IMAGING TAU IN ALZHEIMER'S DISEASE AND NORMAL AGING

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Background

While amyloid plaques are a pathological hallmark of Alzheimer's disease (AD), whether β-amyloid is the causal agent of neurodegeneration in AD remains unclear. Evidence supporting the hypothesis that amyloid is a primary contributor to AD pathogenesis (the amyloid-first hypothesis) include the finding that genetic mutations responsible for inherited forms of AD cause increased amyloid production. Studies using positron emission tomography (PET) to measure amyloid plaque burden in vivo have demonstrated amyloid positivity before obvious atrophy or cognitive decline in healthy older controls. While tau positive neurofibrillary tangles represent the second hallmark of AD, tau mutations are seen in patients with variants of frontotemporal dementia, not AD. The propagation of tau pathology is thought to follow amyloidosis, suggesting amyloid in some way induces tau mediated degeneration. However, the link between amyloid and tau not clear as there are spatial and temporal distinctions. For example, bulk of amyloid burden in medial parietal cortex and frontal cortex early on, while tau burden begins in medial temporal cortex.

While β-amyloid has been shown to have direct neurotoxic effects in vitro, these effects are seen at concentrations of β-amyloid much higher than found in human brain[1].Therefore, amyloid may not confer significant direct toxicity. In addition, autopsy findings of pre-tangle pathology occurring in midlife prior to amyloidosis[2] suggest that tauopathy may begin prior and independent to significant amyloid plaque deposition. Since amyloid burden correlates poorly with cognition[3], tau may be a more important mediator of neurodegeneration in AD.

Investigational Agent

^{18}F-MK-6240 is a PET radioligand that binds to paired helical filament tau aggregates. This radioligand has only been used for research purposes. ^{18}F-MK-6240 will be administered in tracer doses (≤20 μg) at activity of 4 to 5 mCi (148 - 185 MBq) ±10% per injection.

Study Objectives

The primary objective is to determine the extent and spatial distribution of tau at different stages along the cognitive spectrum of aging (cognitively normal older adults, adults with mild cognitive impairment, and adults with Alzheimer's disease dementia).

Secondary objectives are to determine how ^{18}F-MK-6240 binding in brain relates to cognitive performance, amyloid binding, atrophy on MRI, and CSF concentrations of markers of inflammation and neurodegeneration.

Study Design

150 subjects will undergo screening including history, physical examination, routine laboratory studies, neuropsychological testing, and brain MRI.

Target sample size is 100 elders with impairment (50 amnestic MCI and 50 Alzheimer's disease) and 50 elders without impairment (150 subjects total).

One brain MRI will be performed on each subject using a 3 T Philips scanner. Sequences performed will include 3D T1 (MPRAGE, 180 slice 1 mm resolution, 256 x 256 voxel count) for volumetric analysis and clinical sequences to exclude subjects with significant intracranial pathology unrelated to AD, such as malignant brain tumor of subdural hematoma. PET scans will take place on a Biograph mCT PET scanner (Siemens Healthcare) at the CUMC Kreitchman PET Center. Subjects will have one PET scan with ^{18}F-MK-6240 (injected activity 4 to 5 mCi = 148 - 185 MBq ±10%). PET imaging will be performed without arterial sampling. Vital signs

(blood pressure, heart rate, respiratory rate, and temperature) will be checked prior to injection of ^{18}F-MK-6240, then at the completion of the PET scan. ^{18}F-MK-6240 will be purchased from Cerveau Technologies, Inc. via a licensed production facility. Subjects will not be informed of ^{18}F-MK-6240 PET scan results, as this scan is used only in research and have not yet been validated for clinical use. Subjects will be informed if a clinically important abnormality is detected on MRI or PET imaging (e.g., brain tumor).

FreeSurfer (http://surfer.nmr.mgh.harvard.edu/), the MRI software package comprising a suite of automated tools for segmentation, reconstruction, and derivation of regional volumes and surface-based rendering, will be used for derivation of regions-of-interest (ROIs). Eleven ROIs will be extracted from the structural T1 image: entorhinal cortex, hippocampus, inferior temporal cortex, combined superior and middle temporal cortex, superior parietal lobule, inferior parietal lobule, precuneus, occipital cortex, prefrontal cortex, striatum, and thalamus.

