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Reductions in Biomarkers of Alzheimer's Disease Pathophysiology Following Treatment With Aducanumab Were Associated With Slowing in Clinical Decline

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OBJECTIVE

- To examine whether aducanumab-induced reduction in brain Aβ plaques and downstream biomarkers of Alzheimer's disease pathophysiology are associated with a slowing in clinical decline.

CONCLUSIONS

- Aducanumab-induced changes in biomarkers of Alzheimer's disease pathophysiology were correlated with clinical measures consistent with the hypothesized mechanism of action for aducanumab (ie, a direct effect of aducanumab on lowering brain Aβ pathology with a subsequent effect on reducing tau pathology and neurodegeneration and slowing of clinical decline).
  - Change from baseline in Aβ PET SUVR was correlated with all key clinical measures (CDR-SB, MMSE, ADAS-Cog13, ADCS-ADL-MCI) in EMERGE.
  - In PRIME, change from baseline in Aβ PET SUVR was correlated with both CDR-SB and MMSE, which is supportive of the findings from EMERGE.
- Group-level analyses based on data from EMERGE, ENGAGE, and PRIME demonstrated a positive association between aducanumab treatment effect on brain Aβ plaques and clinical measures.
- In all 3 studies, a smaller magnitude of decline across key clinical measures was observed in patients for whom Aβ plaque levels were lowered to a threshold[5] considered to be amyloid negative (relative to those who did not reach this threshold).

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Introduction

- Aducanumab is a human, immunoglobulin γ1 monoclonal antibody directed against aggregated soluble and insoluble forms of Aβ (**Figure 1**).[1]
- Aducanumab is the first FDA-approved Alzheimer's disease treatment that reduces Aβ plaques, a defining pathophysiological feature of Alzheimer's disease.[2]
- A robust dose-dependent reduction in brain Aβ plaque levels, as measured by amyloid PET, was demonstrated across aducanumab clinical studies (PRIME, NCT01677572; EMERGE, NCT02484547; and ENGAGE, NCT02477800).[1,3]
- Here, we examine the association between aducanumab-induced reduction in biomarkers of Alzheimer's disease pathophysiology and clinical measures from 3 clinical trials evaluating aducanumab in patients with early Alzheimer's disease.

Figure 1. Therapeutic hypothesis

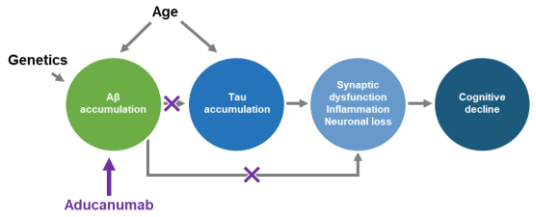


Illustration modified from Sperling RA, et al.[4]

Methods

- EMERGE and ENGAGE were 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies that evaluated low-dose (titration to 3 or 6 mg/kg) and high-dose (titration to 10 mg/kg) aducanumab in patients with early Alzheimer's disease with evidence of amyloid pathology.[3]
- PRIME was a Phase 1b study that evaluated aducanumab 1, 3, 6, and 10 mg/kg and titration to 10 mg/kg in individuals with early Alzheimer's disease.[1]
- The Phase 3 studies included a longitudinal Aβ PET substudy (n = 488 in EMERGE; n = 585 in ENGAGE) and a CSF substudy evaluating p-tau and t-tau levels (n = 78 in EMERGE; n = 53 in ENGAGE).[3] All studies, including PRIME[1], used ^{18}F-florbetapir for longitudinal Aβ PET imaging.
- The following analyses were conducted in the respective biomarker substudies; the primary postbaseline visit for these analyses was Week 78 in EMERGE and ENGAGE and Week 54 in PRIME:
  - **Group-level analysis:** Association between the treatment effects (relative to placebo) on Aβ PET SUVR and CDR-SB across all aducanumab dose groups and all 3 studies was examined.
  - **Participant-level analysis**: Spearman correlation adjusting for baseline values was examined between:
    - Change from baseline in Aβ PET SUVR and clinical measures
    - Change from baseline in Aβ PET SUVR and downstream biomarkers of disease pathophysiology (CSF p-tau, t-tau; in Phase 3 studies only)
    - Change from baseline in CSF p-tau/t-tau and clinical measures (in Phase 3 studies only)
  - **Analysis of clinical decline by Aβ status at follow-up**: Change from baseline in clinical measures stratified by whether the magnitude of Aβ PET SUVR at primary postbaseline visit is >1.10 (considered Aβ positive) or ≤1.10 (considered Aβ negative).[5]

