Moderation of Amyloid-β Deposition on the Effect of Cholinesterase Inhibitors on Cognition in Mild Cognitive Impairment

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Abstract.

Background: Clinical trial findings on cholinesterase inhibitors (ChEIs) for mild cognitive impairment (MCI) are inconclusive, offering limited support for their MCI treatment. Given that nearly half of amnestic MCI cases lack cerebral amyloid-β (Aβ) deposition, a hallmark of Alzheimer's disease; this Aβ heterogeneity may explain inconsistent results.

Objective: This study aimed to assess whether Aβ deposition moderates ChEI effects on amnestic MCI cognition.

Methods: We examined 118 individuals with amnestic MCI (ages 55–90) in a longitudinal cohort study. Baseline and 2-year follow-up assessments included clinical evaluations, neuropsychological testing, and multimodal neuroimaging. Generalized linear models were primarily analyzed to test amyloid positivity's moderation of ChEI effects on cognitive change over 2 years. Cognitive outcomes included Mini-Mental Status Examination score, the total score of the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery, and Clinical Dementia Rating-sum of boxes.

Results: The analysis found no significant ChEI use x amyloid positivity interaction for all cognitive outcomes. ChEI use, irrespective of Aβ status, was associated with more cognitive decline over the 2-year period.

Conclusions: Aβ pathology does not appear to moderate ChEI effects on cognitive decline in MCI.

Keywords: Alzheimer's disease, amyloid-β, cholinesterase inhibitor, cognitive change, mild cognitive impairment

INTRODUCTION

Numerous clinical trials have established the efficacy of cholinesterase inhibitors (ChEIs) in the treatment of Alzheimer's disease (AD) dementia, leading to their approval by the US FDA for mild to moderate AD dementia.[1] However, the application

of ChEIs in the context of mild cognitive impairment (MCI), often considered a risk or prodromal stage of dementia, especially AD dementia,[2] has yielded inconsistent findings, lacking strong support for their use in MCI patients.[3,4]

Conceptually, MCI represents a diverse clinical state resulting from a variety of etiological conditions.[2] Notably, amnestic MCI is closely associated with AD[5] and has been a focal point in most ChEI trials for MCI.[6–8] Nonetheless, approximately half of amnestic MCI cases do not exhibit amyloid-β (Aβ) deposition, a fundamental AD pathology, in the brain.[9,10] Given that amnestic MCI patients lacking Aβ deposition likely possess distinct pathophysiological characteristics from those with Aβ deposition, this heterogeneity in Aβ presence or the AD process could elucidate the inconsistencies and less favorable results in ChEI trials for MCI.

A previous study,[11] retrospectively analyzing data from a memory clinic to assess the impact of 1-year ChEI treatment on cognitive decline in amnestic MCI patients while accounting for the presence of Aβ deposition, found no significant difference between ChEI users and non-users, irrespective of Aβ status. However, this study did not investigate whether the presence of Aβ modulates the ChEI effect on cognitive decline, and it's worth noting that one year may not provide sufficient time to ascertain the effect of ChEI use.

Within this context, the aim of this study is to examine the hypothesis that the presence of Aβ deposition moderates the impact of ChEI treatment on cognition in individuals with amnestic MCI.

METHODS

Participants

This study is part of the ongoing Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), initiated in 2014. As of June 2023, the study enrolled 118 participants with MCI who completed baseline and 2-year follow-up assessments, ranging in age from 55 to 90. Additional participant details are available in a previous study.[12] All MCI participants met the current consensus criteria for amnestic MCI, which include: (i) a memory complaint validated by an informant, (ii) objective memory impairment, (iii) preserved global cognitive function, (iv) independence in functional activities, and (v) the absence of

dementia.[13] Notably, the criterion (ii) required age-, education-, and gender-adjusted z-scores for at least one of four episodic memory tests to be below –1.0. These memory tests consist of Word List Memory, Word List Recall, Word List Recognition, and Construction Recall tests, all part of the Korean versions of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) neuropsychological battery.[14] The study protocol received approval from the Institutional Review Boards of Seoul National University Hospital (C-1401-027-547) and SNU-SMG Boramae Center (26-2015-60), Seoul, South Korea. The research adhered to the current Declaration of Helsinki guidelines, and all participants provided written informed consent.

History of ChEI use

Information regarding the current drug regimens, including the names of all drugs, was obtained from prescriptions in the KBASE cohort. In this study, the ChEI administration group consisted of participants currently taking ChEIs, including donepezil, rivastigmine, and galantamine. Additionally, the administration of memantine was investigated and used as a covariate.

