18F-THK5351 PET Positivity and Longitudinal Changes in Cognitive Function in β-Amyloid-Negative Amnestic Mild Cognitive Impairment

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Purpose: Neuroinflammation is considered an important pathway associated with several diseases that result in cognitive decline. 18F-THK5351 positron emission tomography (PET) signals might indicate the presence of neuroinflammation, as well as Alzheimer’s disease-type tau aggregates. β-amyloid (Aβ)-negative (Aβ–) amnestic mild cognitive impairment (aMCI) may be associated with non-Alzheimer’s disease pathophysiology. Accordingly, we investigated associations between 18F-THK5351 PET positivity and cognitive decline among Aβ– aMCI patients.

Materials and Methods: The present study included 25 amyloid PET negative aMCI patients who underwent a minimum of two follow-up neuropsychological evaluations, including clinical dementia rating-sum of boxes (CDR-SOB). The patients were classified into two groups: 18F-THK5351-positive and -negative groups. The present study used a linear mixed effects model to estimate the effects of 18F-THK5351 PET positivity on cognitive prognosis among Aβ– aMCI patients.

Results: Among the 25 Aβ– aMCI patients, 10 (40.0%) were 18F-THK5351 positive. The patients in the 18F-THK5351-positive group were older than those in the 18F-THK5351-negative group (77.4±2.2 years vs. 70.0±5.5 years; p<0.001). There was no difference between the two groups with regard to the proportion of apolipoprotein E ε4 carriers. Interestingly, however, the CDR-SOB scores of the 18F-THK5351-negative group deteriorated at a faster rate than those of the 18F-THK5351-positive group (B=0.003, p=0.033).
INTRODUCTION

18F-THK5351 is a single S-enantiomer quinoline-derivative probe that was originally developed as a tau positron emission tomography (PET) tracer, on account of its high affinity for pathologic Alzheimer’s disease-type (AD-type) tau aggregates.1,2 However, previous studies have reported that increased 18F-THK5351 uptake might also be associated with increased neuroinflammation, as well as tau aggregates.3,4 Previous studies have demonstrated that 18F-THK5351 can bind to monoamine oxidase B (MAO-B),4,5 a marker of neuroinflammation, and that the administration of selegiline, an MAO-B inhibitor, results in decreased uptake of 18F-THK5351.5 Hence, 18F-THK5351 might indicate neuroinflammation induced by reactive astrocytes as well as AD-type tau aggregates.6,7

Amnestic mild cognitive impairment (aMCI) refers to the prodromal stage of dementia. Previously, it was considered that patients with aMCI had a high likelihood of exhibiting β-amyloid (Aβ) deposition and progression to AD dementia. However, approximately 50% of patients with aMCI appear to be Aβ negative (Aβ−) on radiographic evaluation using PET.8,9 Previously, we demonstrated that Aβ− aMCI might be related to non-AD pathophysiology, including other neurodegenerative diseases, cerebrovascular diseases, or psychiatric diseases.10,11 Furthermore, in a previous study, 25% of the patients with Aβ− aMCI progressed to dementia within 3 years.12 Since neuroinflammation is considered to be an important common pathway associated with several diseases that eventually result in cognitive decline, Aβ− aMCI patients might have underlying neuroinflammation in the brain.13,14 However, to the best of our knowledge, the effects of neuroinflammation on cognitive decline in Aβ− aMCI patients have not been meticulously investigated. Considering that increased 18F-THK5351 uptake may indicate the presence of neuroinflammation in patients with Aβ− aMCI, it is reasonable to expect that a sizeable proportion of Aβ− aMCI patients will be 18F-THK5351 positive, which might lead to a rapid cognitive decline in such patients.

In the present study, we investigated the proportion of 18F-THK5351-positivity among Aβ− aMCI patients. We also assessed whether 18F-THK5351 PET positivity might be a predictor of poor prognosis in Aβ− aMCI patients, which was determined using the clinical dementia rating-sum of boxes (CDR-SOB).

MATERIALS AND METHODS

Participants

A total of 70 participants with aMCI was prospectively enrolled in the MEMORI trials performed at Asan Medical Center (AMC) and Samsung Medical Center (SMC) from January 2016 to August 2017. The participants with aMCI met the following criteria proposed by Petersen, et al.15: 1) subjective memory complaints by the patient or an informant; 2) relatively normal performance in other cognitive domains; 3) normal activities of daily living, as judged clinically; 4) objective memory decline below -1.0 standard deviation (SD) on either verbal or visual memory tests; and 5) not demented.

