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A Voxel-Based Morphometric Pilot Study of Longitudinal Hippocampal and Cortical Changes during Sequential Lecanemab to Donanemab Therapy

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Abstract

Introduction: The anti-amyloid monoclonal antibodies lecanemab and donanemab were approved in Japan 11 months apart, creating a unique situation in which patients completing lecanemab often transitioned to donanemab for convenience. Sequential administration of these two agents has not been previously reported to evaluate longitudinal structural brain changes by using the voxel-based specific regional analysis system for Alzheimer's disease (VSRAD). **Methods**: In this retrospective, single-center pilot study, a total of 21 subjects with Alzheimer's disease were included: sequential therapy group (n = 8) and untreated controls (n = 13) matched by age, sex, and disease severity. Participants underwent two 3D T1-weighted magnetic resonance imaging scans separated by a treatment or observation interval. The four VSRAD quantitative indices of medial temporal and cortical atrophy were calculated. **Results**: Patients receiving sequential therapy showed a significantly greater increase in the proportion of grey matter with detectable atrophy compared with controls (p = 0.020). A numerically greater progression of hippocampal atrophy was observed in the therapy group, though the difference was not statistically significant (p = 0.083). Other measures did not differ between groups. **Conclusion**: This is the first pilot study to report sequential lecanemab followed by donanemab therapy using a standardized voxel-based morphometric approach for longitudinal monitoring in this context. The findings suggest that sequential therapy may influence region-specific patterns of brain volume loss, warranting confirmation in larger studies integrating molecular biomarkers.

Keywords

Alzheimer's Disease, Voxel-Based Morphometric Analysis, Anti-Amyloid

Monoclonal Antibody, Lecanemab, Donanemab, Brain Atrophy

1. Introduction

Anti-amyloid monoclonal antibodies (mAbs) such as lecanemab and donanemab have recently entered clinical use for Alzheimer's disease (AD), with pivotal phase 3 trials demonstrating amyloid clearance and cognitive benefit [1]-[3]. In Japan, lecanemab and donanemab were approved 11 months apart, creating a unique naturalistic scenario in which patients completing lecanemab often transitioned to donanemab, partly motivated by infusion convenience (monthly ~30 minutes for donanemab vs biweekly ~1 hour for lecanemab). Sequential administration of two distinct anti-amyloid mAbs is unprecedented in the literature and may engage complementary clearance mechanisms, as lecanemab preferentially binds soluble protofibrils [1] [4] whereas donanemab targets N-terminal pyroglutamate–modified amyloid-β fibrils [2] [5].

The longitudinal effects of such sequential therapy on brain structure remain unexplored. Volumetric MRI studies in anti-amyloid mAb trials have reported mixed outcomes—ranging from accelerated whole-brain and ventricular atrophy despite amyloid clearance to minimal hippocampal changes [1]-[3] [6] [7]. These patterns have been attributed in part to "pseudoatrophy," reflecting resolution of inflammation, periplaque gliosis, and associated water content rather than irreversible neuronal loss [4] [8].

The voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) is a validated morphometric tool for detecting medial temporal and neocortical grey matter loss [9]-[11]. While extensively used in diagnosis and disease monitoring, its responsiveness to disease-modifying therapy has not been established. We therefore conducted a retrospective pilot study to characterize hippocampal and cortical volumetric trajectories during sequential lecanemab → donanemab therapy, compared with untreated AD controls, using all four VSRAD indices.

2. Methods

2.1. Study Design and Participants

This single-center retrospective pilot study leveraged a unique therapeutic sequence that emerged from Japan's distinct regulatory timeline. A total of 21 subjects with AD were included and groups were:

1) Sequential therapy (lecanemab → donanemab [L + D]: n = 8, received 12 months 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.

2) Untreated controls: n = 13, underwent two high-resolution 3D T1-weighted

scans separated by 4 - 46 months (mean 18.6, SD 13.4) without anti-amyloid therapy.

