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Sequential Lecanemab→Donanemab Therapy in Alzheimer's Disease: Real-World PET Findings

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Abstract

Anti-amyloid monoclonal antibodies such as lecanemab and donanemab have shown robust amyloid clearance and modest clinical benefit in Alzheimer's disease. Japan's staggered regulatory approvals of these agents provided a unique opportunity for sequential therapy. To evaluate real-world amyloid PET evidence of sequential lecanemab→donanemab therapy compared with lecanemab monotherapy and untreated controls. Thirty-one individuals who underwent amyloid PET between 2019 and 2025 were retrospectively analyzed. Participants were classified into sequential therapy (n = 16), lecanemab monotherapy (n = 5), and untreated controls (n = 14). Global and regional standardized uptake value ratios were calculated and converted into Centiloid units. Statistical comparisons were performed using Wilcoxon signed-rank and Welch's t-tests with Cohen's d. Significant amyloid reductions were observed in both treated groups, with greater decreases in sequential therapy group (−70.6 Centiloids) than in lecanemab monotherapy (−48.4). Sequential therapy induced significant reductions across all cortical regions, particularly in the precuneus (p = 0.034, d = 0.95). Cognitive scores remained stable in sequential therapy group but declined in controls. No amyloid-related imaging abnormalities were detected. Sequential lecanemab→donanemab therapy achieved stronger and regionally distinct amyloid reductions than monotherapy, without safety concerns. This real-world evidence suggests that sequential antibody use may extend the biological effects of anti-amyloid therapy in Alzheimer's disease. Prospective trials are warranted to confirm clinical efficacy and optimize treatment sequencing.

Keywords: Molecular Medicine, Alzheimer's Disease, Lecanemab, Donanemab, Sequential Antibody Therapy, Amyloid PET.

Introduction

Alzheimer's disease (AD) is pathologically defined by progressive accumulation of amyloid-β (Aβ) plaques, which precedes clinical symptoms by years or decades [1, 2]. Advances in disease-modifying therapies have yielded monoclonal antibodies (mAbs) capable of substantially reducing cerebral amyloid burden, as demonstrated in large phase 3 trials. Lecanemab, an IgG1 mAb selectively targeting soluble Aβ protofibrils, produced robust amyloid clearance and slowed cognitive decline in the CLARITY AD study [3]. Donanemab, an IgG1 mAb directed against pyroglutamate-modified Aβ (N3pE), showed similar efficacy in the TRAILBLAZER-ALZ2 trial [4]. These two antibodies possess distinct binding profiles, suggesting the possibility of complementary clearance mechanisms. Lecanemab preferentially removes soluble protofibrils, whereas donanemab targets highly aggregated, truncated Aβ species resistant to early-phase removal. Sequential administration might therefore extend and deepen amyloid clearance beyond that achieved by either drug alone.

In Japan, regulatory approval of lecanemab (December 2023) preceded that of donanemab (November 2024) by approximately one year, creating a unique natural therapy protocol in which patients completing the standard lecanemab regimen opted to tran-

sition to donanemab, often for convenience due to its monthly dosing and shorter infusion time. This real-world circumstance provided a rare opportunity to examine the effects of sequential therapy. We aimed to quantify, utilizing amyloid positron emission tomography (PET), the magnitude and regional pattern of amyloid reduction following sequential lecanemab to donanemab therapy, comparing results with lecanemab monotherapy and with untreated controls representing normal aging trajectories.

Subjects and Methods

Participants

We conducted a retrospective review of 31 individuals who underwent amyloid PET at our institution between June 2019 and June 2025. Clinical diagnosis, baseline assessments, treatment indications, infusion administration, cognitive assessment by Clinical Dementia Rating–Global Score (CDR-GS), and MRI monitoring were performed in accordance with the Japanese best practice recommendations [5].

Groups Were

(1) Sequential therapy (lecanemab to donanemab [L+D]: n=16, received ~12 months (mean 11.1, SD 2.1) of lecanemab followed by 6 months of donanemab. Informed consent was obtained from all patients and their families after providing detailed explanations of the risks and benefits of donanemab. Four participants also had a PET scan immediately prior to switching therapy.

(2) Lecanemab monotherapy (L): One AD patient completed a 12-month regimen, but data during the first one-year lecanemab treatment of the above-mentioned four cases were also used for assessment of lecanemab monotherapy.