Clinical and neuropsychological assessment (Fig. 1)

At both baseline and the 2-year follow-up, participants underwent standardized clinical assessments conducted by trained board-certified psychiatrists. These assessments were based on the Korean Brain Aging Study's clinical assessment protocol, incorporating the CERAD-K clinical assessment.[15] The Clinical Dementia Rating (CDR) score was rated for all participants, evaluating the severity of cognitive impairment. The CDR-Sum-of-Box (CDR-SOB) score was computed as the sum of the CDR scores from all domains.[16] Comprehensive neuropsychological assessments were administered at both time points by trained psychometrists, following a standardized protocol that included eight tests from the CERAD-K neuropsychological battery: the Mini-Mental State Examination (MMSE), Verbal Fluency (VF), 15-item Boston Naming Test (BNT), Word List Memory (WLM), Word List Recall (WLR), Word List Recognition (WLRc), Constructional Praxis (CP), and Constructional Recall (CR).[14] The CERAD total score (CERAD-TS) was calculated by summing
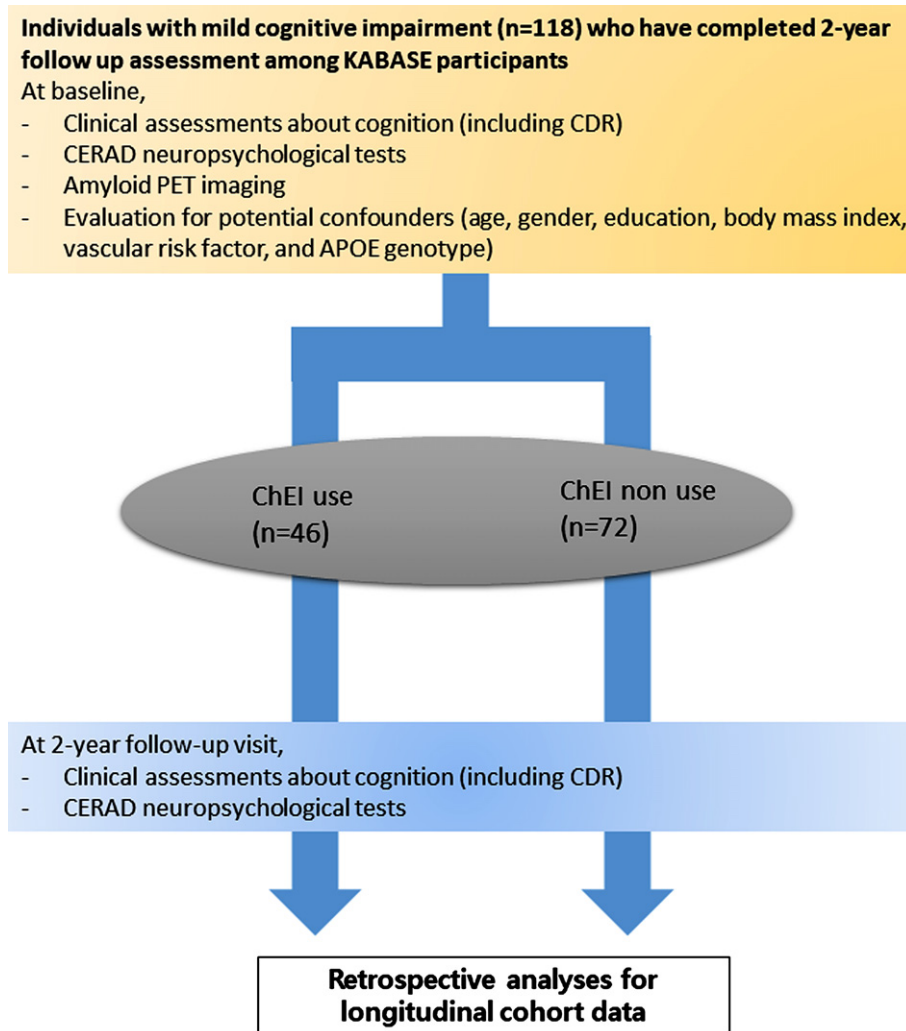
Fig. 1. Flow chart of current study. ChEI, cholinesterase inhibitor; CERAD, The Korean version of the Consortium to Establish a Registry for Alzheimer's Disease.

the scores of six tests from the CERAD-K neuropsychological battery (VF, BNT, WLM, WLR, WLRc, and CP).[17,18]

Measurement of potential confounders

Demographic information included age (in years), gender, and years of education. Participants were systematically assessed for vascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, transient ischemic attack, and stroke. A vascular risk score (VRS) reflecting vascular risk burden was determined.[19] Genomic DNA was extracted from whole blood, and apolipoprotein E (*APOE*) genotyping was performed,[20] with *APOE4*

positivity defined as the presence of at least one $\varepsilon4$ allele.

