J Prev Alz Dis 2023;3(10):357-358
Published online April 8, 2023, http://dx.doi.org/10.14283/jpad.2023.44

Editorial

Lecanemab: Appropriate Use Recommendations – A Commentary from a European Perspective

L. Frölich[1], *F. Jessen*[2,3,4]

1. Department of Geriatric Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Germany; 2. Department of Psychiatry, University of Cologne, Faculty of Medicine & University Hospital Cologne, Cologne, Germany; 3. German Center for Neurodegenerative Diseases (DZNE), Bonn/ Cologne, Germany; 4. Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany

Corresponding Author: Lutz Frölich, Department of Geriatric Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Germany, lutz.froelich@zi-mannheim.de

Cummings et al. propose detailed recommendations on the appropriate use (AUR) of Lecanemab (Leqembi®) in clinical practice. We congratulate the authors on their comprehensive work, which is highly instrumental for adequate and safe implementation. Lecanemab was granted accelerated approval by the FDA in January 2023 and regulatory review in Europe is ongoing. Recently, similar recommendations have been published on the appropriate use of Aducanumab (1, 2), which was not licensed In Europe after the withdrawal of the application by the company during the review and discussion process with the European Medical Agency (EMA) (2). Thus, Aducanumab will not be available in Europe until the ENVISION Study, which has just recently started, provides the clinical data required for a resubmission and potential licensing (3). There is great hope, however, that Lecanemab will be fully approved in Europe for the treatment of early Alzheimer's disease (AD) within the near future. This would be a major milestone, as Lecanemab will be the first drug of new class of disease modifying medication on the European market acting directly on the pathological aggregation of amyloid in early Alzheimer's disease.

The AUR are neither a guideline nor a prescribing information, but they fill a gap in aiding physicians in identifying the right patients, providing adequate information for shared decision making and supporting clinical management throughout the course of the treatment, including safety monitoring. The latter is critically important, because anti-amyloid antibodies are a new class of drugs, for which there is very limited experience outside of clinical trials and which will be provided to a large, potentially frail and heterogeneous patient population. Important information on long-term use of Lecanemab is still missing, which will require systematic documentation and evaluation of the effects of Lecanamab in clinical practice. Treatment registries are therefore discussed in several European countries. A pan-European registry studies for this purpose would be highly desirable, but a successful set-up is challenging due to country specific aspects of the healthcare systems, particularly with regard to pathways of care and reimbursement. However, single country registry data and, of course, clinical experience will feed into an updated version of the AUC over the coming years.

The AUR are written by experts on behalf of the Alzheimer's Disease and Related Disorders Therapeutics Work Group and not by a scientific society or similar authorities. European countries have their own approaches for the development and implementation of clinical guidelines. For example, in Germany, the dementia guideline process is based on a systematic evaluation of evidence and a consensus process, which involves representatives from other disciplines, e.g. neuropsychology, neuroradiology and nuclear medicine. The AUR provided by Cummings et al. is an excellent starting point for this discussion.

The AUR states, that a patient should be amyloid positive on PET imaging, using any of the approved amyloid ligands, visually read by an experienced nuclear medicine physician, or by having abnormal CSF levels as the diagnostic prerequisites for treatment with Lecanemab. Given the more wide-spread use of CSF biomarkers across Europe and the limited reimbursement of PET imaging so far, we would suggest to specify that, if CSF studies were used for demonstrating amyloid pathology, these may also show abnormal CSF abeta 1-42 levels or an abnormal ratio abeta42/abeta40 (4) in addition to the p-tau/ Aβ42 ratio mentioned in the AUR. This had been suggested in a commentary on the AUR for aducanumab, before (5). In the future, plasma biomarkers may be useful to screen patients, specifically to rule out amyloid pathology due to a high negative predictive value as mentioned in the AUR paper. It is unlikely that plasma biomarkers will fully substitute CSF markers or PET in Europe in the near future. If sufficiently validated also in real world settings outside of highly controlled research studies, however, the high costs and limited accessibility of CSF and PET across Europe could be overcome.

The AUR further stress the need for a patient-centered discussion and shared decision-making before initiating treatment, which may also involve genetic counseling

Received March 28, 2023
Accepted for publication March 30, 2023

on the implications of APOE status. The determination of the APOE status is important given the higher risk of ARIA in E4 carriers, specifically in homozygotes in the case of Lecanemab. Counseling on the APOE genotype will require more knowledge, skills, time and effort even for physicians with experience in AD than presently. Educational programs and AUR on the implementation of Lecanemab treatment should include this aspect and provide guidance for counseling for the treating physicians (6).

Information about ARIA as an MRI phenomenon, which remained asymptomatic in 75% of the participants in the phase III trial, is critical. It is possible that the sensitivity for clinical symptoms associated with ARIA is very high in physician and also patients in clinical care, because of a discussion in the media on safety issues of this treatment. This would potentially increase the demand for immediate access to MRI scanning to rule out or confirm ARIA as the underlying cause of unspecific symptoms, which may be difficult to obtain depending on the region in Europe. There is also a concern that the level of neuroradiological expertise, which was provided in the clinical trial setting through central reading is not readily available in centers without clinical trial experience and may be even less developed in community care settings. Thus, radiologists and the treating physician need to be trained to evaluate ARIA and related clinical side effects, and to manage treatment in case of ARIA.