All participants underwent 18F-THK5351 PET of the brain for the detection of tau proteins, 18F-florbetaben PET for the detection of Aβ, brain magnetic resonance imaging (MRI), and neuropsychological tests. Demographic and clinical data, including the apolipoprotein E (APOE) genotype, were also documented. Participants with brain tumor, stroke, traumatic brain injury, or encephalitis were excluded from the study.

The present study was approved by the Institutional Review Board for Human Research at both institutions (AMC and SMC) and written informed consent was obtained from all the participants (AMC 2016-0023; SMC 2015-09-880) and written informed consent was obtained from all the participants.

Magnetic resonance (MR) image acquisition

A 3.0-Tesla Philips Intera Achieva MR scanner (Philips Healthcare; Eindhoven, The Netherlands) was used to obtain three-dimensional, volumetric, T1-weighted MR images (images obtained at AMC: repetition time, 9.9 ms; echo time, 4.6 ms; voxel size, 1.0×1.0×0.5 mm; slice number, 360; images obtained at SMC: repetition time, 6.8 ms; echo time, 3.1 ms; voxel size, 1.11×1.11×1.2 mm; slice number, 170).16 The present study used the resultant data to generate cortical volumes of interest for the quantification and partial volume correction of PET images.

Acquisition of 18F-florbetaben and 18F-THK5351 PET images

A Discovery STE PET/CT scanner (GE Healthcare; at SMC) or Discovery 690, 710, and 690 Elite PET/CT scanners (GE Healthcare; Milwaukee, WI, USA; at AMC) were used to acquire the PET images using uniform imaging/reconstruction protocols, as described previously.17 The 18F-THK5351 PET images were obtained with an acquisition time of 20 min, commencing 50
min after the intravenous administration of 185±18.5 MBq of 18F-THK5351; the 18F-florbetaben PET images were obtained with an acquisition time of 20 min, starting 90 min after the intravenous administration of 300±30 MBq of 18F-florbetaben.

18F-THK5351 PET image processing
The PET image of each participant was precisely co-registered to respective T1-weighted MRI data using the SPM8 (Statistical Parametric Mapping) tool (Wellcome Trust Centre for Neuro-imaging, Institute of Neurology, University College London) in MATLAB R2014b software for Windows (The MathWorks, Natick, MA, USA). A global region of interest (ROI) concerning the regions of the cerebral cortex was created on the basis of images of the frontal, temporal, parietal, and occipital lobes and the posterior cingulate gyri, as described previously. The aforementioned regions of the cortex were segmented from individual T1-weighted MR images using SPM8 and an automated anatomical labeling template. In the present study, global standardized uptake value ratio (SUVR) was calculated using weighted-mean volumes of ROIs and normalized to the mean intensity of the cerebellar gray matter using a mask image.

The present study employed iterative outlier methods with global SUVR values to evaluate 18F-THK5351 PET positivity. A total of 34 cognitively normal participants above the age of 59 years (range: 59–79 years) was assessed to determine the cut-off value of 18F-THK5351 PET global SUVR, which was computed as 1.37. Accordingly, in this study, if the estimated SUVR value of 18F-THK5351 PET exceeded 1.37, the patient was considered to be 18F-THK5351 positive.

Visual assessment of 18F-florbetaben PET images
The present study assessed four cortical regions, including the frontal, lateral temporal, posterior cingulate/precuneus, and parietal cortices, on grayscale 18F-florbetaben PET images acquired in the axial plane. A regional cortical tracer uptake system was used to assess the tracer uptake; the global uptake was evaluated with the brain amyloid plaque load scale. As the current study targeted Aβ- aMCI patients, the 33 (47.2%) 18F-florbetaben-positive aMCI participants were excluded from the analysis (Fig. 1).

Neuropsychological assessments
All participants underwent the Seoul Neuropsychological Screening Battery (SNSB), a standardized neuropsychological test battery that is widely used in South Korea and assesses five cognitive domains: attention, visuospatial function, language, memory, and executive function. A z-score on the SNSB below -1.0 SD of the reference score among patients of comparable age, sex, and education is regarded as abnormal. In addition, the current study assessed the CDR-SOB scores of the participants.

Clinical follow-up
Clinical follow-up was performed until September 2019. Among the 18F-florbetaben-negative aMCI participants, data pertaining to 25 participants who completed a minimum of two follow-up neuropsychological tests were retrospectively collected (Fig. 1). The average duration of follow-up was 14.9±13.7 months, and the follow-up evaluations were performed an average of 2.06±1.01 times.