Measurement of amyloid positivity

All participants underwent simultaneous three-dimensional (3D) [^{11}C] Pittsburgh compound B (PiB) PET and 3D T1-weighted MRI at baseline. After intravenous administration of 555 MBq of ^{11}C-PiB (range, 450–610 MBq), a 30-min emission scan was obtained 40 min after injection. The PiB PET image analysis followed previously described methods.[21] PiB retention index as standardized uptake value ratio (SUVR) for each region of interest was calculated by dividing regional mean value by the individual mean

Table 1
Baseline demographic, clinical and imaging characteristics of subjects

Group	Total ($n = 118$)	ChEI + ($n = 46$)	ChEI – ($n = 72$)	p
Age (y)	73.45 ± 7.08	72.39 ± 6.89	74.13 ± 7.16	0.196
Sex (Female %)	75 (63.6%)	32 (69.6%)	43 (59.7%)	0.279
Education (y)	10.03 ± 4.53	10.20 ± 4.58	9.93 ± 4.53	0.758
VRS	1.18 ± 1.04	0.91 ± .94	1.35 ± 1.06	0.026*
BMI	24.74 ± 3.07	24.28 ± 2.86	25.04 ± 3.17	0.187
APOE ε4 positivity (%)	41 (34.7%)	26 (56.5%)	15 (20.8%)	<0.001*
Amyloid Positivity (%)	54 (45.8%)	35 (76.1%)	19 (26.4%)	<0.001*
CDR-SOB	1.47 ± 0.64	1.95 ± 0.60	1.17 ± 0.46	<0.001*
MMSE	22.54 ± 3.22	21.24 ± 3.25	23.38 ± 2.93	<0.001*
CERAD-TS	49.34 ± 9.61	50.37 ± 9.80	48.68 ± 9.50	0.354

Mean values were presented as Mean ± Standard deviation. Group was divided according to ChEI taking at baseline. *$p < 0.05$. ChEI, cholinesterase inhibitor; VRS, vascular risk score; BMI, body mass index; CDR-SOB, Clinical Dementia Rating Sum of Box; MMSE, Mini-Mental Status Examination; CERAD-TS, The Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Total score.

cerebellar uptake values. The autonomic anatomic labeling algorithm and a region-combining method[22] were applied to determine regions of interest (ROIs) to characterize the PiB retention level in the frontal, lateral parietal, posterior cingulate–precuneus, and lateral temporal regions. Each participant was classified as amyloid positive if the SUVR value was greater than 1.4 in at least one of the four regions of interest or as amyloid negative if the SUVR values of all four regions of interest was equal to or less than 1.4.[22,23]

Statistical analyses

Demographic, clinical, and neuroimaging data were compared between ChEI users and non-users using *t*-tests for continuous variables and chi-square tests (or Fisher's exact tests) for categorical variables. Generalized linear model (GLM) analyses were performed to evaluate the effect of ChEI use and its interaction with amyloid positivity on cognition. GLM models included ChEI use as an independent variable and 2-year changes in MMSE, CERAD-TS, or CDR-SOB (outcome measures) as dependent variables. These models controlled for age, sex, education, *APOE4* positivity, amyloid positivity, baseline values of corresponding outcome variables, VRS, and memantine use. To account for multiple comparisons in the GLM analyses for cognitive change (3 measures), the Bonferroni method was applied, setting the threshold for statistical significance at $p < 0.017$ ($= 0.05/3$). All statistical analyses were performed using the IBM SPSS Statistics 24 software (IBM Corp., Armonk, NY, USA).

RESULTS

Characteristics of participants

Table 1 presents the demographic, clinical, and neuroimaging characteristics of participants based on ChEI use. The ChEI use group exhibited a lower VRS (0.91 ± 0.94 versus 1.35 ± 1.06) and a higher frequency of APOE4 positivity (56.5% versus 20.8%) compared to the non-use group. Furthermore, the ChEI use group displayed higher baseline CDR-SOB scores (1.95 ± 0.60 versus 1.17 ± 0.46) and lower MMSE scores (21.24 ± 3.25 versus 23.28 ± 2.93) than the non-use group. These differences indicated that the ChEI use group included individuals with more advanced MCI in regard of cognitive impairment. Moreover, amyloid positivity ratio was higher in the ChEI use group (76.1% versus 26.4%).