Results

Group-level analysis (**Figure 2**)

- A greater treatment effect on brain Aβ plaque levels was associated with greater treatment effect on CDR-SB (ie, less decline) in aducanumab studies (**Figure 2A**) and other recent studies of anti-Aβ monoclonal antibodies (**Figure 2B**).[6,7,8]

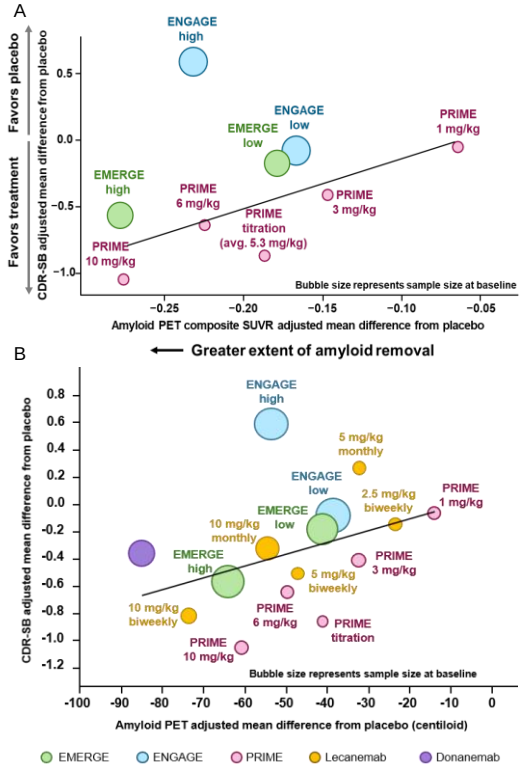
Participant-level analyses (**Figure 3**)

- A greater reduction in Aβ PET SUVR was associated with lesser decline in all key clinical measures in EMERGE (**Figure 3**). In ENGAGE, in which a clinical treatment effect was not observed, correlations were not apparent (not shown). In PRIME, the correlation coefficients (**ρ**) were 0.33 for CDR-SB and −0.32 for MMSE.
- A greater reduction in Aβ PET SUVR was associated with greater reduction in CSF p-tau/t-tau (EMERGE: **ρ** = 0.52 for p-tau and **ρ** = 0.37 for t-tau; ENGAGE: **ρ** = −0.03 for p-tau and **ρ** = 0.42 for t-tau).
- A greater reduction in CSF p-tau was associated with lesser decline in clinical measures in EMERGE (**Figure 3**); a similar pattern of association was also observed in CSF t-tau (data not shown).
- These results are consistent with the hypothesized direct effect of aducanumab on lowering brain Aβ pathology and the subsequent effect on reducing tau pathology (p-tau) and neurodegeneration (t-tau) and slowing of clinical decline.

Analysis of clinical decline by Aβ status at follow-up (**Table**)

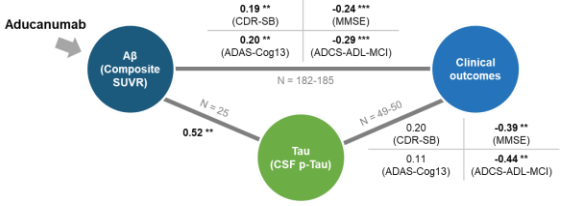
- A numerically smaller magnitude of decline across key clinical measures in all 3 studies was observed in participants in whom Aβ plaque levels were lowered to levels considered to be amyloid negative (SUVR ≤1.10) relative to those who did not reach this threshold (SUVR >1.10).
- These results indicate that the absolute level to which brain Aβ is lowered may also influence longitudinal changes in clinical measures and further support the association between reduced brain Aβ levels and slowing of clinical decline.

