Amyloid Imaging–Based Food and Drug Administration Approval of Lecanemab to Treat Alzheimer Disease—What Lasts Long Finally Becomes Good?

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Alzheimer disease (AD) is a devastating neurologic condition of high socioeconomic relevance. Although today this disease can be accurately diagnosed during a lifetime, especially with the help of molecular imaging approaches such as amyloid PET, tau PET or ^{18}F-FDG PET, no disease-modifying treatment is yet available. The search for a drug able to positively influence the course of AD is a long story of frustration. This search thankfully took a positive turn with the U.S. Food and Drug Administration (FDA) approval of lecanemab (Leqembi; Eisai and Biogen) on January 6, 2023 (*1*). Lecanemab is currently also undergoing evaluation for approval by the European Medicines Agency.

The Tokyo (Japan)-based pharmaceutical company Eisai and the Cambridge (Massachusetts)-based biotech company Biogen developed lecanemab. It is a humanized IgG1 monoclonal antibody that mainly targets larger β-amyloid oligomers (so-called protofibrils). The approval of this drug was the outcome of the FDA's Accelerated Approval pathway, applicable in cases of unmet medical need and if a drug has shown a favorable effect on a surrogate of clinical efficacy. In this case, of note, the reduction of amyloid PET quantitative readouts via lecanemab as shown in a placebo-controlled phase 2 study was accepted by the FDA as a suitable clinical efficacy surrogate. In this study, subjects with mild cognitive impairment or mild AD dementia underwent brain MRI and, importantly, amyloid PET imaging to establish amyloid positivity. Included patients received an intravenous infusion of the drug (up to 10 mg/kg body weight) once every 2 wk or placebo. It was convincingly shown that lecanemab is indeed able to remove amyloid aggregates from the brain.

Consequently, the above phase 2 study methods are replicated in the lecanemab prescribing information. In terms of side effects, potential amyloid removal-related imaging abnormalities need to be monitored by MRI, apart from potential drug infusion–related side effects. The need of a priori amyloid testing is based on the well-known fact that not all patients fulfilling the clinical criteria of AD dementia indeed suffer from an amyloidopathy (*2*). In other words, the amyloid "gate-keeper" test provides evidence for the presence of the drug target and thus avoids the prescription of a drug that will not only not work in amyloid-negative patients (and lecanemab will likely cost around $26,000 USD per patient per year), but also potentially have side effects.

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After aducanumab, lecanemab is the second FDA-approved antiamyloid drug to treat AD. In distinction from the controversial clinical efficacy data (followed by the controversial FDA approval and nonapproval by the European Medicines Agency) with aducanumab, for lecanemab there are convincing results in the clinical efficacy phase 3 study program. In this phase 3 study, the drug was given for 18 mo in the treatment arm, demonstrating a slowing of cognitive decline by 27%. In absolute numbers, this equals a difference of 0.45 points on the Clinical Dementia Rating-Sum of Boxes (a valuable dementia severity measure covering a wider range of memory, orientation, personal care, and other symptoms or problems) between the treatment and placebo arms (*3*). Although some neurologists express concern about the relevance of this achieved primary endpoint to an individual patient (*4,5*), and concerns are also raised about the vascular events safety profile of the drug (*6*), most clinicians in the field seem to be positive about these clinical efficacy data (*7–9*). The FDA is currently reviewing these lecanemab phase 3 clinical efficacy data. In parallel, another antiamyloid antibody, donanemab, developed by Eli Lilly, likewise appears to be making good progress in its development program (*10*).

Regardless, the lecanemab development pipeline convincingly showed the value of amyloid imaging in identifying patients in whom the actual drug target is present and who, as such, qualify for respective drug prescription on a disease pathology ground. Here, amyloid PET also provides a perfect baseline amyloid state readout, which can be used as a starting point for follow-up imaging to monitor the biologic drug effect. As such, it is conceivable that amyloid removal might differ from patient to patient with regard to speed and intensity. Thus, providing that such intraindividual biologic drug effect differences are indeed of relevance, amyloid imaging might allow for a truly personalized, PET-guided drug administration regimen.

