonal antibody; baseline models were adjusted for PET tracer only.

Regional analyses of SUVR patterns in patients achieving global amyloid-PET negativity were exploratory due to limited sample size and lack of validated regional thresholds. All tests were two-sided ($p < 0.05$). Analyses were performed using BlueSky Statistics.

To formally assess whether longitudinal amyloid reduction differed across brain regions, a two-way repeated-measures ANOVA was per-

formed with region of interest and timepoint as within-subject factors (full model specification in Supplementary Methods). Furthermore, to assess longitudinal differences in amyloid burden according to clinical stage and age at onset, linear mixed-effects models were fitted with timepoint as a repeated within-subject factor and clinical group as a between-subject factor (Supplementary Methods).

Spearman's rank correlation was used to assess the association between disease duration and change in global amyloid burden (Δ CL) and in clinical outcomes (Δ MMSE, Δ CDR global score, and Δ CDR-SB) at 6 months.

To contextualize residual occipital SUVR values, regional SUVRs were additionally quantified in a reference cohort of 12 amyloid-negative subjects (median age 70.3 years [64.0 to 75.3]) scanned with [^{18} F]florbetaben, using the same pipeline and reference region as the treated cohort (full methodology in Supplementary Methods).

2.4 | Standard protocol approvals, registrations, and patient consents

The local ethical standards committee on human experimentation approved the study protocol, and all participants provided written informed consent.

3 | RESULTS

3.1 | Sample characteristics

The two treatment groups ($n = 17$ donanemab, $n = 9$ lecanemab) were broadly comparable in terms of demographic and clinical characteristics (Table 1), with no differences in baseline global amyloid burden. The proportion of apolipoprotein E $\epsilon 4$ carriers differed between groups, with a higher frequency of $\epsilon 4$ heterozygotes in the lecanemab group, reflecting local prescribing practice prior to EMA regulatory approval of donanemab. Amyloid-PET tracer distribution and the prevalence of ARIA-E and ARIA-H were similar between groups.

3.2 | Overall baseline and longitudinal regional A β PET patterns: descriptive analysis

Regional amyloid-PET analysis showed heterogeneous amyloid clearance across cortical and subcortical regions over the first 6 months of treatment, with marked regional differences and distinct effects between monoclonal antibodies.

Although CL values declined in both treatment groups, with larger reductions in donanemab-treated patients (Table 1), regional SUVR analyses revealed substantial spatial heterogeneity in amyloid removal (Figure 1). Across the cohort, the largest reductions were observed in the anterior cingulate cortex, followed by the caudate, precuneus, prefrontal, and parietal cortices (Figure 1). In contrast, the mesial temporal cortex showed lower baseline SUVR values and more limited longitudi-

TABLE 1 Baseline demographic, clinical, and imaging characteristics of the cohort by treatment group.

Variable	Donanemab (N = 17)	Lecanemab (N = 9)	p value
Age, years	64.05 (61.76, 73.97)	71.64 (60.62, 72.47)	0.71
Disease duration, months	35 (23, 48)	44 (35, 47)	0.67
CVRF, n	1 (0, 1)	1 (0, 2)	0.39
Sex, females n (%)	9 (53%)	5 (63%)	0.50
Clinical stage, n (%)			0.65
- MCI due to AD	11 (65%)	5 (56%)	–
- Mild dementia due to AD	6 (35%)	4 (44%)	–
Clinical diagnosis, n (%)			0.72
- LOAD	10 (59%)	4 (44%)	–
- EOAD	5 (29%)	4 (44%)	–
- PCA	1 (6%)	1 (11%)	–
- PPA	1 (6%)	0 (0%)	–
ApoE ε4 carriers, n (%)	1 (6%)	7 (78%)	< 0.001
ARIA-E ± ARIA-H, n (%)	4 (24%)	0 (0%)	0.28
Isolated ARIA-H, n (%)	2 (12%)	1 (11%)	0.63
Baseline clinical metrics			
MMSE	26 (23.0, 28.0)	25 (19, 27)	0.18
CDR global score	0.50 (0.50, 1.00)	0.50 (0.50, 1.00)	0.71
CDR-SB	3.50 (1.50, 4.50)	3.50 (2.50, 5.00)	0.76
Clinical metrics at 6 months			
MMSE	23 (22, 28)	23 (19, 24)	0.207
CDR global score	0.50 (0.50, 1.00)	0.50 (0.50, 1.00)	0.664
CDR-SB	3.50 (1.50, 5.00)	4.00 (2.50, 5.50)	0.486
Amyloid PET radiotracer, n (%)			
[¹⁸ F]Florbetaben	8 (47%)	4 (44%)	–
[¹⁸ F]Flutemetamol	9 (53%)	5 (56%)	–
Baseline global amyloid burden (Centiloids)	93.98 (68.70, 106.80)	96.89 (93.63, 102.11)	0.61
Change in global amyloid burden (ΔCentiloids, 6 months – baseline)	–57.11 (–46.70, –90.12)	–30.69 (–15.85, –53.54)	0.009
Percentage of patients reaching <25 Centiloids at 6 months	10 (59%)	1 (11%)	0.02
Percentage of patients reaching <11 Centiloids at 6 months	7 (41%)	0 (0%)	0.02