Statistics
The present study compared the demographic and clinical variables pertaining to the 18F-THK5351-positive and -negative participants among the 18F-florbetaben-negative aMCI patients using Student’s t-test and chi-square test for continuous and categorical variables, respectively. The current study employed a linear mixed effects model to analyze the effects of 18F-THK5351 positivity and negativity on longitudinal changes in CDR-SOB scores, which is represented as follows:

longitudinal CDR-SOB changes = β0 + β1 × THK positivity + β2 × time + β3 × THK positivity × time + 1|subject + covariates,

where the participant was included as a random effect and baseline age, sex, education, and APOE ε4 carrier status were included as covariates.

In the present study, a two-tailed p<0.05 was considered statistically significant. Statistical analysis was performed using the nlme package in R 4.0.3 (Vienna, Austria; http://www.R-project.org/).

RESULTS
Demographics of the participants
The demographic and clinical characteristics of the participants
in this study are summarized in Table 1. Among the 25 18F-florbetaben-negative aMCI participants, 10 (40.0%) were 18F-THK5351 positive. The mean value of 18F-THK5351 SUVR was higher in the 18F-THK5351-positive participants (1.457±0.083) than in the 18F-THK5351-negative participants (1.290±0.093). Also, the participants in the 18F-THK5351-positive group were older than those in the 18F-THK5351-negative group (18F-THK5351-positive 77.4±2.2 years vs. 18F-THK5351-negative 70.4±5.5 years; p<0.001). The present study did not observe any difference between the 18F-THK5351-positive and -negative groups with regard to the proportion of female patients (50.0% vs. 53.3%), APOE ε4 carriers (30.0% vs. 33.3%), years of education (11.6±4.2 years vs. 11.6±5.1 years), and baseline CDR-SOB (1.85±1.13 vs. 1.40±0.81) scores.

Comparison of longitudinal neuropsychological changes in accordance with 18F-THK5351 positivity

Among the 18F-florbetaben-negative aMCI participants, the longitudinal changes in CDR-SOB scores in the 18F-THK5351-positive and -negative groups are shown in Fig. 2. A linear mixed effects model analysis of the CDR-SOB scores in 18F-florbetaben-negative aMCI participants revealed a steeper slope in the 18F-THK5351-positive individuals than 18F-THK5351-negative individuals (B=0.003, p=0.033) (Fig. 2 and Table 2).

**DISCUSSION**

The present study reports novel data regarding the cognitive trajectory of Aβ- 18F-THK5351-positive aMCI patients. The current study found that 40.0% of the Aβ– aMCI patients were 18F-THK5351 positive. Moreover, Aβ– aMCI patients with 18F-THK5351 positivity had a worse cognitive trajectory than Aβ– aMCI patients with 18F-THK5351 negativity. Taken together, the present findings suggest that 18F-THK5351 positivity might be a useful predictor of poor prognosis among Aβ– aMCI patients, which might be associated with increased neuroinflammation.

The first major finding of this study is that 40.0% of patients with amyloid PET negative aMCI display 18F-THK5351 positivity. Because a precise cut-off value to evaluate 18F-THK5351 positivity is lacking in existing literature, we created a cut-off value for 18F-THK5351 positivity using the iterative outlier that is widely used. Previous studies that used other radiotracers for imaging tau aggregation have observed decreased tracer uptake in Aβ– aMCI patients, compared to Aβ+ aMCI patients. However, the proportion of 18F-THK5351-positive patients among the Aβ– aMCI cohort in the present study was higher than expected. The present findings might be related to neuroinflammation in the brain, as Aβ– aMCI might be associated with non-AD pathophysiology. In fact, a previous imaging–pathological correlation study by the authors that involved a patient with Creutzfeldt-Jakob disease showed that increased 18F-THK5351 uptake is related to reactive astrocytes with increased MAO-B activity, but not neurofibrillary tangles. Furthermore, a previous study reported that patients with neuropathologically confirmed progressive supranuclear palsy had high SUVR in an-

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**Table 1.** Demographic and Clinical Characteristics of 18F-Florbetaben PET-Negative aMCI Participants Obtained at Baseline

|                      | 18F-THK5351 positive (n=10) | 18F-THK5351 negative (n=15) | p value |
|----------------------|-----------------------------|------------------------------|---------|
| Age, yr              | 77.4±2.2 (73–80)            | 70.0±5.5 (62–78)             | <0.001  |
| Sex, female          | 5 (50.0)                    | 8 (53.3)                     | 0.870   |
| Education, yr        | 11.6±4.2 (6–18)             | 11.6±5.1 (5.1–18)            | 0.986   |
| Initial CDR-SOB score| 1.85±1.13 (0.5–4)           | 1.40±0.81 (0.5–3)            | 0.256   |
| 18F-THK5351 PET SUVR | 1.457±0.083                 | 1.290±0.093                  |         |

Continuous variables are presented as a mean±standard deviation, and categorical variables are presented as n (%). THK, 18F-THK5351; B, beta coefficient; CDR-SOB, clinical dementia rating-sum of boxes; SUVR, standardized uptake value ratio.