In addition, the positive clinical effect of lecanemab evidences the validity of the amyloid cascade hypothesis. This hypothesis proposes the aggregation of β-amyloid in the brain representing the initial event in AD triggering a cascade of other processes, finally resulting in neurodegeneration and cognitive decline (*11*). Excitingly, now—with the lecanemab development program

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data—we seem to have one missing piece to the puzzle in hand to better understand this devastating disorder on pathobiochemical grounds. It would be the logical next step to apply antiamyloid drugs in earlier or prodromal AD stages, that is, at a time point in which tau accumulation and neurodegeneration have not yet started, thus preventing (instead of slowing down existing) cognitive deterioration and providing ultimate proof of the amyloid cascade theory.

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) recently welcomed the FDA's decision to approve lecanemab (*12*) and echoed that amyloid PET imaging is very well suited both for qualifying patients for drug prescription and for evaluating the drug effect on a biologic ground. The SNMMI will also discuss a respective reimbursement with the Centers for Medicare & Medicaid Services (CMS), with some promising preliminary feedback from the CMS (*13*). Together with the Alzheimer's Association, the SNNMI is also working on updating the Appropriate Use Criteria for amyloid imaging (*14*) by including PET imaging to qualify patients for antiamyloid drug prescription. Our molecular imaging community will need to prepare to fulfil the future requirements of anticipated widespread employment of lecanemab in terms of amyloid tracer, PET scanner, and PET imaging staff availability. Now, more than ever, it is the right time to support the SNMMI and other involved bodies in their respective efforts, for the good of our patients.

REFERENCES

1. FDA grants accelerated approval for Alzheimer's disease treatment. FDA website. www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-disease-treatment. January 6, 2023. Accessed March 6, 2023.
2. Barthel H, Seibyl J, Sabri O. The role of positron emission tomography imaging in understanding Alzheimer's disease. *Expert Rev Neurother.* 2015;15:395–406.
3. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med.* 2023;388:9–21.
4. Mahase E. Lecanemab trial finds slight slowing of cognitive decline, but clinical benefits are uncertain. *BMJ.* 2022;379:o2912.
5. Lecanemab for Alzheimer's disease: tempering hype and hope (editorial). *The Lancet*. 2022;400:P1899.
6. Reardon S. FDA approves Alzheimer's drug lecanemab amid safety concerns. *Nature.* 2023;613:227–228.
7. Alzheimer's Association statement on lecanemab phase 3 full results. Alzheimer's Association website. www.alz.org/news/2022/statement-lecanemab-phase-three-full-results. Accessed March 6, 2023.
8. Treating Alzheimer's: a new era begins with lecanemab. Alzheimer's Association website. www.alz.org/media/Documents/joint-letter-alzheimers-scientists-lecanemab.pdf. Accessed March 6, 2023.
9. Lowe D. Lecanemab and Alzheimer's: more data. www.science.org/content/blog-post/lecanemab-and-alzheimer-s-more-data. November 30, 2022. Accessed March 6, 2023.
10. Donanemab. Alzforum website. www.alzforum.org/therapeutics/donanemab. Updated February 6, 2023. Accessed March 6, 2023.
11. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science.* 1992;256:184–185.
12. FDA approves new treatment for Alzheimer's disease: presence of beta amyloid must be confirmed before treatment. Society of Nuclear Medicine and Molecular Imaging website. www.snmmi.org/NewsPublications/NewsDetail.aspx?ItemNumber=42942. January 6, 2023. Accessed March 6, 2023.
13. U.S. Centers for Medicare & Medicaid Services. CMS statement on FDA accelerated approval of lecanemab. U.S. Centers for Medicare & Medicaid Services website. www.cms.gov/newsroom/press-releases/cms-statement-fda-accelerated-approval-lecanemab. Accessed March 6, 2023.
14. Johnson KA, Minoshima S, Bohnen NI, et al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *J Nucl Med.* 2013; 54:476–490.