Note: Data are reported as median (interquartile range) or number (%). P-values refer to between-group comparisons (donanemab vs lecanemab). Categorical variables were compared using Fisher's exact test, and continuous variables using the Wilcoxon rank-sum test. Bold values indicate statistically significant differences ($p < 0.05$). Global amyloid burden is expressed in Centiloids. ΔCentiloids indicate the change from baseline to 6 months. The proportions of patients reaching < 25 Centiloids and < 11 Centiloids at 6 months are reported as clinically relevant thresholds for amyloid-PET negativity and treatment discontinuation, respectively.

Abbreviations: AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA with edema or effusion; ARIA-H, ARIA with hemosiderin deposition; CDR, Clinical Dementia Rating; CDR-FTD, Clinical Dementia Rating–Frontotemporal Dementia; CDR-SB, CDR Sum of Boxes; CVRF, cardiovascular risk factors; EOAD, early-onset Alzheimer's disease; LOAD, late-onset Alzheimer's disease; MMSE, Mini-Mental State Examination; PCA, posterior cortical atrophy; PPA, primary progressive aphasia.

nal change, while the occipital cortex demonstrated a modest decrease despite intermediate baseline uptake.

When stratified by treatment, lecanemab was associated with smaller regional amyloid reductions than donanemab. ΔSUVR values showed significantly smaller reductions in the lecanemab group for the

composite cortical measure (0.25 vs 0.44, $p = 0.009$) and across multiple regions, including the anterior cingulate (0.39 vs 0.59, $p = 0.015$), prefrontal cortex (0.26 vs 0.49, $p = 0.005$), lateral temporal cortex (0.22 vs 0.37, $p = 0.03$), parietal cortex (0.23 vs 0.41, $p = 0.008$), precuneus (0.29 vs 0.46, $p = 0.04$), caudate (0.32 vs 0.54, $p = 0.007$),