Effect of ChEI use and its interaction with amyloid positivity on cognitive outcome

GLM analyses of the main effect only models demonstrated that ChEI use, regardless of amyloid positivity, had a significant negative impact on cognitive change over the 2-year period. Specifically, the ChEI use group exhibited greater declines in CERAD-TS (β = –0.478, $p < 0.001$) and MMSE scores (β = –0.302, $p = 0.004$), as well as greater increases in CDR-SOB scores (β = 0.299, $p = 0.006$), compared to the ChEI non-use group (Table 2). However, the analyses for the models including interaction terms did not reveal significant interaction effects between ChEI use and amyloid positivity on any cognitive outcome measures. Specifically, on MMSE

Table 2
Association between baseline ChEI use, amyloid positivity and change of primary outcome variables. (Main and interaction effects)

	Outcomes	Predictors	95% CI of B	β	*p*
Main effect only	ΔMMSE	Baseline ChEI	−2.289 (−3.815 − −0.764)	−0.302	0.004*
		Amyloid positivity	−0.115 (−1.708 − 1.478)	−0.016	0.886
	ΔCERAD-TS	Baseline ChEI	−11.722 (−15.825 − −7.620)	−0.479	<0.001*
		Amyloid positivity	−1.841 (−6.068 − 2.387)	−0.077	0.390
	ΔCDR-SOB	Baseline ChEI	1.117 (0.325 − 1.910)	0.299	0.006*
		Amyloid positivity	0.337 (−0.358 − 1.032)	0.092	0.338
Main & interaction effect	ΔMMSE	Baseline ChEI	−2.666 (−4.922 − −0.411)	−0.352	0.021
		Amyloid positivity	−0.355 (−2.270 − 1.560)	−0.048	0.714
		Baseline ChEI X Amyloid Positivity	0.661 (−2.240 − 3.561)	0.082	0.653
	ΔCERAD-TS	Baseline ChEI	−12.195 (−18.954 − −6.877)	−0.527	<0.001*
		Amyloid positivity	−2.698 (−7.996 − 2.600)	−0.113	0.315
		Baseline ChEI X Amyloid Positivity	2.175 (−5.877 − 10.226)	0.083	0.593
	ΔCDR-SOB	Baseline ChEI	1.377 (0.245 − 2.509)	0.368	0.018
		Amyloid positivity	0.507 (−0.366 − 1.380)	0.139	0.252
		Baseline ChEI X Amyloid Positivity	−0.427 (−1.750 − 0.896)	−0.107	0.524

Adjusted variables; Age, Sex, Education, *APOE4* positivity, baseline outcome value, Vascular score, baseline memantine use. *$p < 0.017$; ChEI, cholinesterase inhibitor; CDR-SOB, Clinical Dementia Rating Sum of Box; MMSE, Mini-Mental Status Examination; CERAD-TS, The Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Total score.
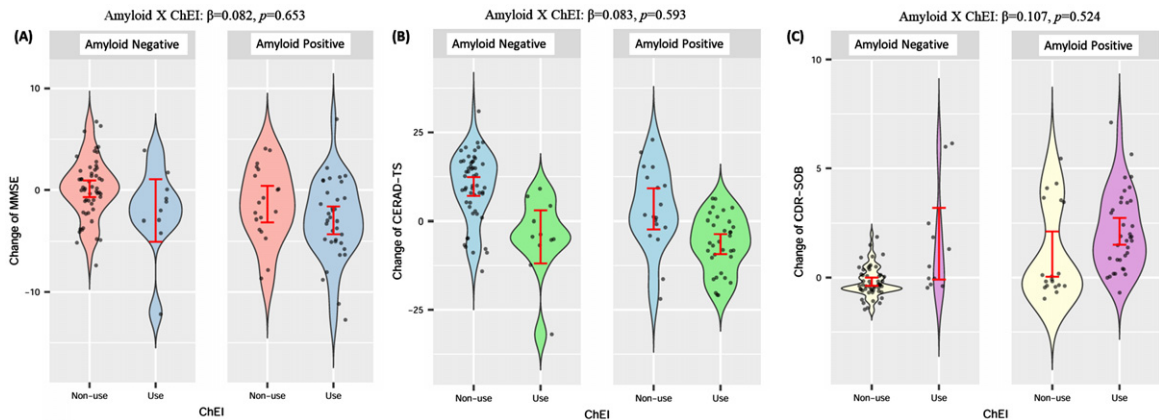

