Tau PET Visual Reads: Research and Clinical Applications and Future Directions

David N. Soleimani-Meigooni¹ and Gil D. Rabinovici^{1,2}

¹Memory and Aging Center, Department of Neurology, University of California, San Francisco, San Francisco, California; and ²Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, California

B iomarkers for tau pathology are essential to the latest Alzheimer disease (AD) research framework (1). Phosphorylated tau, the primary component of neurofibrillary tangles, is measurable in cerebrospinal fluid and plasma, but these fluid biomarkers do not capture the spatial dynamics of tau accumulation and spread (Braak staging) (2–4). Over the last decade, radiotracers that selectively bind to aggregated tau in neurofibrillary tangles have been developed, enabling diagnosis, mapping, and quantification of this pathology in living people (2,4,5). Tau PET correlates with other regional pathologic changes (synaptic loss, hypometabolism, and brain atrophy), domain-specific cognitive scores, and cognitive decline in people with AD (2). In AD clinical trials, tau PET is increasingly being used in participant selection, pretreatment staging, and measurement of treatment response (6). In the future, tau PET could become an important diagnostic and prognostic tool in clinical practice.

¹⁸F-flortaucipir is the most widely used tau PET tracer. Quantitative analysis of ¹⁸F-flortaucipir PET accurately distinguishes clinically diagnosed dementia due to AD from non-AD neurodegenerative diseases and cognitively unimpaired controls (7). Although quantitative analysis has been used primarily in research, newer visual interpretation methods may have important research and clinical applications (8,9). In a PET-to-autopsy study, majority interpretations of 5 raters applying a binary visual read algorithm (negative or positive AD tau pattern) on 64 antemortem scans showed 92% sensitivity and 80% specificity for detecting advanced tau pathology (Braak stages V-VI) at autopsy (mean PET-to-autopsy interval, 2.6 mo) (8). On the basis of these data, the U.S. Food and Drug Administration approved clinical ¹⁸F-flortaucipir PET "to estimate the density and distribution of aggregated tau neurofibrillary tangles in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease" (10). Importantly, the positive AD tau pattern excluded isolated uptake in medial and anterolateral temporal lobes, which is less specific and may represent early neurofibrillary tangle pathology in AD, agerelated tau accumulation in cognitively normal adults, or off-target binding in non-AD neurodegenerative conditions (8). However, accumulation in these regions can be clinically significant, indicating Braak stage III-IV tangle pathology, which in clinicopathologic studies is often associated with mild cognitive impairment (MCI) or dementia during life (11). An alternative visual read method that

classified scans as positive on the basis of uptake in these regions showed increased sensitivity but lower specificity for MCI and mild dementia due to AD compared with the Food and Drug Administration–approved visual read method (9). Both visual read methods were developed for diagnostic purposes, and neither was intended to track disease progression or treatment response on longitudinal imaging.

Several other tau radiotracers have advanced to investigational human studies (5). 6-(fluoro-¹⁸F)-3-(1H-pyrrolo[2,3-c]pyridin-1-yl) isoquinolin-5-amine (¹⁸F-MK-6240) has high affinity and selectivity for AD neurofibrillary tangles. Compared with ¹⁸F-flortaucipir, ¹⁸F-MK-6240 has a 2-fold higher dynamic range and less off-target binding in the choroid plexus, which may be advantageous for detecting early medial temporal neurofibrillary pathology (Braak stages I–II) and small changes in longitudinal studies or clinical trials (*12,13*). On the other hand, ¹⁸F-MK-6240 has more off-target binding in the meninges, which may be misinterpreted as tracer uptake in the medial and inferior temporal lobes (*12*).

In the March 2023 issue of The Journal of Nuclear Medicine, Seibyl et al. describe and evaluate an ¹⁸F-MK-6240 PET visual read method to assess the in vivo presence of tau pathology, measure the regional pattern and extent of tau, and classify abnormal regional patterns as either AD (temporal and extratemporal cortical tracer uptake without subcortical uptake) or non-AD neurodegeneration (subcortical tracer uptake, with some cortical uptake allowable) (14). Three expert nuclear medicine physicians applied this algorithm in masked reads of cross-sectional ¹⁸F-MK-6240 PET data from 102 participants at 60-90 min after injection, including cognitively healthy controls and patients with clinical diagnoses of MCI, AD dementia, or non-AD neurodegenerative diseases. Scans were read in gray scale, without corresponding structural neuroimaging data and with images scaled to mean activity in a cerebellar gray matter reference region. Majority visual reads were 81% sensitive and 93% specific for distinguishing patients with MCI or dementia due to AD from non-AD patients and controls. Reliability was high ($\kappa = 0.91$), with discordant reads occurring because of technical artifacts from scan processing or reconstruction, difficulty distinguishing cortical tracer retention in medial and inferior temporal lobes from nearby meningeal off-target binding, and low interrater agreement in regions of early tau accumulation (hippocampus and medial temporal lobes). Majority visual reads had higher accuracy than individual reads and higher sensitivity than various quantitative methods. The high accuracy and reliability support the plausibility of tau PET visual reads performed by experienced readers.