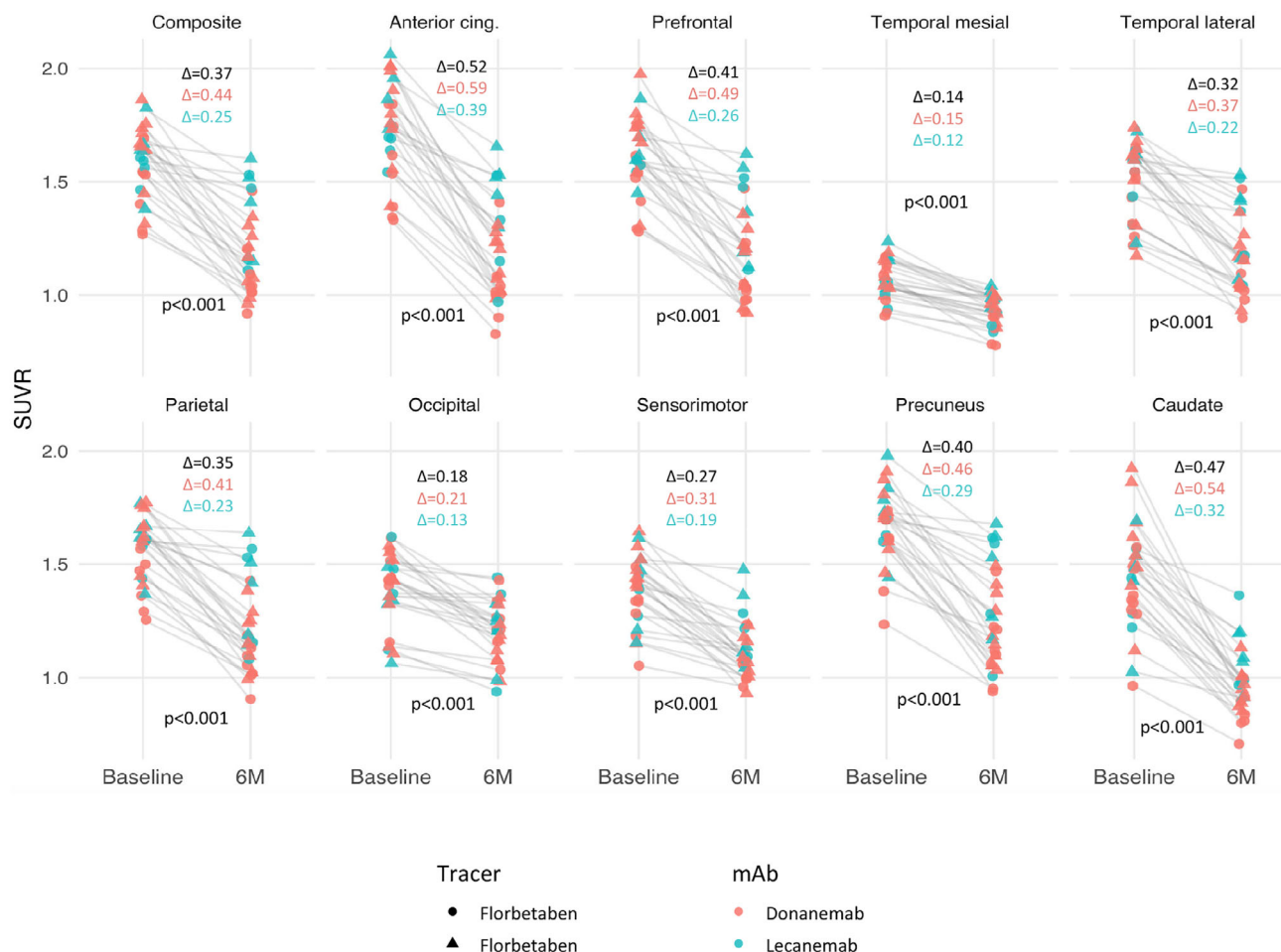


FIGURE 1 Regional and composite standardized uptake value ratios (SUVRs) changes over 6 months by monoclonal antibody treatment. Longitudinal changes in SUVR are shown for patients treated with donanemab (red) and lecanemab (blue) across multiple brain regions. Points represent individual subjects at each time point: circles for baseline, triangles for 6 months. Across most regions, SUVR values decrease from baseline to 6 months for both treatment groups, indicating reduction in amyloid burden.

and sensorimotor cortex (0.19 vs 0.31, $p = 0.04$). Differences in the mesial temporal (0.12 vs 0.15) and occipital (0.13 vs 0.21) cortices were smaller and did not reach statistical significance. These between-group comparisons should, however, be interpreted with caution, as the two treatment groups were substantially imbalanced in ApoE $\epsilon 4$ carrier frequency (6% donanemab vs 78% lecanemab).

To formally test whether amyloid reduction differed across regions, a two-way repeated-measures ANOVA confirmed a significant region of interest (ROI) $\times$ timepoint interaction ($F[3.56, 85.46] = 60.82$, $p < 0.001$, $\eta^2 = 0.717$). Post-hoc comparisons showed significant reductions in all ROIs (all $p < 0.001$), largest in the anterior cingulate (0.52) and caudate (0.47), and smallest in the mesial temporal (0.14) and occipital (0.18) regions (Tables S1 and S2).

3.3 | Baseline and longitudinal A β PET patterns by clinical stage

When patients were stratified by clinical stage (mild cognitive impairment [MCI], $n = 16$; mild dementia, $n = 10$), no significant differences

emerged in terms of baseline CL between groups (MCI: 87.2 [SD 22.4]; mild dementia: 97.1 [SD 20.6]; $p = 0.26$) (Figure 2A). Furthermore, no significant correlation was found between disease duration and Δ CL ($\rho = -0.29$, $p = 0.16$), Δ MMSE ($\rho = -0.10$, $p = 0.63$), Δ CDR global score ($\rho = -0.18$, $p = 0.39$), or Δ CDR-SB ($\rho = 0.10$, $p = 0.64$). Despite similar starting levels, patients with MCI showed a significantly greater reduction in global amyloid burden at 6 months (Δ CL -67.8 [SD 25.8] vs -39.1 [SD 21.6]; $p = 0.005$).

