Is the Amyloid Imaging Tsunami Really Happening?

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Although the original translation of the Japanese word *tsunami*, or "harbor wave," has a neutral connotation, the term is now generally associated with a dangerous situation. When the editorial team of *The Journal of Nuclear Medicine* proposed the above title for this article, we assumed *tsunami* was not meant to connote panic. Our optimism in this regard is mainly based on the recent approval of novel antiamyloid antibodies showing positive effects on biologic and clinical parameters in early Alzheimer disease (AD). In this context, the question of whether and to what extent amyloid PET imaging will be used is of great relevance. In the case of a positive answer, we would need to be prepared to do more amyloid imaging.

We recently proposed the use of amyloid imaging–guided antiamyloid antibody treatment in AD as 1 example of theranostics in the nononcologic arena (*1*). This approach not only promises to make a significant difference in terms of clinical benefit to patients with AD but also supports the amyloid cascade theory, which proposes that cerebral β-amyloid (Aβ) pathology is causally involved in the development of AD (*2*). In this context, as well as that of proposals to define and diagnose AD using biomarkers of amyloid pathology, tau pathology, and neurodegeneration (*3,4*), PET imaging and cerebrospinal fluid (CSF) sampling are used to determine the presence or absence of Aβ pathology in the brain. Amyloid PET, however, is the only technique than can provide a quantitative assessment of the brain's regional distribution of Aβ aggregates.

Three ^{18}F-labeled amyloid PET tracers are currently approved for clinical use to detect, exclude, and quantify Aβ aggregate levels in the brain. In the era before antiamyloid antibodies, in which no specific treatment of AD was available, amyloid PET imaging was clinically used to diagnose AD in patients with mild cognitive impairment, patients with dementia whose clinical picture was not unambiguously attributable to AD, and unusually young patients with suspected AD dementia (*5*). Regular reimbursement for amyloid PET imaging, however, was not provided until recently, as scientific evidence of positive outcomes with this technique was lacking. As a consequence of the promising developments related to antiamyloid therapies, which will require amyloid biomarker–based qualification of individual patients for drug prescription, these reimbursement restrictions were removed in October 2023 by the Centers for Medicare and Medicaid Services (*6*). The reimbursement situation might turn to good account soon on a global scale, as the abovementioned antiamyloid drugs gain approval outside the United States.

In parallel to the optimistic predictions for amyloid PET tracers, there are exciting developments in PET technology that may directly impact the future amyloid imaging. New generations of PET detector technology, together with advancements in PET data reconstruction and supported by artificial intelligence, have led to steady increases in sensitivity and spatial resolution (the brain gray matter in which Aβ aggregates accumulate in AD is only a couple of millimeters thick) and possible decreases in required scan times and tracer doses. For example, the use of artificial intelligence in a hybrid PET/MRI system allows physicians to obtain the amyloid pathology diagnosis from a 60-s PET scan (*7*). Another interesting development is the advent of brain-dedicated PET systems, which will be easier to use in terms of acquisition, running costs, and space requirements within PET imaging suites (*8*), potentially contributing to broader access to PET brain imaging. In fact, approval of amyloid-targeting therapies and the need for accurate patient selection may be the main drivers for adoption of this new type of brain-dedicated technology.

Two antiamyloid antibodies are promising to impact the care of patients with AD: lecanemab (Eisai) and donanemab (Lilly). Lecanemab gained accelerated approval from the Food and Drug Administration in January 2023 based on amyloid PET results as an accepted surrogate for clinical efficacy in a phase 2 study (*9*) and received traditional approval from the Food and Drug Administration in July 2023 after a successful phase 3 study showing moderate clinical benefits related to the drug's use (*10*). Approval for clinical use of this drug is expected to be granted soon by the European Medical Agency. In the meantime, coverage of lecanemab by the Centers for Medicare and Medicaid Services was also granted, and appropriate-use recommendations were published (*11*). These recommendations state that biomarker evidence for the presence of the drug target is required to qualify a patient for drug prescription and that either amyloid PET imaging or CSF sampling, but not blood testing, is appropriate for this purpose (*11*). Donanemab, for which positive results of a pivotal phase 3 study were published in August 2023 (*12*), is approved in the United States and other countries. Of interest, the trials that led to the clinical approval for donanemab differed from those for lecanemab in their study design in that amyloid PET and tau PET imaging were performed for patient selection and that drug use was stopped once Aβ aggregate levels decreased to formally "amyloid-negative" values in follow-up amyloid PET imaging (*12*).

Regardless of which of the antiamyloid antibodies is considered for clinical use, the concept of using amyloid PET imaging as a baseline test for patient qualification and during follow-up to prove

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drug-target engagement or biologic drug efficacy has proven extremely successful in clinical research and is currently translated into clinical routine care (*13*). It remains to be seen how the alternative use of PET imaging or CSF sampling translates into clinical standards. The main advantages of PET imaging are evident, including the directness of the relationship between the test readout and the actual drug target (i.e., amyloid aggregate expression), the level of invasiveness, and the level of standardization. Furthermore, global and quantitative baseline Aβ aggregate levels and their reduction via treatments can be reliably assessed only by PET imaging tools. Geographic differences regarding the use of CSF sampling are likewise evident. The main disadvantages of PET imaging over CSF sampling include higher costs and radiation exposure. Regardless, it is estimated that about one third of potential candidates for antiamyloid drug therapy will either refuse CSF sampling, have contraindications to CSF sampling, or have inconclusive CSF results, all qualifying them for amyloid PET imaging. In this scenario, it is estimated that the demand of amyloid imaging will increase by more than 10-fold (*14*). As a new development, very promising blood-based AD biomarkers are currently being evaluated, but their reliability for patient selection regarding amyloid-targeting therapies in clinical practice is not yet established (*11*). The suggested high negative predictive value and potential access by low-threshold clinics to these diagnostic tools may qualify them as an ideal screening tool to channel access to amyloid PET imaging in the future.

Even after the approval of amyloid-targeting therapies, there is still great uncertainty about the actual number—a tsunami or a small rise—of additional amyloid PET examinations that will be requested. Some experts and professional organizations, such as the European Association of Nuclear Medicine Neuroimaging Committee (*14,15*), have predicted increases of up to 20-fold. The actual case numbers in the United States do not yet indicate an extreme rise in the number of patients prescribed these therapies. For example, data collected up until November 2024 revealed that approximately 9,000 patients in the United States received treatment with lecanemab since its approval in January 2023 (*16*). The various contraindications and exclusion criteria, the costs of these treatments, and reported side effects of the amyloid-targeting therapies may somewhat slow the rush to use them. Also, some international regulatory authorities are still hesitant regarding approval or reimbursement. The nuclear medicine community has the opportunity to realize and adapt to the possible increase in demand for scanner time, instrumentation, logistics, and qualified personnel. A recent survey in Germany, for example, revealed the potential to increase the use of amyloid PET by 7-fold (*17*).

Taken together, discussions on how and to what degree we should prepare to expand our capacities in terms of PET tracers, PET scanners, and qualified personnel to perform more amyloid PET imaging in the future should be intensified. The scientific community is currently supporting this endeavor by updating the appropriate-use criteria for amyloid imaging and providing more information on available amyloid imaging sites globally (*18*). We leave it to the reader to judge whether such a development should be considered a tsunami to hide from or the perfect wave to surf to embrace the future of our field. Personally, we believe this is a promising positive development for the good of our patients and their caregivers.

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