Fig. 2. Change of outcome variables according to ChEI use and amyloid positivity (raw data). A) Change of MMSE according to ChEI use and amyloid positivity; B) Change of CERAD-TS according to ChEI use and amyloid positivity; C) Change of CDR-SOB according to ChEI use and amyloid positivity. Amyloid X ChEI interaction term was derived from GLM adjusted by age, sex, education, *APOE4* positivity, baseline outcome value, vascular risk score, and baseline memantine use. The standardized coefficient and *p* value are represented. ChEI, cholinesterase inhibitor; VRS, vascular risk score; CDR-SOB, Clinical Dementia Rating Sum of Box; MMSE, Mini-Mental Status Examination; CERAD-TS, The Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Total score.

($β = 0.082$, $p = 0.653$) (Table 2 and Fig. 2A), CERAD-TS ($β = 0.083$, $p = 0.593$) (Table 2 and Fig. 2B), and CDR-SOB ($β = −0.107$, $p = 0.524$) (Table 2 and Fig. 2C).

DISCUSSION

Amnestic MCI patients likely exhibit different pathophysiological characteristics based on the presence of amyloid pathology. We hypothesized that amyloid positivity moderates the effect of ChEI on cognitive decline. However, contrary to our hypothesis, we did not find evidence of such moderation by amyloid positivity for the ChEI effect on cognitive change. This suggests that the presence of brain Aβ deposition cannot explain the inconsistent and non-significant findings from previous ChEI trials in MCI patients. It also suggests that the action of ChEI, increasing cholinergic neurotransmission, may not be related to the presence of amyloid pathology. Cholinergic deficit, the target of ChEI, has been observed not only in AD dementia but also in other types of cognitive disorders, including vascular dementia and dementia with Lewy bodies.[24-26]

ChEI use was associated with more rapid cognitive decline (i.e., greater decreases in MMSE score

and CERAD-TS and greater increases in CDR-SOB score over 2 years) regardless of amyloid positivity. This finding aligns with results from other studies that retrospectively analyzed data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort.[27,28] The negative effect of ChEI treatment on cognitive decline observed in observational cohorts is likely due to differences in baseline disease severity. More severely impaired AD cases tend to progress more rapidly than less severe cases.[29] In clinical practice for MCI, patients with more severe cognitive impairment are likely to receive ChEI treatment, leading to a selection bias.[30] As shown in Table 1, the ChEI use group had more advanced cognitive impairment at baseline. Although the baseline values of each outcome variable were adjusted as covariates, it may not have been possible to fully control the influence of baseline disease severity on progression speed because the two groups could not be entirely matched in terms of severity, as is done in randomized controlled trials.

This study stands out by being the first to explore whether the presence of AD pathology, especially amyloid pathology, moderates the impact of ChEI use on cognitive change. However, several limitations require attention. First, this study did not rely on a randomized clinical trial but rather on retrospective analyses of observational cohort study data. Consequently, latent confounding variables could not be adequately controlled, and the comparison groups were not well-matched in terms of baseline characteristics. Thus, randomized controlled trials are still necessary to address the issues we have raised more rigorously. Second, the sample size of the study population may not be sufficiently large to conclusively establish the moderating effect of AD pathology.

In conclusion, our findings do not support the possibility that AD pathology, particularly Aβ deposition, moderates the effect of ChEI on cognitive decline in MCI.

AUTHOR CONTRIBUTIONS

Gihwan Byeon (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Software; Validation; Visualization; Writing – original draft; Writing – review & editing); Min Soo Byun (Funding acquisition; Investigation; Methodology; Project administration; Resources); Dahyun Yi (Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources); Hyejin Ahn (Data curation; Investigation; Project administration; Resources); Gijung Jung (Data curation; Methodology; Project administration; Resources); Yun-Sang Lee (Investigation; Methodology; Project administration; Resources); Yu Kyeong Kim (Investigation; Methodology; Resources); Koung Mi Kang (Investigation; Methodology; Project administration; Resources; Software); Chul-Ho Sohn (Methodology; Project administration; Resources; Software); Dong Young Lee (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing).

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FUNDING

CONFLICT OF INTEREST

Dong Young Lee received research funding from the company Eisai Korea, Inc. The other authors declare no conflict of interest.

DATA AVAILABILITY

The datasets generated and analyzed during the present study are not publicly available, owing to ethics considerations and privacy restrictions. Data

might be obtained from the corresponding author after approval by the Institutional Review Board of the Seoul National University Hospital, South Korea.

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