A repeated-measures mixed-effects model demonstrated a significant timepoint $\times$ stage interaction ($F[1, 24] = 8.52$, $p = 0.008$), confirming that longitudinal amyloid reduction differed according to clinical stage (Table S3); results were robust to a sensitivity analysis excluding the duplicate treatment episode (Supplementary Methods).

Similarly, baseline regional SUVR values did not differ between stages (Table S4). Longitudinally, MCI patients demonstrated significantly and consistently greater amyloid reductions across all cortical regions, whereas no significant stage-related differences were observed in the caudate.

Mixed-effects models confirmed a significant timepoint $\times$ stage interaction for composite SUVR and most cortical regions (anterior cin-

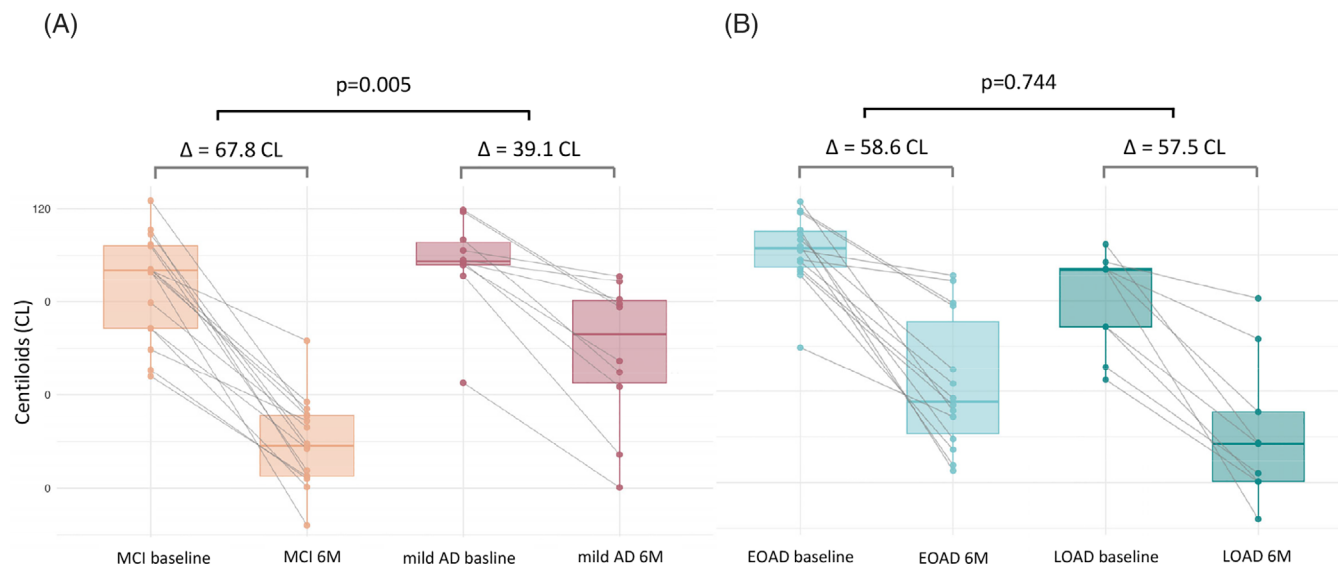


FIGURE 2 Centiloid changes over 6 months of therapy in MCI and mild AD patients. Boxplots present Centiloids (CL) changes after 6 months of therapy in MCI and mild AD patients (A) and in EOAD compared to LOAD (B). The p value refer to ANCOVA model corrected by tracer and monoclonal antibody. EOAD, early-onset Alzheimer's disease; LOAD, late-onset Alzheimer's disease; MCI, mild cognitive impairment.

gulate, prefrontal, parietal, precuneus; all $p < 0.04$), but not for the occipital, temporal, sensorimotor, and caudate regions (Table S5).

3.4 | Baseline and longitudinal A β PET patterns by clinical diagnoses

When stratified by clinical diagnosis (late-onset AD [LOAD], $n = 9$; early-onset AD [EOAD], $n = 14$), baseline global amyloid burden was significantly higher in EOAD than in LOAD (101.9 [SD 15.9] vs 97.6 [SD 21.7]; $p = 0.01$). At the 6-month visit, amyloid burden remained higher in EOAD (43.3 [SD 29.8] vs 22.0 [SD 31.6] CL; $p = 0.03$), and the magnitude of global amyloid reduction did not differ between groups (Δ CL -58.6 [SD 30.7] vs -57.5 [SD 28.6]; $p = 0.744$; Figure 2B).