(3) Untreated controls: n=14, underwent two PET scans separated by ~46 months (mean 21.0, SD 11.4) without anti-amyloid therapy. These were obtained from the PET data performed before December 2023 (approval time of lecanemab).

Imaging and Quantification

Amyloid PET was performed with approved tracer (^{18}F-florbetapir) following established clinical standards.

Quantitative amyloid burden is first expressed as a standardized uptake value ratio (SUVR) computed as the mean uptake in a cortical composite volume-of-interest divided by the mean uptake in a reference region (commonly, the whole cerebellum). To place different tracers on a common scale, tracer-specific SUVRs are then linearly transformed to a Pittsburgh compound B (PiB)-equivalent SUVR using published calibration equations, and finally converted to Centiloids by anchoring 0 CL to the mean of young controls (YC) and 100 CL to the mean of

Typical AD Patients

CL=100×SUVR PiB-equivalent −μYC / μAD-μYC

In this expression, μ (mu) represents the mean cortical SUVR for a given reference population. Specifically, μYC denotes the mean SUVR of YC who are assumed to have no amyloid deposition (defined as 0 CL), while μAD represents the mean SUVR of typical Alzheimer's disease patients (defined as 100 CL). PiB serves as the reference tracer that defines this Centiloid scale, providing a common calibration anchor so that SUVRs from other tracers (e.g., 18F-florbetapir, 18F-florbetaben, 18F-flutemetamol) can be linearly transformed into PiB-equivalent CL units [6].

Statistical Analysis

Wilcoxon signed-rank tests assessed within-group changes; Welch's t-tests with effect size (Cohen's d) compared between groups. Significance was set at $p < 0.05$ (two-tailed). Analyses were performed using Python (SciPy, Pingouin).

Results

No significant differences in baseline demographics were found among the groups. Mean ages were 75.6 ± 9.4 (L+D), 76.0 ± 12.3 (L), and 76.1 ± 7.6 years (controls). Sex ratios were balanced (L+D: 8M/8F, L:3M/2F and control: 6M/8F). Baseline CDR–Global Scores (CDR-GS) were 0.78 ± 0.26 (L+D), 1.00 ± 0.00 (L) and 0.75 ± 0.26 (controls). Baseline Centiloid were 84.6 ± 33.0(L+D), 69.1 ± 35.9(L) and control 70.2 ± 36.2. Baseline SUVR values were 1.52 ± 0.19 (L+D), 1.43 ± 0.21 (L), and 1.43 ± 0.22 (controls). Mild infusion reactions occurred in three treated patients; no amyloid-related imaging abnormalities (ARIA) were observed.

Both treated groups demonstrated significant amyloid reduction versus controls. Mean Centiloid change was −70.6 ± 29.3 in L+D, −48.4 ± 29.4 in L, and +6.0 ± 19.8 in controls ($p < 0.001$; Figure 1). Sequential therapy produced significant SUVR decreases across all cortical regions ($p < 0.001$; Figure 2).