^{18}F-MK-6240 PET images will be analyzed as follows: Freesurfer based ROIs will be applied to coregistered PET images. Correction for partial volume effects using a region-based voxel-wise method[23] will be applied. Regional time-activity curves using 60-120 min of scan data will be extracted from the PET scans, including cerebellum which will be used as a reference region. Standard uptake value ratio (SUVR) values will be calculated by dividing SUV values for each target region by that of the cerebellum.

Subjects will have the option of having one lumbar puncture (LP) for CSF collection. Subjects may refuse the LP and still participate in the other study procedures. CSF analysis will be performed to determine CSF concentrations of total tau, phospho-tau, β-amyloid, and markers of inflammation such as IL-1β, TNF-α, glial fibrillary acidic protein, S100B, and YLK-40.

Primary Study Endpoints

Because the drugs used in this study are radioligands given at tracer doses, there are no clinical endpoints of the study.

The primary outcome measures are:

1. Amount of ^{18}F-MK-6240 binding.

Secondary outcome measures are:

1. Correlation Between Tau, Neurodegeneration and Inflammation

Statistical Plan

Sample Size Determination

Because ^{18}F-THK-5351 is a recently developed radioligand, we do not have adequate preliminary data for a formal power calculation. This protocol is designed to generate information about 18F-MK-6240 binding in a large number of subjects over the spectrum from normal aging to mild cognitive impairment to Alzheimer's disease.

Statistical Methods

The primary outcome measure will be regional standardized uptake value ratio (SUVR) values for ^{18}F-MK-6240 using cerebellum as reference region. Multiple brain regions will be

measured, with particular attention to medial temporal cortex structures such as hippocampus and entorhinal cortex. Analysis will be performed using a one-way ANOVA with cognitive status (AD vs. MCI vs. normal) as independent variable. Effect of age and education will be determined in post-hoc analysis.

Regression models will be fit for ^{18}F-MK-6240 binding as dependent variable and cognitive scores, voxel count on MRI, and CSF concentrations of markers of inflammation and neurodegeneration as independent variables.

References

1. McGeer PL, McGeer EG. The amyloid cascade-inflammatory hypothesis of Alzheimer disease: implications for therapy. Acta Neuropathol. 2013;126(4):479-97. doi:10.1007/s00401- 013-1177-7.

2. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol. 2011;70(11):960-9. doi:10.1097/NEN.0b013e318232a379.

3. Ossenkoppele R, van der Flier WM, Verfaillie SC, Vrenken H, Versteeg A, van Schijndel RA et al. Long-term effects of amyloid, hypometabolism, and atrophy on neuropsychological functions. Neurology. 2014;82(20):1768-75. doi:10.1212/WNL.0000000000000432.

4. Hernandez F, Avila J. Tauopathies. Cellular and molecular life sciences : CMLS. 2007;64(17):2219-33. doi:10.1007/s00018-007-7220-x.

5. Braskie MN, Klunder AD, Hayashi KM, Protas H, Kepe V, Miller KJ et al. Plaque and tangle imaging and cognition in normal aging and Alzheimer's disease. Neurobiology of aging. 2010;31(10):1669-78. doi:10.1016/j.neurobiolaging.2008.09.012.

6. Ossenkoppele R, Tolboom N, Foster-Dingley JC, Adriaanse SF, Boellaard R, Yaqub M et al. Longitudinal imaging of Alzheimer pathology using [11C]PIB, [18F]FDDNP and [18F]FDG

PET. European journal of nuclear medicine and molecular imaging. 2012;39(6):990-1000. doi:10.1007/s00259-012-2102-3.

7. Shoghi-Jadid K, Small GW, Agdeppa ED, Kepe V, Ercoli LM, Siddarth P et al. Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer disease. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2002;10(1):24-35.

8. Tolboom N, Yaqub M, van der Flier WM, Boellaard R, Luurtsema G, Windhorst AD et al. Detection of Alzheimer pathology in vivo using both 11C-PIB and 18F-FDDNP PET. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2009;50(2):191-7. doi:10.2967/jnumed.108.056499.

9. Kepe V, Bordelon Y, Boxer A, Huang SC, Liu J, Thiede FC et al. PET imaging of neuropathology in tauopathies: progressive supranuclear palsy. Journal of Alzheimer's disease : JAD. 2013;36(1):145-53. doi:10.3233/JAD-130032.

10. Small GW, Kepe V, Siddarth P, Ercoli LM, Merrill DA, Donoghue N et al. PET scanning of brain tau in retired national football league players: preliminary findings. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2013;21(2):138-44. doi:10.1016/j.jagp.2012.11.019.