A repeated-measures mixed-effects model confirmed the absence of a timepoint $\times$ clinical diagnosis interaction for CL change ($F[1,40] = 0.01$, $p = 0.937$), as well as for all 10 regional SUVRs (all interaction $p > 0.24$; Tables S6 and S7), indicating uniform longitudinal amyloid clearance across EOAD and LOAD regardless of cortical region.

This finding was robust to a sensitivity analysis excluding the duplicate patient (Supplementary Methods).

Consistently, EOAD showed higher baseline and 6-month regional SUVRs than LOAD, particularly in prefrontal, parietal, temporal lateral, and sensorimotor cortices and the caudate, with no differences in longitudinal Δ SUVR. Baseline and follow-up regional data stratified by diagnosis are reported in Table S8 and Figure 2. Focal AD variants (primary progressive aphasia [PPA] $n = 1$ and posterior cortical atrophy [PCA] $n = 2$) are displayed for descriptive purposes only and were excluded from statistical analyses due to small sample size.

3.5 | Longitudinal clinical metrics

Clinical outcomes, including CDR, CDR-SB, and MMSE, were evaluated at baseline and after 6 months of therapy. Changes over time did not differ significantly between the donanemab and lecanemab groups (Δ MMSE, -1.2 vs -1.2 , $p = 0.9$; Δ CDR-SB, 0.4 vs 0.7 , $p = 0.31$). Likewise, no significant differences in treatment response emerged after stratification by clinical stage or age at onset in terms of MMSE, CDR-SB, or proportion of patients with stable CDR (Figure 3). These exploratory clinical outcome analyses should be interpreted cautiously.

3.6 | Regional amyloid-PET patterns after achievement of global negativity

After 6 months of therapy, 11 patients reached amyloid-PET values below the positivity threshold (< 25 CL); 10 were treated with donanemab and one with lecanemab¹² (Table 1, Figure 3). Among these, seven patients achieved < 11 CL at 6 months (Figure 3, Subjects 5 to 11). All of them were treated with donanemab. Six discontinued treatment according to appropriate use recommendations stopping rules,⁶ while one discontinued treatment early due to severe ARIA (Figure 3, Subject 7). Interestingly, all patients with < 11 CL had a negative PET also at visual read, except for Subject 5, which had very mild residual temporal uptake, and Subject 7, which had persistent moderate occipital uptake.

Four additional patients reached global amyloid-PET values < 25 but above 11 CL (Figure 3, Subjects 1 to 4). Among them, one continued donanemab (Subject 3), one discontinued donanemab due to two episodes of moderate ARIA-E (Subject 1), and the single patient on lecanemab continued biweekly dosing (Subject 2).^{6,7} Subject 4 had



FIGURE 3 Composite and regional SUVRs of patients with an amyloid PET < 25 CL after 6 months of therapy. Subjects 1 to 4: patients reaching at 6 months global amyloid PET values $11 < CL < 25$; subjects 5 to 11: patients reaching at 6 months global amyloid PET values $CL < 11$. Both Centiloid value (CL) and visual assessment (V) are reported. SUVR values are color-coded for descriptive purposes only, according to previously described cutoff: green = $SUVR < 1.1$; yellow = $1.1 \leq SUVR \leq 1.2$; red = $SUVR > 1.2$. Occipital residual uptake is evident in most of amyloid-negative patients. EOAD, early-onset AD; FBB, florbetaben; FMM, flutemetamol; LOAD, late-onset AD.

previously received 6 months of biweekly lecanemab, with limited biological response (baseline CL = 102.11; post-lecanemab CL = 91), and was subsequently switched to donanemab, with a marked response thereafter (Figure 3). After three additional doses of donanemab, treatment was discontinued following a shared decision-making process with the patient. At visual read, Subject 2 was negative, while Subjects 1, 3, and 4 were mildly positive.

