Detection and topographic characterization of amyloid-removal-related pseudo-atrophy in sporadic early-onset Alzheimer's disease

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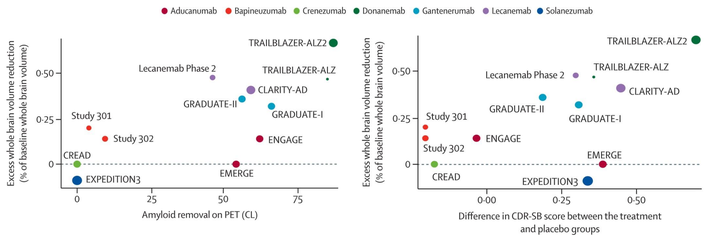
BACKGROUND

- Clinical trials of anti-amyloid therapies with successful amyloid removal consistently demonstrate that individuals with Alzheimer's disease (AD) who receive treatment show excess gray matter volume loss and ventricular enlargement compared with placebo, a phenomenon called **Amyloid-Removal-related Pseudo-Atrophy (ARPA)**.[1]
- Therapies that show greater change in cerebral and ventricular volume also show greater amyloid clearance and greater slowing of clinical decline as measured by CDR-SB scores.[1]



Goal: To characterize the topography and magnitude of ARPA in a real-world cohort of sporadic early-onset Alzheimer's disease.

Hypotheses: Longitudinal brain structural change will follow anti-amyloid treatment and be primarily observed in areas with relatively less tau deposition and neurodegeneration.

MATERIALS AND METHODS

We analyzed data from 30 individuals with sporadic EOAD in the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS)[2] who received lecanemab therapy. Each participant had MCI or mild dementia at baseline and longitudinal structural MRI and ^{18}F-Florbetaben PET data, with at least one observation before and after treatment initiation. MRI data were processed with FreeSurfer to derive regional morphometric measures. Each treated EOAD participant was matched with a 1:2 ratio to untreated participants for key demographic, clinical, genetic, and imaging variables. Piecewise mixed-effects models were used to estimate post-treatment slopes of brain structural and amyloid change.

Sample characteristics

	Lecanemab (n = 30)	Untreated (n = 60)	*p*
Age, years	58.6 (55.3, 62.5)	58.9 (57.4, 62.3)	0.56
Sex, female	23 (76.7%)	36 (60%)	0.18
APOE ε4 status			0.46
Heterozygote	9 (30.0%)	25 (41.7%)	
Homozygote	5 (16.7%)	11 (18.3%)	
CDR global			0.87
0.5	23 (76.7%)	45 (75%)	
1	7 (23.3%)	15 (25%)	
Clinical severity			0.65
MCI	13 (43.3%)	23 (38.3%)	
Dementia	17 (56.7%)	37 (61.7%)	
Centiloids	96.2 (83.9, 101.9)	93.7 (71.8, 105.1)	0.59
Follow-up duration, months	25.3 (14.2, 29.0)	25.0 (14.0, 30.2)	0.86

Values indicate: Median (Q1, Q3) for numerical variables; n (%) for ordinal and nominal variables.

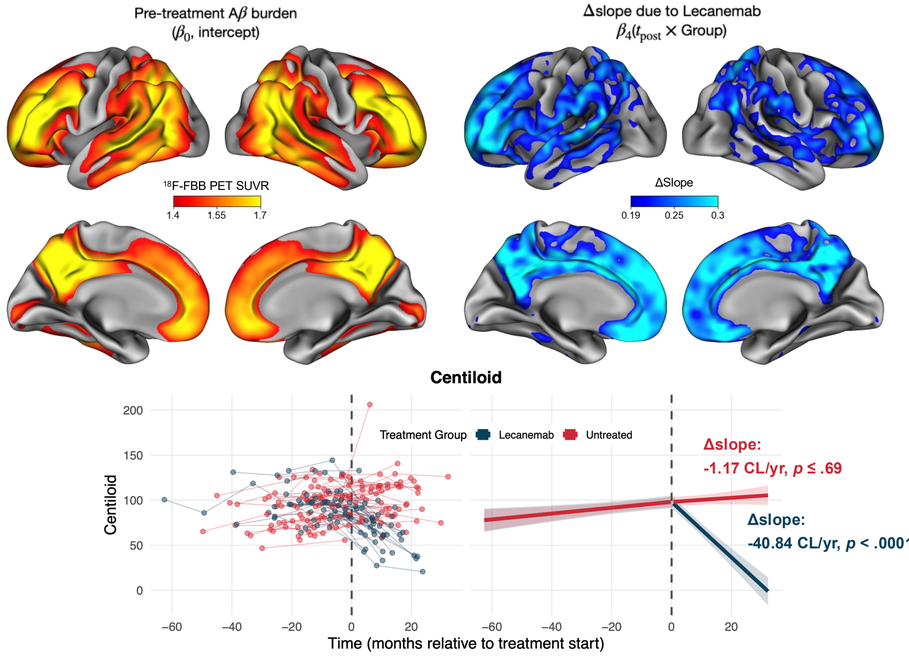
RESULTS

Modeling approach:

$$\text{Outcome} \sim \beta_0 + \beta_1(t) + \beta_2(t_{\text{post}}) + \beta_3(\text{Group}) + \beta_4(t_{\text{post}} \times \text{Group}) + (1 \mid \text{Participant})$$