**Fig. 2.** Cognitive changes during the course of follow-up in the 18F-THK5351-positive and -negative groups among the 18F-florbetaben-negative aMCI participants. Among the 18F-florbetaben-negative participants, the 18F-THK5351-positive group displayed a more rapid decline in CDR-SOB scores in accordance with 18F-THK5351 positivity in the brain, as Aβ– aMCI might be associated with non-AD pathophysiology. In fact, a previous imaging–pathological correlation study by the authors that involved a patient with Creutzfeldt-Jakob disease showed that increased 18F-THK5351 uptake is related to reactive astrocytes with increased MAO-B activity, but not neurofibrillary tangles. Furthermore, a previous study reported that patients with neuropathologically confirmed progressive supranuclear palsy had high SUVR in an-

**Table 2.** Results of the Linear Mixed Effect Model for CDR-SOB Scores

|                      | THK effect | Time effect | THK×Time |
|----------------------|------------|-------------|-----------|
|                      | B (SE) (95% CI) | p value | B (SE) (95% CI) | p value | B (SE) (95% CI) | p value |
| CDR-SOB              | 0.384 (0.985) (1.670–2.438) | 0.701 | 0.002 (0.0007) (0.0006–0.004) | 0.009 | 0.003 (0.001) (0.0003–0.005) | 0.033 |

B, beta coefficient; CDR-SOB, clinical dementia rating-sum of boxes; THK, 18F-THK5351; SE, standard error; CI, confidence interval.
Moreover, since increased 18F-THK5351 uptakes in Aβ dysfunction could contribute to cognitive decline in all types of inflammation caused by oxidative damage and mitochondrial SOB scores than the 18F-THK5351-negative group. Since CDR-THK5351-positive group exhibited a faster decline in the CDR-neurodegeneration disorders, including Aβ− aMCI.

The second major finding in the current study is that the 18F-THK5351-positive group exhibited a faster decline in the CDR-SOB scores than the 18F-THK5351-negative group. Since CDR-SOB is widely accepted as a reliable measure for the assessment of the six domains of cognitive and functional performance, CDR-SOB scores are important in the assessment of severity of aMCI. Furthermore, a previous study by the authors revealed that brain regions with increased 18F-THK5351 uptake in Aβ− frontotemporal dementia are consistent with those in brain atrophy on MRI scans. The relationship between increased 18F-THK5351 uptake and cognitive decline or brain atrophy might be explained by increased neuroinflammation. Indeed, research has shown that alterations in the functions of astrocytes and microglia could induce the production and secretion of inflammatory cytokines, such as interleukin-6 (IL-6), which might eventually cause neuronal injury. Furthermore, neuroinflammation caused by oxidative damage and mitochondrial dysfunction could contribute to cognitive decline in all types of neurodegenerative dementia, as well as AD.

The strength of the current study is that longitudinal follow-up neuropsychological evaluations were performed to determine the significance of 18F-THK5351 PET positivity on the cognitive prognosis of Aβ− aMCI patients. However, the present study has several limitations. First, the sample size was relatively small. Second, the age difference between the 18F-THK5351-positive and -negative groups may have affected the cognitive trajectories. Third, other factors related to inflammation, such as serum C-reactive protein, erythrocyte sedimentation rate, and IL-6, as well as the results pertaining to cerebrospinal fluid glial markers (e.g., chitotriosidase 1, chitinase-3-like protein 1, and glial fibrillary acidic protein) were not included for analysis. Moreover, since increased 18F-THK5351 uptakes in Aβ− participants might reflect other pathobiology, rather than neuroinflammation, further studies with neuroinflammation PET may be needed. Fourth, the present study involves limited pathological data to validate the findings. Fifth, the present study did not consider other pathological conditions that could contribute to cognitive impairment, including TAR DNA-binding protein, hippocampal sclerosis, argyrophilic grain disease, and Lewy body pathologies. There was no 18F-THK5351 uptake pattern suggesting non-AD pathology. Finally, we decided Aβ negativity using visual assessment, which may raise the possibility that discernment of Aβ negativity was inaccurate. However, this might be mitigated to some extent in that visual assessment by experienced doctors has shown high agreement with SUVRI cut-off optimization method. Regardless of the abovementioned limitations, the current study is noteworthy as this is the first study to demonstrate that increased 18F-THK5351 uptake can predict cognitive decline among Aβ− aMCI patients.

In conclusion, increased 18F-THK5351 uptake might be a useful predictor of poor prognosis among Aβ− aMCI patients, which might be related to increased neuroinflammation in the brain.

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