Given the absence of validated regional SUVR cutoffs for [^{18}F]florbetaben and [^{18}F]flutemetamol, regional amyloid burden in patients reaching global amyloid-PET negativity was assessed descriptively. Horizontal reference levels at SUVR 1.1 and 1.2 are shown in Figure 3 for visual interpretation only. SUVR values around 1.1 have been reported as tracer- and pipeline-specific thresholds for amyloid positivity in prior studies using whole cerebellum normalization,¹³⁻¹⁵ whereas the 1.2 level highlights clearly elevated regional uptake for illustrative purposes.¹⁶ To facilitate appreciation of both baseline amyloid burden and the magnitude of regional change at the individual patient level, Figures 4 and 5 display baseline regional SUVR values and Δ SUVR maps, respectively, for all patients achieving global amyloid negativity at 6 months. Among patients achieving < 11 CL (Subjects 5 to 11), only three showed SUVR values < 1.1 across all examined regions. In the remaining patients, residual regional

tracer uptake was most frequently observed in the occipital cortex and precuneus, while caudate SUVR values were < 1.1 in all cases. No inferential statistics were performed due to limited sample size and lack of validated regional thresholds. Two of five patients with persistent elevated occipital SUVR (> 1.2) at 6 months experienced ARIA. Upon visual inspection, although not formally included in the standard positivity evaluation scheme for either tracer, all patients with occipital SUVR > 1.2 showed appreciable residual occipital tracer uptake, consistent with the quantitative finding.

To determine whether residual occipital SUVR reflects true amyloid signal rather than baseline anatomical variation, we quantified regional SUVRs in a reference cohort of 12 amyloid-negative subjects scanned with [^{18}F]florbetaben (full methodology in Supplementary Methods; results in Table S9). No amyloid-negative subject exceeded an occipital SUVR of 1.2 (maximum 1.15), supporting this threshold as a biologically meaningful upper boundary for residual occipital signal in treated patients.

Representative amyloid-PET images at baseline and 6-month follow-up for all patients achieving global amyloid negativity are shown in Figure 4, highlighting the distinction between subjects with complete occipital clearance and those with residual occipital uptake despite global negativity.

