APOE4/4 Subjects with Early Alzheimer's Disease Show Accelerated Loss of Cortical Thickness and Cognitive Decline Compared to APOE3/3 Subjects

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Background & Objectives

The apolipoprotein ε4 allele (APOE4) is a major genetic risk factor for Alzheimer's disease (AD), with APOE4 carriers (homozygotes and heterozygotes) comprising ~65% of AD patients. APOE4 gene dose-dependently increases the burden of beta amyloid (Aβ) soluble oligomers, which are thought to be primary drives of neurotoxicity. APOE4/4 homozygotes have shown high rates of hippocampus atrophy (Abushakra et al. CTAD 2018) and early cognitive decline. Therefore, APOE4/4 homozygotes are an optimal target population for drugs that inhibit Aβ oligomer formation, such as tramiprosate or its prodrug ALZ-801 (Abushakra et al. 2017, Kocis et al. 2017, Hey et al. 2018, Tolar et al. 2019).

Background on ALZ-801

- An oral pro-drug of tramiprosate, with improved oral absorption and gastrointestinal tolerability
- Shows improved brain penetration of tramiprosate, 40% of drug in plasma enters brain (Hey et al. 2018)
- Tramiprosate and its active metabolite, 3-SPA, inhibit formation of Aβ42 oligomers (Kocis et al. 2017))
- Tramiprosate showed significant efficacy in APOE4/4 homozygotes in a Phase 3 study (Abushakra 2016 and 2017)
- Tramiprosate showed favorable safety in ~2000 AD patients, with no organ toxicity or ARIA-E (Abushakra 2016)
- Main adverse events with tramiprosate were mild to moderate nausea and vomiting
- Tramiprosate showed dose dependent protection of hippocampus atrophy in a prior AD study (Gauthier et al. 2009)
- ALZ-801 development program for AD, has received Fast Track Status from the FDA
- We are planning a Phase 3 study of ALZ-801 in APOE4/4 homozygotes with Early AD (MCI due to AD and Mild AD)
- Hippocampus volume on MRI will be designated as main imaging biomarker in the Phase 3 study

Our objectives are to:

1. Optimize imaging biomarker selection for the planned ALZ-801 Phase 3 trial in APOE4/4 patients
2. Evaluate rates of cortical thickness loss in APOE4/4 and APOE3/3 subjects
3. Evaluate correlations of cortical thickness loss to clinical decline in APOE4/4 patients

Methods

We analyzed clinical and imaging datasets from ADNI-1, and the subset of a tramiprosate Phase 3 study with serial volumetric MRI. We compared clinical and imaging data from APOE3/3 versus APOE4/4 subjects in late MCI and Mild AD groups of ADNI-1.

ADNI-1 Dataset:

- Enrolled 722 subjects: 255 Cognitively Normal (CN), 301 Late Mild Cognitive Impairment (LMCI) and 166 Mild AD.
- LMCI group had 228 APOE3/3 non-carriers and 73 APOE4/4 carriers.
- Mild AD group had 101 APOE3/3 and 65 APOE4/4 subjects.
- Clinical scores (MMSE, ADAScog13, CDR-SB) were collected at Baseline and Months (M) 3, 6, 9, 12, 18 and 24.
- Data from MRI subgroup was evaluated at baseline, 12 and 24 months (http://adni.loni.ucla.edu), and included: LMCI (93 APOE3/3, 29 APOE4/4) and AD (29 APOE3/3, 21 APOE4/4).
- 3D T1-weighted MRI collection consisted of MP RAGE (Siemens), 3D TFE (Philips) and 3D Fast SPGR (General Electric) pulse sequences, with 1.25×1.25×1.2 mm3 voxel resolution in sagittal orientation.
- **Cortical thickness** (**Mayo Index**) was measured using FreeSurfer, Mayo AD signature ROI (Jack 2017) was calculated at baseline and changes from baseline (CBL) were analyzed by a Jacobian-based method.
- Whole brain volume (**WBV**) and hippocampus volume (**HV=L+R**) were derived & CBL assessed using Boundary Shift Integral
- Baseline volumetric measures were adjusted for age, years of education, and head size.
- Clinical score CBL were estimated by fitting a linear model for each subject. Correlations between baseline cortical thickness, clinical decline, and changes in cortical thickness at M24 were analyzed by Pearson's correlations.

ADNI-1 Dataset: Baseline Characteristics in Late MCI and Mild AD

Baseline Characteristics ADNI-1 Clinical Set Baseline Characteristics ADNI-1 Clinical Set

Late MCI Group: Noncarriers vs. APOE4/4

Baseline characteristics – LMCI

		LMCI Non-carriers	LMCI Homozygotes	p-value
2	N	228	73	
3	AGE	74.83 (8.13)	70.81 (6.19)	<0.001
4	PTGENDER	65.8 (% Male)	57.5 (% Male)	N/A
5	APOE4	0.00 (0.00)	2.00 (0.00)	<0.001
6	PTEDUCAT	15.92 (2.97)	16.07 (2.78)	0.700
7	MMSE	27.30 (1.79)	26.78 (1.90)	0.035
8	ADAS13	17.30 (6.43)	20.14 (5.72)	<0.001
9	CDRSB	1.53 (0.87)	1.60 (0.91)	0.520

Mild AD Group: Noncarriers vs. APOE4/4

Baseline characteristics – AD

		AD Non-carriers	AD Homozygotes	p-value
2	N	101	65	
3	AGE	76.51 (8.76)	71.14 (7.30)	<0.001
4	PTGENDER	53.5 (% Male)	58.5 (% Male)	N/A
5	APOE4	0.00 (0.00)	2.00 (0.00)	<0.001
6	PTEDUCAT	15.39 (3.17)	15.12 (2.52)	0.574
7	MMSE	23.23 (2.08)	23.34 (1.97)	0.733
8	ADAS13	29.76 (8.76)	28.70 (7.06)	0.418
9	CDRSB	4.48 (1.70)	4.39 (1.61)	0.740