Mean age was 73.4 ± 6.2 years in the sequential therapy group (3 male, 5 female) and 74.1 ± 5.9 years in controls (5 male, 8 female). Baseline Clinical Dementia Rating–Global Score (CDR-GS) was 0.5 in 4/8 and 1.0 in 4/8 patients in the sequential group, and 0.5 in 7/13 and 1.0 in 6/13 controls. Groups were explicitly matched for baseline disease severity using CDR-GS. Clinical diagnosis, baseline assessments, treatment indications, infusion administration, cognitive assessment by CDR-GS, and MRI monitoring were performed in accordance with best practice recommendations [12].

2.2. MRI Acquisition and VSRAD Analysis

Participants underwent two high-resolution 3D T1-weighted MRI scans separated by either a treatment or observation interval. Analyses were standardized to an 18-month interval (Δ18M = Δ/months × 18), consistent with the planned 12-month lecanemab followed by 6-month donanemab regimen. VSRAD Advance software (Eisai Co., Ltd., Tokyo, Japan) was used to quantify grey matter loss by comparing individual data to a normal database [9].

Four indices were extracted:

1) Severity—the mean Z-score within a predefined volume of interest (VOI) encom-passing the bilateral hippocampi and adjacent entorhinal cortices, reflecting the degree of medial temporal grey matter loss;

2) Extent of GM (%)—the percentage of total cerebral grey matter voxels exceeding a Z-score threshold of 2, reflecting the overall burden of cortical atrophy;

3) Extent of VOI (%)—the percentage of voxels within the VOI exceeding the same threshold, indicating the proportion of the medial temporal ROI affected;

4) VOI/GM ratio—the ratio of Extent of VOI (%) to Extent of GM (%), providing a relative measure of focal (medial temporal) versus global cortical atrophy.

Higher Severity and Extent values indicate greater atrophy, whereas changes in the VOI/GM ratio may reflect shifts in the distribution of atrophy between focal and diffuse regions. Operational definitions for hippocampal volumetry as a biomarker have been harmonized across consortia [13].

2.3. Statistical analysis

Changes were computed as Δ = post−pre. To account for unequal intervals, Δ was standardized to 18 months (Δ18M = Δ/months × 18). In controls, age-adjusted linear regression modeled per-month change as a function of age; the expected 18-month change at the mean control age was derived. Δ values were compared within each group using paired t-tests; Δ values (post−pre) were compared between groups using Welch t-tests. Statistical significance was set at $p < 0.05$ (two-tailed). Analyses were performed using Python 3.11. A generative artificial intelligence (Chat GPT®) has been used in this paper (graphics, analysis and Language editing).

3. Results

3.1. Adverse Events

No participant developed clinically overt cerebrovascular events, severe amyloid-related imaging abnormalities (ARIA) [14], or other major medical complications during the observation period.

3.2. Changes in Cognitive Function

Over the treatment/observation interval, mean CDR-GS increased slightly in the sequential group from 0.75 ± 0.25 to 0.81 ± 0.28, and in controls from 0.77 ± 0.26 to 0.85 ± 0.30, with no significant between-group difference in change.

3.3. Within-Group Analysis of VSRAD Indices

Within-group analyses confirmed significant progression in Severity and global grey matter atrophy in both cohorts, underscoring that neurodegenerative change in medial temporal and cortex continued regardless of treatment (**Table 1**).

Table 1. Pre- and post-observation/treatment VSRAD indices in sequential lecanemab-donanemab (L + D) and control groups.

Metric	Group	n	Pre	Post	Delta	Within-group p
VSRAD Severity	L + D	8	2.20 ± 1.03	2.67 ± 1.30	0.47 ± 0.40	0.013
VSRAD Severity	control	13	1.44 ± 0.83	1.62 ± 0.89	0.17 ± 0.19	0.006
Extent of GM (%)	L + D	8	6.71 ± 3.47	8.57 ± 4.13	1.86 ± 1.03	0.001
Extent of GM (%)	control	13	3.21 ± 1.95	3.97 ± 2.11	0.77 ± 0.40	<0.001
Extent of VOI (%)	L + D	8	45.06 ± 31.26	56.23 ± 34.87	11.17 ± 9.37	0.012
Extent of VOI (%)	control	13	20.00 ± 21.45	27.48 ± 25.02	7.48 ± 8.87	0.010
Ratio VOI/GM	L + D	8	6.32 ± 3.97	6.24 ± 3.21	−0.07 ± 1.68	0.903
Ratio VOI/GM	control	13	5.36 ± 4.14	6.33 ± 4.46	0.97 ± 1.32	0.021

Data are mean ± SD. p values from paired t-tests compare pre- and post-values within each group. GM, gray matter; VOI, volume of interest.