11. Barrio JR, Small GW, Wong KP, Huang SC, Liu J, Merrill DA et al. In vivo characterization of chronic traumatic encephalopathy using [F-18]FDDNP PET brain imaging. Proceedings of the National Academy of Sciences of the United States of America. 2015;112(16):E2039-47. doi:10.1073/pnas.1409952112.

12. Chien DT, Bahri S, Szardenings AK, Walsh JC, Mu F, Su MY et al. Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. J Alzheimers Dis. 2013;34(2):457-68. doi:10.3233/JAD-122059.

13. Ossenkoppele R, Schonhaut DR, Baker SL, O'Neil JP, Janabi M, Ghosh PM et al. Tau, amyloid, and hypometabolism in a patient with posterior cortical atrophy. Annals of neurology. 2015;77(2):338-42. doi:10.1002/ana.24321.

14. Maruyama M, Shimada H, Suhara T, Shinotoh H, Ji B, Maeda J et al. Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls. Neuron. 2013;79(6):1094-108. doi:10.1016/j.neuron.2013.07.037.

15. Kimura Y, Ichise M, Ito H, Shimada H, Ikoma Y, Seki C et al. PET Quantification of Tau Pathology in Human Brain with 11C-PBB3. Journal of nuclear medicine : official publication, Society of Nuclear Medicine.

2015. doi:10.2967/jnumed.115.160127.
16. Hashimoto H, Kawamura K, Igarashi N, Takei M, Fujishiro T, Aihara Y et al. Radiosynthesis, photoisomerization, biodistribution, and metabolite analysis of 11C-PBB3 as a clinically useful PET probe for imaging of tau pathology. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2014;55(9):1532-8. doi:10.2967/jnumed.114.139550.
17. Harada R, Okamura N, Furumoto S, Tago T, Maruyama M, Higuchi M et al. Comparison of the binding characteristics of [18F]THK-523 and other amyloid imaging tracers to Alzheimer's disease pathology. European journal of nuclear medicine and molecular imaging. 2013;40(1):125-32. doi:10.1007/s00259-012-2261-2.
18. Ishiki A, Okamura N, Furukawa K, Furumoto S, Harada R, Tomita N et al. Longitudinal Assessment of Tau Pathology in Patients with Alzheimer's Disease Using [18F]THK-5117 Positron Emission Tomography. PloS one. 2015;10(10):e0140311. doi:10.1371/journal.pone.0140311.
19. Harada R, Okamura N, Furumoto S, Furukawa K, Ishiki A, Tomita N et al. 18F-THK5351: A Novel PET Radiotracer for Imaging Neurofibrillary Pathology in Alzheimer's Disease. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2015. doi:10.2967/jnumed.115.164848.
20. Ng KP, Pascoal TA, Mathotaarachchi S, Therriault J, Kang MS, Shin M et al. Monoamine oxidase B inhibitor, selegiline, reduces 18F-THK5351 uptake in the human brain. Alzheimers Res Ther. 2017;9(1):25. doi:10.1186/s13195-017-0253-y.
21. Walji AM, Hostetler ED, Selnick H, Zeng Z, Miller P, Bennacef I et al. Discovery of 6- (Fluoro-(18)F)-3-(1H-pyrrolo[2,3-c]pyridin-1-yl)isoquinolin-5-amine ([(18)F]-MK-6240): A Positron Emission Tomography (PET) Imaging Agent for Quantification of Neurofibrillary Tangles (NFTs). J Med Chem. 2016;59(10):4778-89. doi:10.1021/acs.jmedchem.6b00166.
22. Hostetler ED, Walji AM, Zeng Z, Miller P, Bennacef I, Salinas C et al. Preclinical Characterization of 18F-MK-6240, a Promising PET Tracer for In Vivo Quantification of Human Neurofibrillary Tangles. J Nucl Med. 2016;57(10):1599-606. doi:10.2967/jnumed.115.171678.
23. Thomas BA, Erlandsson K, Modat M, Thurfjell L, Vandenberghe R, Ourselin S et al. The importance of appropriate partial volume correction for PET quantification in Alzheimer's disease. European journal of nuclear medicine and molecular imaging. 2011;38(6):1104-19. doi:10.1007/s00259-011-1745-9.
24. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2011;7(3):270-9. doi:10.1016/j.jalz.2011.03.008.
25. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., Kawas CH et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2011;7(3):263-9. doi:10.1016/j.jalz.2011.03.005.