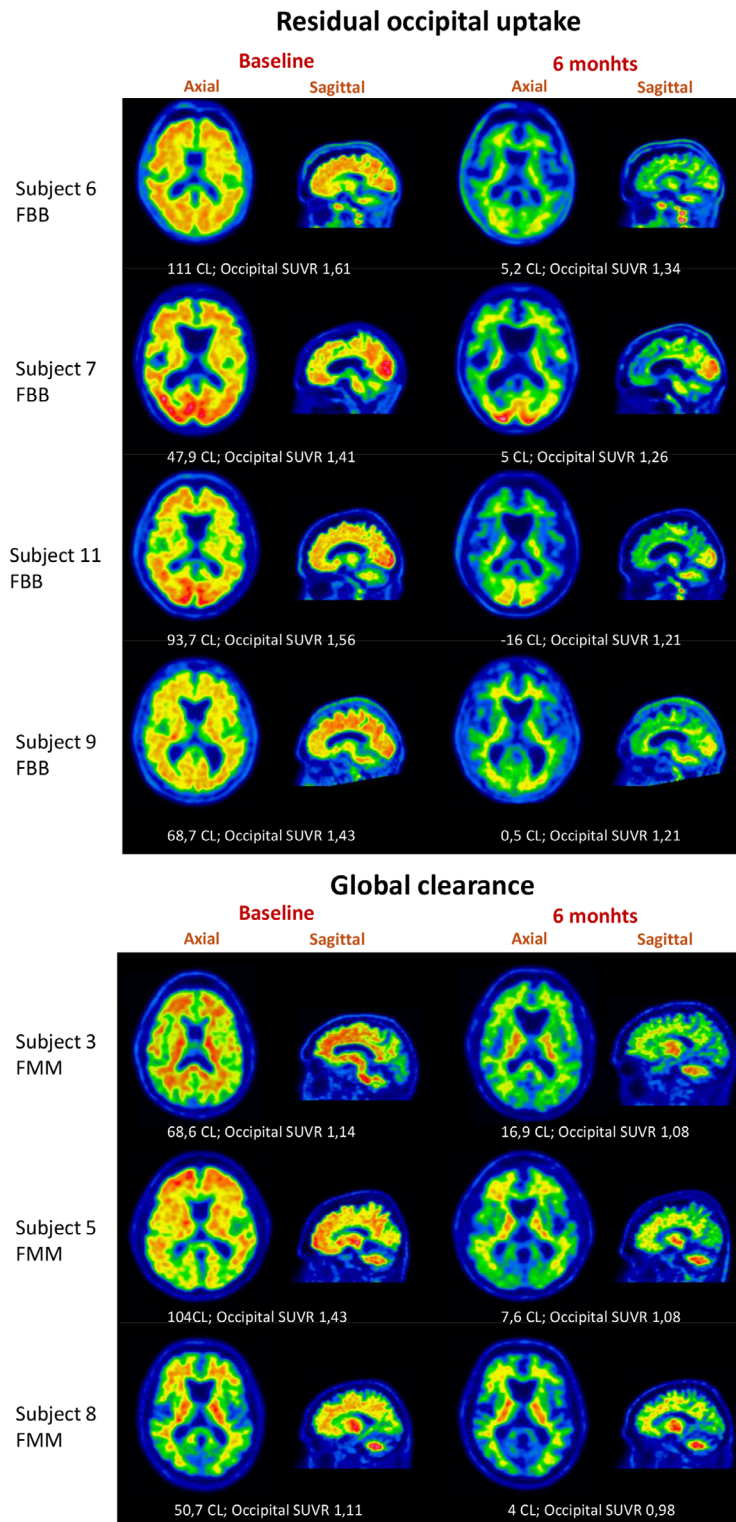


FIGURE 4 Regional amyloid-PET before and after anti-amyloid immunotherapy. Representative axial and sagittal amyloid-PET images at baseline and 6-month follow-up for patients treated with lecanemab or donanemab. Upper panel – residual occipital uptake: subjects achieving global amyloid negativity ($CL \leq 11$) but with persistent occipital SUVR above 1.2 (whole cerebellar reference); all four subjects were scanned with [^{18}F]florbetaben (FBB). Lower panel – global clearance: subjects achieving both global amyloid negativity ($CL \leq 11$ except Subject 3 – $CL = 19$) and complete occipital clearance (occipital $SUVR \leq 1.2$); all three subjects were scanned with [^{18}F]flutemetamol (FMM). CL values are shown below each scan pair. CL, Centiloid; SUVR, Standardised Uptake Value Ratio. Images are displayed on a standardised rainbow color scale.

4 | DISCUSSION

In this real-world cohort of early symptomatic AD patients treated with anti- $A\beta$ antibodies, amyloid clearance over the first 6 months was regionally heterogeneous and modulated by treatment and clinical stage. Global and regional amyloid burden revealed non-uniform clearance, with larger reductions in anterior and associative cortices

and more modest changes in mesial temporal and occipital regions (Figure 1).

Consistent with data from pivotal clinical trials^{1,2} and recent real-world experience literature,¹⁷ donanemab was associated with substantially greater global amyloid reduction than lecanemab (approximately -60 vs -30 CL), supporting the external validity of our real-world findings despite the limited sample size (Table 1). Of note, the

two groups were imbalanced in ApoE ϵ 4 carrier frequency, reflecting European prescribing guidelines; this represents a potential confound preventing definitive conclusions about differential drug efficacy.

The largest regional reductions involved anterior cingulate, prefrontal, precuneus, parietal cortices, and the caudate nucleus (Figure 1). The prominent anterior cingulate reduction is consistent with its high baseline amyloid burden and its major contribution to standard cortical composite metrics.¹⁸ Substantial caudate reduction suggests target engagement beyond cortical regions, consistent with striatal amyloid deposition as a marker of advanced amyloid spread and later Thal phases.^{12,19–22} However, absolute post-treatment caudate SUVR values remain constrained by methodological heterogeneity and the lack of validated striatal-specific thresholds. Although *post mortem* studies of gantenerumab and solanezumab have demonstrated regional amyloid reductions,²² including the caudate, no region-specific thresholds were established. This highlights the need for dedicated *post mortem* validation studies to define robust regional cutoffs for subcortical structures.

The proportion of patients reaching a global amyloid PET value below 25 CL at 6 months also differed by treatment: 60% of patients treated with donanemab compared with 11% of those treated with lecanemab. This difference is consistent with the distinct biological target profiles of the two antibodies, with donanemab more specifically targeting deposited amyloid plaque and lecanemab binding soluble A β protofibrils with high affinity while also promoting plaque reduction.^{1,2} A recent Chinese real-world lecanemab study found that seven of 29 patients reached PET values below 11 CL by 6 months, versus none of our nine lecanemab-treated patients, despite a similar magnitude of reduction ($\sim$ 30 CL), likely reflecting the Chinese cohort's lower baseline CL values (59 vs 97 in our group),¹⁷ possibly explaining this difference in PET negativity.