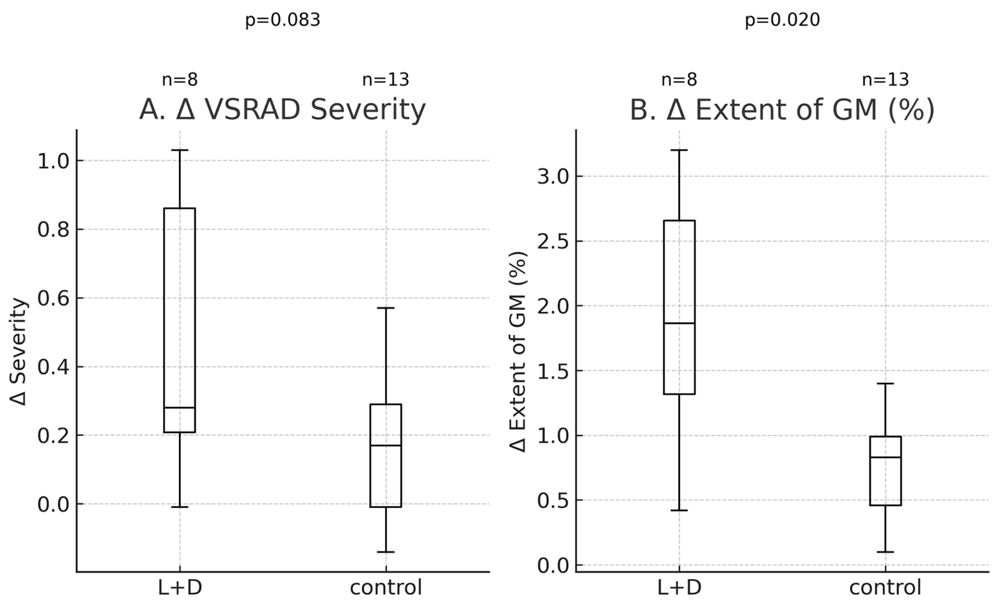
3.4. Between-Group Analysis Od VSRAD Indecies

The L + D cohort demonstrated a markedly greater increase in the proportion of grey matter with atrophy compared to controls (mean $\Delta \approx +1.86\%$ vs $+0.77\%$, $p = 0.020$) (**Figure 1** and **Table 2**). This difference suggests that sequential therapy may accelerate diffuse cortical volumetric change detectable within a short interval, a pattern previously associated with anti-amyloid monoclonal antibody therapy in phase 3 trials [1] [2] [6] [7]. For the hippocampal/parahippocampal Severity index, a numerically greater progression of hippocampal atrophy was observed in the therapy group, though the difference did not reach statistical significance ($p = 0.083$) (**Figure 1**). Indices restricted to the medial temporal volume of interest (Extent of VOI [%] and VOI/GM ratio) did not differ significantly between groups, indicating that the treatment effect was more prominent in global cortical measures than in focal medial temporal metrics (shown in **Table 2**). This pattern is consistent with prior observations that anti-amyloid therapy-related pseudoatrophy may manifest more diffusely rather than being confined to the hippocampus [8]-[11] [13] [15] [16].

Table 2. Between-group comparison of change (Δ) in VSRAD indices.

Metric	L+D Δ (n = 8)	Control Δ (n = 13)	Between-group p
VSRAD Severity	0.47 ± 0.40	0.17 ± 0.19	0.083
Extent of GM (%)	1.86 ± 1.03	0.77 ± 0.40	0.020
Extent of VOI (%)	11.17 ± 9.37	7.48 ± 8.87	0.386
Ratio VOI/GM	−0.07 ± 1.68	0.97 ± 1.32	0.158

Data are mean ± SD of Δ (post−pre) values. p values from Welch t-tests compare Δ between L + D and control groups. GM, gray matter; VOI, volume of interest.