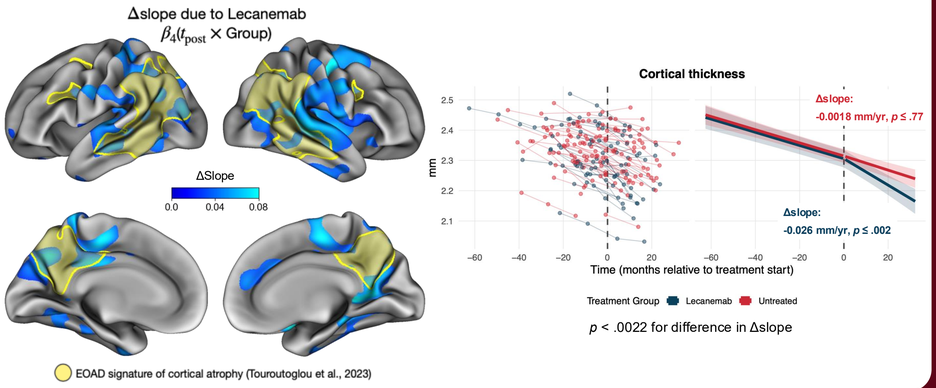
$$t_{\text{post}} = \begin{cases} 0 & \text{if } t < 0 \\ 1 & \text{if } t \geq 0 \end{cases} \qquad \text{Group} = \begin{cases} 0 & \text{if Untreated} \\ 1 & \text{if Treated} \end{cases}$$

Baseline Aβ burden and longitudinal Aβ clearance due to lecanemab treatment



As previously shown in LEADS, treated participants showed substantial post-treatment reduction in neocortical Aβ burden compared with untreated participants ($p < .0001$ for difference in Δslope).

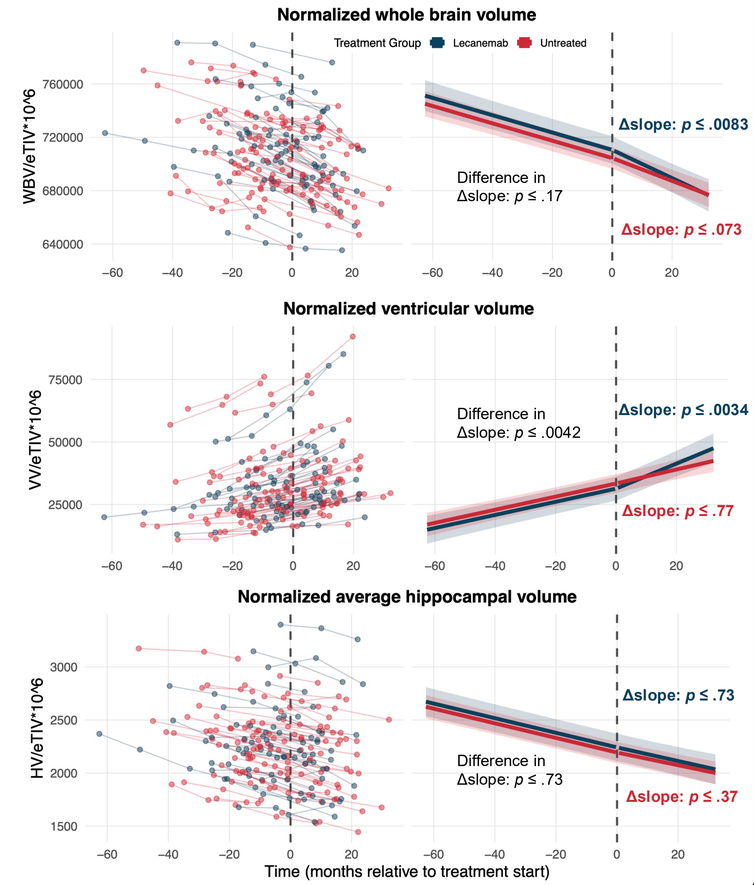
Longitudinal change in cortical thickness due to lecanemab treatment



$p < .0022$ for difference in Δslope

RESULTS, CONT'D

Longitudinal change in global and regional brain volumetric measures due to lecanemab treatment



CONCLUSIONS & FUTURE DIRECTIONS

- Characterization of ARPA with increased anatomical specificity may help refine outcome measures for clinical trials by establishing more accurate biomarkers for evaluating anti-amyloid treatment efficacy in EOAD.
- Ongoing analyses examine the relationship between the magnitudes of longitudinal change in Aβ and brain morphometry to more directly link treatment-related amyloid clearance and brain structural change.

REFERENCES & ACKNOWLEDGMENTS

[1]Belder et al. (2024). *The Lancet Neurol*; [2]Apostolova et al. (2021). *Alzheimers Dement.* We would like to thank all members of the LEADS Consortium. This study was in part generously supported by NIH (R56 AG057195, U01 AG6057195, U24 AG021886, K01 AG084820) and Alzheimer's Association (LEADS GENETICS-19-639372, LDRFP-21-818464, LDRFP-21-824473, LDRFP-21-828356, AARG-24-1309264).