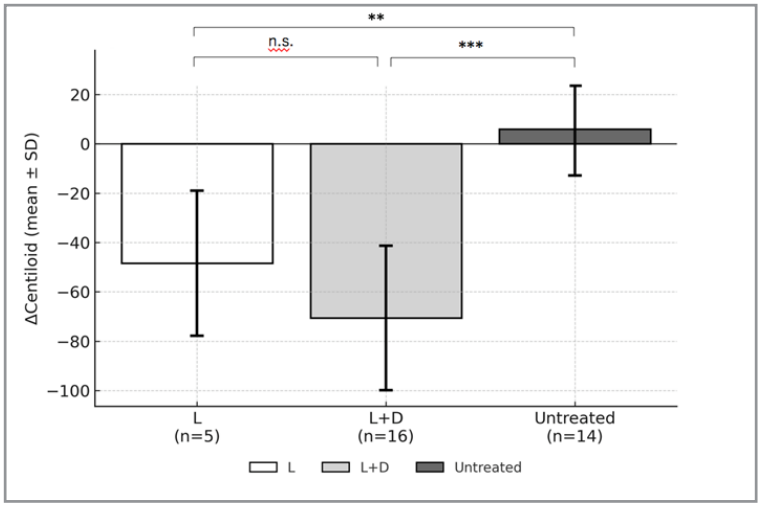

Figure 1: Change in Centiloid Values in the Three Groups

Change in Centiloid values (ΔCentiloid, mean ± SD) from baseline to follow-up in the L (n=5), L+D (n=16), and untreated (n=14) groups. Error bars indicate standard deviation. Pairwise comparisons were assessed by the Mann–Whitney U test. n.s., not significant; **, p<0.01; ***, p<0.001. Legend: White bar = Lecanemab monotherapy (L); Light gray bar = Sequential Lecanemab→Donanemab therapy (L+D); Dark gray bar = Untreated controls.

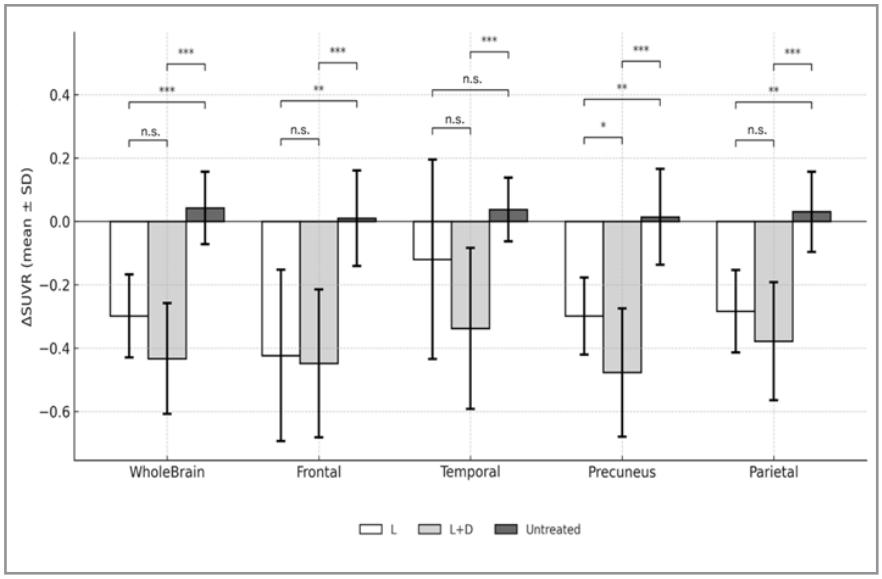

Figure 2: Regional Changes in Suvr in the Three Groups

Regional changes in SUVR (ΔSUVR, mean ± SD) across whole brain, frontal, temporal, precuneus, and parietal cortices in the L (n=5), L+D (n=16), and untreated (n=14) groups. Error bars indicate standard deviation. Pairwise comparisons were assessed by the Mann–Whitney U test. n.s., not significant; *, p<0.05; **, p<0.01; ***, p<0.001. Legend: White bar = Lecanemab monotherapy (L); Light gray bar = Sequential Lecanemab→Donanemab therapy (L+D); Dark gray bar = Untreated controls.

The largest regional effect occurred in the precuneus (p = 0.034, d = 0.95), while frontal, parietal, temporal, and global SUVRs also showed marked reductions compared to controls (Table 1). CDR-GS remained stable in L+D (Δ +0.09 ± 0.20; p = 0.083) but worsened in controls (+0.14 ± 0.23; p = 0.046). There was no correlation between Centiloid change and CDR-GS change.

Table 1: Comparison of ΔCDR-GS and ΔSUVR between Sequential Therapy Group and Untreated Participants

Region	L +D N	LD Mean (SD)	Untreated N	Untreated Mean (SD)	Mean_ Difference	p_value
CDR-GS	16	+0.094 (0.202)	14	+0.143 (0.234)	-0.049	0.547
Frontal SUVR	16	-0.448 (0.234)	14	+0.010 (0.150)	-0.458	<0.000001
Parietal SUVR	16	-0.378 (0.186)	14	+0.030 (0.126)	-0.409	<0.000001
Precuneus SUVR	16	-0.477 (0.202)	14	+0.014 (0.151)	-0.491	<0.000001
Temporal SUVR	16	-0.338 (0.254)	14	+0.037 (0.100)	-0.375	0.000025
WholeBrain SUVR	16	-0.433 (0.174)	14	+0.042 (0.114)	-0.475	<0.000001

ΔCDR-GS and ΔSUVR values represent the change between baseline and follow-up. Welch's t-test p-values are reported for between-group differences. Negative values indicate amyloid reduction; positive values indicate amyloid accumulation except for CDR-GS (positive values indicate cognitive decline).