Boxes represent the interquartile range (IQR), whiskers extend to 1.5 × IQR, and the horizontal line indicates the median. Sample sizes (n) are shown for each group.

Figure 1. Change in VSRAD indices in sequential lecanemab-donanemab (L + D) and control groups.

4. Discussion

This pilot study provides the first description of longitudinal hippocampal and cortical volumetric trajectories during sequential lecanemab followed by donanemab therapy in AD, assessed using a standardized voxel-based morphometric method. No prior report has evaluated MRI structural changes in sequential anti-amyloid mAb treatment, and none has applied VSRAD in this therapeutic context.

The principal finding was that sequential therapy was associated with greater progression in whole-brain grey matter atrophy than in untreated controls, together with a non-significant trend toward greater medial temporal Severity index increase. This pattern mirrors findings from pivotal lecanemab [1] [6] and donanemab [2] [7] trials, as well as the phase 2 donanemab study [3], in which cortical atrophy acceleration occurred despite amyloid clearance.

One possible mechanism is pseudoatrophy—volume reduction due to plaque removal, resolution of gliosis, and fluid shifts, rather than direct neuronal loss [4] [8]. This effect may reflect resolution of neuroinflammation or clearance of plaque-associated tissue volume, which could manifest as diffuse cortical thinning. Because lecanemab [1] [4] and donanemab [2] [5] target distinct amyloid conformers, their sequential use may confer additive or synergistic clearance, providing a biologically plausible basis for the diffuse volumetric changes observed. Importantly, despite these structural changes, no significant between-group difference was observed in functional decline as measured by CDR-GS. This dissociation underscores that therapy-related volumetric trajectories may not immediately translate into clinical benefit or impairment.

The absence of significant differences in medial temporal–restricted indices aligns with biomarker models of AD [8] in which neocortical amyloid deposition and its clearance precede or exceed hippocampal involvement. Longitudinal studies in untreated AD have suggested that hippocampal atrophy may plateau in later stages [15], while neocortical loss continues.

VSRAD's whole-brain atrophy metric may thus be more sensitive to therapy-related pseudoatrophy than its medial temporal Severity index. Prior validations against histopathology [9] and differential diagnosis studies [10] [11] underscore its robustness, but our findings extend its potential utility to monitoring disease-modifying therapy effects.

Nevertheless, both treated and untreated groups exhibited ongoing neurodegeneration over the study interval. This echoes trial data showing that anti-amyloid mAbs slow but do not arrest clinical and structural decline [1]-[3] [6] [7]. Future studies should integrate structural MRI with amyloid and tau biomarkers to clarify the pathological basis and clinical relevance of therapy-related volumetric changes.

Limitations include small sample size, single-center design, lack of biomarker correlation, and short follow-up. These factors preclude definitive conclusions but underscore the feasibility and potential value of sequential therapy research.

As a conclusion, sequential lecanemab → donanemab therapy in Alzheimer's disease is associated with greater whole-brain grey matter atrophy over an 18-month interval compared with untreated controls, consistent with pseudoatrophy observed in monoclonal antibody trials. This study is the first to apply VSRAD in this context, demonstrating its capacity to detect diffuse cortical changes potentially related to sequential amyloid clearance. Larger, prospective, biomarker-integrated studies are warranted to determine the clinical implications of these volumetric patterns.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Statement of Ethics

The Institutional Review Board determined that formal approval was not required for de-identified retrospective analysis of data obtained from routine clinical works. Written informed consent was obtained from the participants for publication of the details of their medical data and any accompanying images.

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Author Contributions

Heii Arai: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Validation; Writing original draft.

Hideo Yamamoto, Yuki Akiba and Junpei Takayama; Methodology, Data curation, Validation, Investigation.

Satoko Aiba: Data curation; Investigation; Methodology; Validation.

Reiko Arai: Conceptualization; Supervision; Visualization; Writing—review & editing.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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