Received Nov. 16, 2022; revision accepted Nov. 28, 2022.

For correspondence or reprints, contact David N. Soleimani-Meigooni (david.soleimani-meigooni@ucsf.edu).

Published online Dec. 8, 2022.

COPYRIGHT @ 2023 by the Society of Nuclear Medicine and Molecular Imaging. DOI: 10.2967/jnumed.122.265017

This research represents a major advance by introducing the first systematic approach to visual interpretation of ¹⁸F-MK-6240 PET. The study also raises several important follow-up questions. First, is this an optimal ¹⁸F-MK-6240 visual read algorithm? Visual read approaches require standardization of many image visualization and classification parameters (i.e., color scale, thresholds, image scaling, target regions, and classification rules). The parameters selected for ¹⁸F-MK-6240 were notably different from those for ¹⁸F-flortaucipir. Most important was the decision to consider scans showing focal temporal uptake as AD-positive. The initial proposed criteria considered these scans negative because of concerns about inaccurate classification due to possible misinterpretation of meningeal off-target binding. However, the researchers found that visual raters could be trained to distinguish off-target binding from ontarget temporal signal by applying multiple planar views, which could theoretically increase sensitivity for detecting earlier Braak stages. However, even without choroid plexus contamination, many concerns around the specificity of signal in temporal regions observed with ¹⁸Fflortaucipir also apply to ¹⁸F-MK-6240. Ultimately, PET-to-autopsy studies are needed to determine the trade-off between increased sensitivity and potentially decreased specificity associated with interpretation of isolated temporal lobe signal as consistent with AD-related tau.

Second, how will this visual read method generalize to less experienced brain PET readers? Although most readers in the present study were naïve to ¹⁸F-MK-6240, all had substantial experience with amyloid PET and other tau radiotracers. As tau radiotracers are rolled out into broader research and clinical use, the reliability of visual reads by less experienced clinicians will need to be established. Encouraging early data from the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study found high agreement between visual reads of amyloid PET scans performed and interpreted in the community and scan classification by image quantification (15). However, unlike amyloid PET radiotracers, all of which show similar off-target binding in white matter, each tau PET tracer has unique off-target binding patterns, which can complicate visual interpretation (5,9,12,16). Novice readers may need additional radiotracerspecific training to accurately identify and discriminate off-target binding, especially near the medial temporal lobes, with the same accuracy and reproducibility as experts.

Third, should a single clinician's qualitative read be the standard for tau PET interpretation? For both ¹⁸F-MK-6240 and ¹⁸F-flortaucipir, majority visual reads show generally higher accuracy than individual visual reads, but requiring multiple expert reads for each scan is not practical (8, 14). Hybrid read approaches, which incorporate both a visual read and quantitative information from the image, have been proposed to leverage the complementary strengths, and counterbalance the weaknesses, of qualitative versus quantitative approaches to image classification (17). Further research is needed to measure the effect of additional quantitative information on the accuracy and reliability of tau PET visual reads.

Fourth, will visual ratings be useful for measuring longitudinal changes in tau in individual patients? The authors propose this as a potential application of their visual read algorithm, but validation in longitudinal observational research or clinical trials is needed. The proposed region-based method may be too time-consuming for routine clinical or research purposes, and there are a variety of challenges (e.g., variable reliability of reads in different regions of interest, difficulty grading the extent of tracer binding in regions without complementary structural neuroimaging) that may impact the reliability of this method, even in the hands of expert readers. Given these challenges, quantitative approaches to measuring signal intensity and spatial spread will likely be necessary to most precisely evaluate longitudinal changes in tau PET signal.

Lastly, how well will the visual read algorithm perform in MCI? The present study included only 21 MCI patients in the visual read test group, yet this early clinical stage represents one of the highest-priority populations for tau PET in clinical trials and future clinical practice. Patients with MCI are functionally independent and have subtle symptoms that overlap those of non-AD neurodegenerative diseases; thus, accurate and timely identification of these patients is important and may be particularly crucial for administration of future disease-modifying therapies (18). At autopsy, MCI patients have on average intermediate Braak stage III–IV neurofibrillary pathology, and the antemortem tau PET signal can be modest and subtle at this stage (8,11,19). A more sensitive visual read schema that identifies early signal in the medial temporal lobes may be particularly beneficial for detection of AD tau pathology in MCI.