Faster Cortical Thinning in APOE4/4 than APOE3/3 Subjects

Panel A: Rates in LMCI

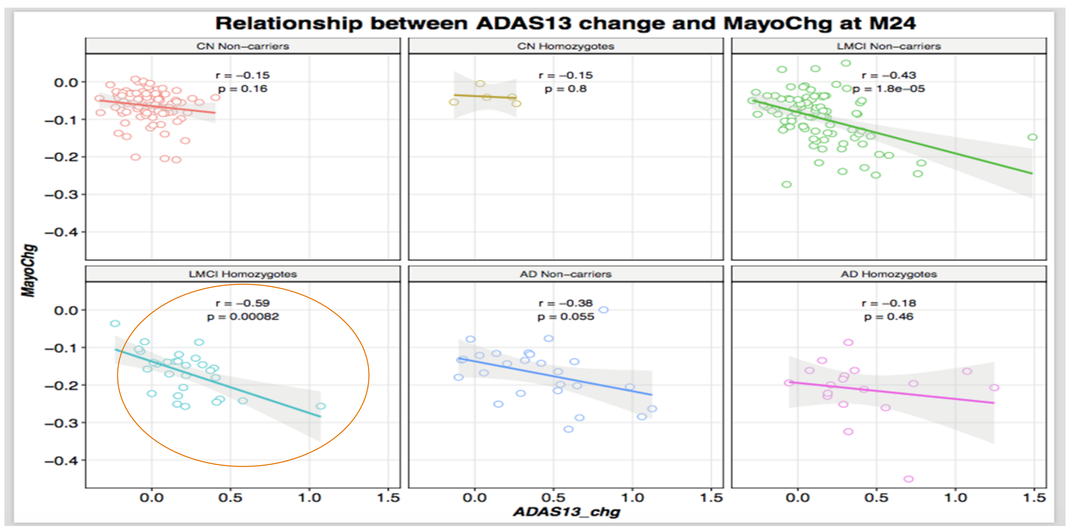
	Cortical Thickness			WBV		
Timepoint	APOE3/3 N = 93	APOE4/4 N = 29	*P* value*	APOE3/3 N = 93	APOE4/4 N = 29	*P* value*
Baseline						
Mean	2.65	2.62	**.38**	1022.6	1020.6	.918
(SD)	(0.16)	(0.19)		(107.6)	(84.4)	
12 months						
Change	-0.05%	-0.09%	**< .001**	-0.78%	-1.08%	.12
(SD)	(0.04)	(0.03)		(0.98)	(0.87)	
24 months						
Change	-0.09%	-0.17%	**< .001**	-1.62%	-2.37%	**.008**
(SD)	(0.07)	(0.06)		(1.35)	(1.24)	

Panel B: Rates in Mild AD

	Cortical Thickness			WBV		
Timepoint	*APOE*3/3 N = 29	*APOE*4/4 N = 21	*P* value*	*APOE*3/3 N = 29	*APOE*4/4 N = 21	*P* value*
Baseline						
Mean	2.51	2.50	**.04**	978.1	997.0	.568
(SD)	(0.24)	(0.17)		(103.8)	(121.3)	
12 months						
Change	-0.09%	-0.12%	**.06†**	-1.47%	-1.53%	.801
(SD)	(0.04)	(0.06)		(1.00)	(0.73)	
24 months						
Change	-0.17%	-0.22%	**.005**	-2.73%	-3.25%	.122
(SD)	(0.08)	(0.08)		(1.22)	(1.09)	

Abbreviations: LMCI, late mild cognitive impairment; SD, standard deviation; vMRI, volumetric magnetic resonance imaging; WBV, whole blood volume.
All vMRI measures were adjusted for age, years of education, and head size. *P value = *APOE*4/4 vs. *APOE*3/3, $P < 0.05$ is considered statistically significant, †$P < 0.1$ is considered a positive trend

Significant Correlation of Cortical Thinning to Cognitive Decline in MCI Subjects



Cortical thickness to cognitive decline: r=0.59, p<0.0001; while HV correlation r=0.55, p<0.002 (Abushakra et al., CTAD 2018)

Conclusions

ADNI-1 analysis comparing APOE4/4 to APOE3/3 AD subjects showed the following:

- Baseline cortical thickness was significantly different between APOE4/4 and APOE3/3 subjects in Mild AD, but not MCI
- In contrast, hippocampus volume was significantly smaller in APOE4/4 subjects with MCI and Mild AD
- Rates of cortical thickness loss at 12 and 24 months were significantly higher in APOE4/4 with MCI
- Differences between APOE4/4 and APOE3/3 in cortical thickness loss were larger at MCI than AD stage

- Cortical thickness is strongly correlated with cognitive decline in the MCI, but not Mild AD stage
- Correlations between cortical thickness and cognitive decline are stronger in APOE4/4 MCI subjects
- These analyses highlight cortical thickness as a useful biomarker of neurodegeneration in APOE4/4 population
- Cortical thickness may complement & support use of hippocampus volume as imaging biomarker in Early AD trials
- In the planned Phase 3 trial of ALZ-801 in Early AD, cortical thickness will be a secondary imaging biomarker

References:

- S. Abushakra et al. J Prev Alz Dis 2017.
- P. Kocis et al. CNS Drugs 2017.
- J. Hey et al. CNS Drugs 2018.
- M. Tolar et al. Alzheimers Dement 2019.