Starting rules for treatment are well defined, based on what is known from the participants in the phase III studies. There has been an effort of defining stopping rules, including severe ARIA, severe symptoms in relation to ARIA or loss of access to clinical and MRI monitoring. A main question in clinical practice and for payers is also, if and when the treatment should be stopped in case of progressing dementia or increasing frailty. These questions, however, can only be answered once data on real word treatment is available (7).

Finally, these AUC only apply to Lecanemab and not automatically to similar upcoming other drugs, due to the expected differences in target population characteristics, application and safety profiles (8, 9).

It is beyond the scope of these AUC, but some pharmacoeconomic considerations are important. Conservative estimations of the population potentially eligible for treatment in the 27 EU countries arrive at 5.7 million individuals. Assuming that the drug is priced similarly as in the United States, treating all of these patients with Lecanemab would consume over half of the total pharmaceutical expenditures in the EU. The ability to pay for high-priced therapies varies substantially across European countries. This includes the risk that disparities in access to novel amyloid-targeting agents would deepen the inequalities across Europe in access to health care and potentially health outcomes (10).

Overall, the AUR are very helpful for European dementia experts for explaining the requirements and procedures for this treatment to colleagues in clinical care, to patients and families and to the administration of local institutions as well as to payers. They will also support country specific guideline development. Finally, they demonstrate the complexity of the treatment, implying that not all regions in Europe are sufficiently prepared and equipped yet. If Lecanemab is approved for the European market by the EMA, we hope that these AUR can be applied by all sites in order to minimize regional differences and and to maximize individual patients' benefit.

Acknowledgement: Lutz Frölich and Frank Jessen chair the European Alzheimer's Disease Consortium (EADC).

Conflict of interest: Frank Jessen has received personal fees for advice and presentations from: AC immune, Biogen, Danone/Nutricia, Eisai, Grifols, Janssen, Lilly, Roche. Lutz Frölich has received personal fees for advice and presentations from: Biogen, Eisai, Grifols, Hummingbird, InfectoPharm, Janssen Cilag, MerckSharpe&Dohme, Neurimmune, Neuromodulation, Noselab, NovoNordisk, Roche, TauRX, Schwabe and has received compensation for work in clinical trial committees from: Avanir/Otsuka, Pharmatropix, Forschungszentrum Jülich, Charité Berlin, Neuroscios, Vivoryon.

References

1. Cummings J, Aisen P, Apostolova LG, Atri A, Salloway S, Weiner M. Aducanumab: Appropriate Use Recommendations. J Prev Alzheimers Dis. 2021; 8(4):398-410.
2. Cummings J, Rabinovici GD, Atri A, Aisen P, Apostolova LG, Hendrix S, Sabbagh M, Selkoe D, Weiner M, Salloway S. Aducanumab: Appropriate Use Recommendations Update. J Prev Alzheimers Dis. 2022; 9(2):221-230.
3. https://www.clinicaltrials.gov/ct2/show/NCT05310071
4. Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P. Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease. Alzheimers Res Ther. 2019; 11(1):34.
5. Scheltens P, Vijverberg EGB. Commentary: Aducanumab: Appropriate Use Recommendations. J Prev Alzheimers Dis. 2021; 8(4):412-413.
6. Frederiksen KS, Nielsen TR, Winblad B, Schmidt R, Kramberger MG, Jones RW, Hort J, Grimmer T, Georges J, Frölich L, Engelborghs S, Dubois B, Waldemar G. European Academy of Neurology/European Alzheimer's Disease Consortium position statement on diagnostic disclosure, biomarker counseling, and management of patients with mild cognitive impairment. Eur J Neurol. 2021; 28(7):2147-2155.
7. Ekram ARMS, Ryan J, Espinoza S, Newman AB, Murray AM, Orchard SG, Fitzgerald S, McNeil JJ, Ernst ME, Woods RL. The association between frailty and dementia-free and physical disability-free survival in community-dwelling older adults. Gerontology. 2023 Jan 7. doi: 10.1159/000528984. Epub ahead of print.
8. Perneczky R, Jessen F, Grimmer T, Levin J, Flöel A, Peters O, Frölich L. Anti-amyloid antibody therapies in Alzheimer's disease. Brain. 2023; 146(3):842-849
9. Shcherbinin S, Evans CD, Lu M, Andersen SW, Pontecorvo MJ, Willis BA, Gueorguieva I, Hauck PM, Brooks DA, Mintun MA, Sims JR. Association of Amyloid Reduction After Donanemab Treatment With Tau Pathology and Clinical Outcomes: The TRAILBLAZER-ALZ Randomized Clinical Trial. JAMA Neurol. 2022; 79(10):1015-1024.
10. Jönsson L, Wimo A, Handels R, Johansson G, Boada M, Engelborghs S, Frölich L, Jessen F, Kehoe PG, Kramberger MG, Mendonça A, Ousset PJ, Scarmeas N, Visser PJ, Waldemar G, Winblad. The affordability of amyloid-targeting therapies for Alzheimer's Disease: an EADC viewpoint. The Lancet Regional Health – Europe 2023; in the press

How to cite this article: L. Frölich, F. Jessen. Editorial: Lecanemab: Appropriate Use Recommendations – A Commentary from a European Perspective. J Prev Alz Dis 2023;3(10):357-358; http://dx.doi.org/10.14283/jpad.2023.44