Clinical stage shaped early amyloid dynamics: Despite comparable baseline burden, MCI patients showed greater 6-month amyloid reduction than those with mild dementia, driven primarily by cortical regions (Figure 2A; Table S4).^{2,1} Although differences in amyloid clearance were observed at 6 months, we found no evidence that MCI patients with greater amyloid reduction derived greater clinical benefit (Figure 3). A longer observation period is likely required to detect appreciable differences in clinical scores, and these results should be considered preliminary. Differential amyloid clearance between MCI and mild dementia did not appear explained by disease duration, as no significant correlation emerged between disease duration and Δ CL or clinical change; other factors likely underlie this stage-dependent difference, though findings warrant cautious interpretation given the small sample.

When stratifying by age at onset, in line with previous studies, patients with EOAD exhibited higher baseline amyloid burden than those with LOAD – particularly in associative areas and the caudate¹⁸ – but exhibited comparable global and regional amyloid reduction (Figure 2B), as well as clinical outcomes, suggesting similar early biological responsiveness across age-at-onset groups.¹⁸ Although a recent meta-analysis reported that donanemab was associated with cognitive benefit across all age groups, while lecanemab showed no significant

effect in participants younger than 65 years,²³ biological efficacy data remain limited; another real-world lecanemab cohort similarly found that PET-negative patients at 6 months were significantly older.¹⁷ Comparable early clearance dynamics were observed, though our heterogeneous lecanemab/donanemab cohort may obscure antibody-specific effects; observations on focal variants (PPA, PCA) remain purely descriptive.

Achievement of global amyloid-PET negativity does not necessarily correspond to uniform regional amyloid clearance.⁴ Among patients reaching <11 or <25 CL, residual uptake persisted in several cortical regions, particularly in the occipital cortex. This finding aligns with the TRAC framework,⁴ which formalizes CL-based longitudinal reductions while acknowledging regional heterogeneity of amyloid removal.⁴ Since all cases of residual occipital SUVR above 1.2 were observed in [^{18} F]florbetaben-scanned patients, this finding is consistent with our reference-cohort analysis, supporting occipital SUVR > 1.2 as more likely to reflect genuine residual amyloid signal than anatomical noise.

In our cohort, all patients achieving <11 CL discontinued donanemab according to appropriate use recommendations.⁶ Nevertheless, regional SUVR analyses continued to show persistent cortical tracer uptake (Figure 3), a finding only partially reflected by visual assessment, which did not include the occipital lobe according to tracer-specific visual read procedures.^{9,10} This pattern is in keeping with reported associations between occipital amyloid burden and ARIA-E during donanemab treatment.²⁴ These findings underscore the need for longitudinal post-discontinuation studies.

Available thresholds are largely based on global measures or studies using different tracers and pipelines (i.e., the global cutoffs of 1.10 [^{18} F]florbetaben – 13.5 CL,¹⁶ 1.03 for [^{18} F]flutemetamol,¹³ and 1.10 for [^{18} F]florbetapir^{14,15}). Residual regional uptake should therefore be interpreted descriptively pending dedicated *post mortem* validation studies.

Several limitations should be acknowledged, including the small sample size, short follow-up, use of multiple PET tracers, and the lack of validated region-specific post-treatment SUVR thresholds. Despite these constraints, our findings show that longitudinal amyloid-PET captures regionally heterogeneous amyloid removal during anti-A β therapy, modulated by antibody and clinical stage, though without translating into appreciable clinical advantage at 6 months. These results support the clinical value of amyloid-PET at baseline and follow-up to document target engagement, inform treatment discontinuation, and contextualize biological response. Larger multicenter studies with longer follow-up are needed to clarify the clinical implications of persistent regional amyloid signal and refine current PET cutoffs.

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CONFLICT OF INTEREST STATEMENT

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F. Agosta is Associate Editor of *NeuroImage: Clinical* and the *European Journal of Neurology*; has received speaker honoraria from Biogen Idec, Bristol Myers Squibb, Eisai, Eli Lilly, GE Healthcare, Neuraxpharm, and Roche; and receives or has received research supports from the Italian Ministry of Health, the Italian Ministry of University and Research, AriSLA (Fondazione Italiana di Ricerca per la SLA), the European Research Council (ERC), the EU Joint Programme – Neurodegenerative Disease Research (JPND), and Foundation Research on Alzheimer Disease (France). Author disclosures are available in the [Supporting Information](#).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT STATEMENT

All participants provided written informed consent before study initiation. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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