Figure 2. Greater treatment effect on brain Aβ plaque levels was associated with greater treatment effect on CDR-SB (group-level analysis)



Results for the aducanumab studies were from the Aβ PET substudy population, in which longitudinal Aβ PET data was available. The high-dose group in ENGAGE was not included for the regression line in 2A but was included for the regression line in 2B.

Figure 3. Aducanumab–induced biomarker changes are correlated with clinical measures in EMERGE (participant-level analysis)



All associations are partial Spearman correlation of change from baseline to Week 78 between each variable assessed in pooled low- and high-dose groups adjusting for baseline biomarker and efficacy values.
** p<0.01; *** p<0.001 (nominal).

Table. Clinical decline by Aβ PET status at follow-up in clinical studies of aducanumab

	Phase 3 studies (by Aβ PET status at Week 78)			
	ENGAGE		EMERGE	
	SUVR >1.10 (n = ≈185)	SUVR ≤1.10 (n = ≈65)	SUVR >1.10 (n = ≈140)	SUVR ≤1.10 (n = ≈65)
CDR-SB , median/mean				
Baseline	2.50/2.44	2.50/2.45	2.50/2.51	2.00/2.38
Change at Week 50	0.50/0.84	0.50/0.82	0.50/0.84	0.00/0.45
Change at Week 78	1.00/1.44	1.00/1.24	1.00/1.30	0.50/0.53
MMSE, median/mean				
Baseline	26.0/26.4	26.0/26.4	26.0/26.2	27.0/26.8
Change at Week 50	−2.0/−2.3	−2.0/−1.8	−2.0/−2.2	0.0/−0.9
Change at Week 78	−3.0/−3.4	−2.0/−2.8	−2.5/−3.2	−1.0/−1.4
ADAS-Cog 13, median/mean				
Baseline	21.2/21.9	20.8/21.3	22.0/22.3	20.0/20.0
Change at Week 50	2.7/3.0	0.3/1.6	1.7/2.2	−0.5/0.3
Change at Week 78	5.0/5.5	3.7/3.3	4.3/5.1	1.0/1.1
ADCS-ADL-MCI, median/mean				
Baseline	44.0/43.3	43.5/42.2	44.0/43.4	44.0/43.9
Change at Week 50	−1.0/−1.5	−1.0/−1.7	−1.0/−1.0	0.0/−0.6
Change at Week 78	−2.0/−3.3	−2.0/−2.6	−2.0/−2.9	0.0/−1.4

	Phase 1b PRIME study (by Aβ PET status at Week 54)	
	SUVR >1.10 (n = 83)	SUVR ≤1.10 (n = 24)
CDR-SB, median/mean		
Baseline	3.00/3.23	2.50/2.94
Change at Week 26	0.50/0.94	0.00/−0.13
Change at Week 54	1.00/1.55	0.00/−0.15
MMSE, median/mean		
Baseline	24.0/23.8	25.0/25.8
Change at Week 26	−1.0/−0.9	−0.5/−0.7
Change at Week 54	−1.0/−1.6	0.0/0.0

For EMERGE and ENGAGE, patients treated with aducanumab (low or high dose) who had a PET assessment at Week 78 are included. For PRIME, patients treated with aducanumab who had a PET assessment at Week 54 are included. Cells where median decline in the SUVR ≤1.10 subgroup is smaller than in the SUVR >1.10 subgroup or where the median decline is the same and the mean decline is smaller are shaded in green.

Abbreviations: Aβ, amyloid beta; ADCS-ADL-MCI,Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment; ADAS-Cog13, Alzheimer's disease assessment scale cognitive subscale; CDR-SB, Clinical Dementia Rating Scale-Sum of Boxes; CSF, cerebrospinal fluid; FDA, US Food and Drug Administration; MMSE, Mini-Mental State Examination; PET, positron emission tomography; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio; t-tau, total tau.

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