Ultimately, visual reads will need to be applied to large numbers of longitudinally scanned patients who have a broad range of neurodegenerative disease diagnoses and excellent clinical characterization and amyloid biomarker data and who eventually undergo autopsy. These data will clarify the sensitivity and specificity of tau tracers to neurofibrillary tangle pathology, elucidate causes of off-target binding, and determine how longitudinal visual tracking of regional tracer uptake corresponds to pathologic progression of AD. Another area of interest is head-to-head comparisons of different tau PET ligands in the same patients, which may lead to development and validation of unified approaches to tau PET quantification and visual reads (20). Although each tau radiotracer has its idiosyncrasies, the overall spatial pattern of binding is remarkably consistent, suggesting that standardized approaches will be feasible (7). The maturation of tau PET as a powerful biomarker for diagnosis, staging, and prognosis in AD is occurring hand in hand with the emergence of novel molecular therapies that modify the course of AD pathophysiology (21). Collectively, the field seems to be at an inflection point, heralding a new era of early detection, biomarker-based diagnosis, and disease-modifying therapy.

DISCLOSURE

David Soleimani-Meigooni receives research support from the National Institute on Aging (K23-AG076960). Gil Rabinovici receives research support from National Institute on Aging, National Institute of Neurological Disorders and Stroke, the Alzheimer Association, the American College of Radiology, the Rainwater Charitable Foundation, Avid Radiopharmaceuticals, GE Healthcare, Life Molecular Imaging, and Genentech; has served as a consultant for Eli Lilly, Genentech, Roche, Merck, and Johnson & Johnson; and is an associate editor for *JAMA Neurology*. No other potential conflict of interest relevant to this article was reported.

REFERENCES

- Jack CR, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* 2018;14:535–562.
- Ossenkoppele R, Hansson O. Towards clinical application of tau PET tracers for diagnosing dementia due to Alzheimer's disease. *Alzheimers Dement.* 2021;17: 1998–2008.
- Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol (Berl). 1991;82:239–259.
- Schöll M, Lockhart SN, Schonhaut DR, et al. PET imaging of tau deposition in the aging human brain. *Neuron*. 2016;89:971–982.
- Leuzy A, Chiotis K, Lemoine L, et al. Tau PET imaging in neurodegenerative tauopathies: still a challenge. *Mol Psychiatry*. 2019;24:1112–1134.

- Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer's disease. N Engl J Med. 2021;384:1691–1704.
- Ossenkoppele R, Rabinovici GD, Smith R, et al. Discriminative accuracy of [¹⁸F]flortaucipir positron emission tomography for Alzheimer disease vs other neurodegenerative disorders. *JAMA*. 2018;320:1151–1162.
- Fleisher AS, Pontecorvo MJ, Devous MD, et al. Positron emission tomography imaging with [¹⁸F]flortaucipir and postmortem assessment of Alzheimer disease neuropathologic changes. *JAMA Neurol.* 2020;77:829–839.
- Sonni I, Lesman Segev OH, Baker SL, et al. Evaluation of a visual interpretation method for tau-PET with ¹⁸F-flortaucipir. *Alzheimers Dement (Amst)*. 2020;12: e12133.
- Highlights of prescribing information. TAUVIDTM (flortaucipir F 18 injection), for intravenous use. Initial U.S. Approval: 2020. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212123s000 lbl.pdf. Accessed December 22, 2022.
- Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement.* 2012;8:1–13.
- Gogola A, Minhas DS, Villemagne VL, et al. Direct comparison of the tau PET tracers ¹⁸F-flortaucipir and ¹⁸F-MK-6240 in human subjects. *J Nucl Med.* 2022;63:108–116.
- Pascoal TA, Therriault J, Benedet AL, et al. ¹⁸F-MK-6240 PET for early and late detection of neurofibrillary tangles. *Brain*. 2020;143:2818–2830.

- Seibyl JP, DuBois JM, Racine A, et al. A visual interpretation algorithm for assessing brain tauopathy with ¹⁸F MK-6240 PET. J Nucl Med. 2023;64:444–451.
- Iaccarino L, La Joie R, Koeppe R, et al. rPOP: robust PET-only processing of community acquired heterogeneous amyloid-PET data. *Neuroimage*. 2022; 246:118775.
- Chapleau M, Iaccarino L, Soleimani-Meigooni D, Rabinovici GD. The role of amyloid PET in imaging neurodegenerative disorders: a review. *J Nucl Med.* 2022; 63(suppl 1):13S–19S.
- Apostolova LG, Aisen P, Eloyan A, et al. The Longitudinal Early-Onset Alzheimer's Disease Study (LEADS): framework and methodology. *Alzheimers Dement*. 2021;17:2043–2055.
- Cummings J, Rabinovici GD, Atri A, et al. Aducanumab: appropriate use recommendations update. J Prev Alzheimers Dis. 2022;9:221–230.
- Soleimani-Meigooni DN, Iaccarino L, La Joie R, et al. ¹⁸F-flortaucipir PET to autopsy comparisons in Alzheimer's disease and other neurodegenerative diseases. *Brain.* 2020;143:3477–3494.
- Head-to-head harmonization of tau tracers in Alzheimer's disease (HEAD). Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT05361382. Published May 4, 2022. Updated November 9, 2022. Accessed December 16, 2022.
- van Dyck CH, Swanson CJ, Aisen PA, et al. Lecanemab in early Alzheimer's disease. N Engl J Med. November 29, 2022 [Epub ahead of print].