Discussion

This real-world PET study provides quantitative molecular evidence that sequential lecanemab→donanemab therapy yields greater and regionally distinct amyloid reductions than lecanemab monotherapy. To our knowledge, this is the first clinical dataset demonstrating additive effects of two anti-amyloid monoclonal antibodies under naturalistic conditions. The sequential approach may be mechanistically complementary: lecanemab removes soluble protofibrils, potentially exposing compact N3pE-modified plaques that become accessible to donanemab [7]. The observed enhancement in precuneus and posterior cingulate—key hubs of the default mode network—supports the hypothesis that successive immunotherapies may progressively normalize cortical amyloid distribution [8, 9].

Compared with pivotal trials such as CLARITY AD and TRAILBLAZER-ALZ2 [3, 4], our data show even larger mean Centiloid reductions, possibly reflecting cumulative antibody

exposure and differences in baseline plaque burden. Notably, in our recent voxel-based morphometric study, sequential lecanemab→donanemab therapy was associated with transient cortical pseudatrophy despite pronounced amyloid clearance, suggesting dynamic volumetric responses rather than irreversible neurodegeneration [10]. The present PET-based findings, demonstrating cognitive stability alongside deeper amyloid removal, complement that structural observation—indicating that apparent cortical thinning during sequential immunotherapy may reflect physiological remodeling rather than treatment-induced damage.

From a translational viewpoint, the findings imply that sequential antibody use could serve as a feasible bridge strategy in regions where access or reimbursement cycles are staggered between products. Japan's unique timeline, with approvals separated by 11 months, offered a natural experiment enabling this real-world validation. The absence of amyloid-related imaging abnormalities (ARIA) further supports the biological tolerability of back-to-back mAb administration, though cautious MRI monitoring remains warranted. In the context of real-world practice in Japan, data on 18-month lecanemab monotherapy are not available, because amyloid PET scanning is reimbursed only once prior to lecanemab initiation, whereas donanemab coverage includes baseline and 12-month follow-up scans. As a result, extended lecanemab monotherapy cannot be evaluated with serial PET in routine care, precluding a direct comparison with the sequential regimen. Accordingly, the present findings should not be construed as demonstrating superiority of sequential lecanemab→donanemab therapy over prolonged lecanemab monotherapy, but rather as highlighting its feasibility and potential utility as a pragmatic treatment approach.

Maintaining amyloid suppression may be key to altering disease trajectory. In our cohort, cognitive stability in the sequential group contrasts with decline in controls, echoing long-term extension data suggesting sustained clinical benefit with continued amyloid removal [10].

Nevertheless, this study has limitations. The sample size was small, retrospective, and region-specific, and cognitive outcomes were limited to CDR-GS rather than composite neuropsychological measures. In addition, tracer heterogeneity (18F-florbetapir vs 18F-florbetaben) could influence absolute Centiloid scaling, although within-subject comparisons mitigate this concern. Future multicenter, prospective trials should examine optimal sequencing intervals, effects on tau burden, and longitudinal clinical endpoints [11].

Overall, our findings highlight that the biological effects of anti-amyloid therapy can be extended and deepened through rational sequencing of agents with distinct binding profiles. Such approaches may become increasingly relevant as new antibodies emerge, transforming AD from a single-agent to a precision combination era of molecular therapeutics.

Conclusion

Sequential lecanemab→donanemab therapy achieved robust and regionally specific amyloid reductions without safety concerns. These findings highlight the feasibility of sequential antibody use and its potential to extend the therapeutic benefits of disease-modifying therapies in AD. Future prospective investigations are warranted to confirm long-term cognitive and functional outcomes.

Declarations

Ethical Approval

The Institutional Review Board determined that approval was not required for de-identified retrospective analysis. Written informed consent was obtained from all participants.

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Conflict of Interest

The authors declare no competing interests.

Use of AI

During manuscript preparation, the authors used ChatGPT (OpenAI, GPT-5) for language refinement under author supervision. The authors reviewed and approved the final version.

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