Survival time in Alzheimer's disease: An overlooked measure of safety and efficacy of disease-modifying therapies

Markku Kurkinen[1,A,C–F], Timothy Daly[2,A,B,D–F]

[1] NeuroActiva, Inc., San Jose, USA
[2] Bioethics Program, Facultad Latinoamericana de Ciencias Sociales (FLACSO) Argentina, Buenos Aires, Argentina

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online) *Adv Clin Exp Med*. 2024;33(10):1039–1043

Address for correspondence
Timothy Daly
E-mail: tdaly@flacso.org.ar

Funding sources
None declared

Conflict of interest
None declared

Received on June 3, 2024
Reviewed on August 14, 2024
Accepted on October 1, 2024

Published online on October 16, 2024

Abstract

It is of vital importance to patients and physicians, as well as administrators and drug regulators, that the treatment for a disease has been shown to be safe and clinically meaningful in long-term use. Recent literature has highlighted 3 major categories of arguments for and against modification of the underlying disease process in Alzheimer's disease (AD): pathophysiology, biomarkers and data from clinical trials. We argue that the Alzheimer's arena is over-reliant on theories of disease modification based solely on brain positron emission tomography (PET) imaging and blood biomarkers of tau and Aβ peptides. Here, we instead focus on a historically-grounded empirical criterion from other fields of medicine to overcome the weak interpretations of short Alzheimer's trials: survival time (ST). Our analysis has identified 3 key points. First, if anti-amyloid therapies are AD-modifying treatments, then we argue that they should increase ST more than the standard "symptomatic" care with memantine and acetylcholinesterase inhibitors. Second, we question memantine and cholinesterase inhibitors being labeled simply as "symptomatic" Alzheimer's drugs since long-term use of them can produce disease modification, that is, increase ST. Third, we make a case for memantine or cholinesterase inhibitors being used as controls in clinical trials with amyloid-lowering and other drugs, and argue against their current under-use in care of Alzheimer's patients.

Key words: clinical trials, survival time, amyloid-β, Alzheimer's disease, anti-amyloid antibodies

Cite as
Kurkinen M, Daly T. Survival time in Alzheimer's disease: An overlooked measure of safety and efficacy of disease-modifying therapies. *Adv Clin Exp Med*. 2024;33(10):1039–1043. doi:10.17219/acem/194003

DOI
10.17219/acem/194003

Introduction

It is of vital importance to patients and physicians, as well as administrators and drug regulators, that the treatment for a disease has been shown to be safe and clinically meaningful in long-term use. Recent 12–18 month clinical trials in early Alzheimer's disease (AD) patients with anti-Aβ monoclonal antibodies have demonstrated significant reduction of amyloid plaques in the brain as seen in amyloid positron emission tomography (PET) scans. However, a clinically meaningfull effect on slowing disease progression and cognitive decline has not been demonstrated.

On June 7, 2021, the U.S. Food and Drug Administration (FDA) approved aducanumab (Aduhelm®; Biogen, Cambridge, USA), an anti-Aβ monoclonal antibody, the first new drug in 18 years for the treatment of patients with AD, citing the "evidence that Aduhelm reduces amyloid beta plaques in the brain and that the reduction in these plaques is reasonably likely to predict important benefits to patients".[1] On January 31, 2024, Biogen announced that it would stop manufacturing Aduhelm and would also stop the ENVISION clinical trial, a confirmatory trial requested by the FDA to determine whether Aduhelm could actually slow disease progression and cognitive decline in AD patients. In the words of Christopher Viehbacher, CEO of Biogen: "When searching for new medicines, one breakthrough can be the foundation that triggers future medicines to be developed. Aduhelm was that groundbreaking discovery that paved the way for a new class of drugs and reinvigorated investments in the field."[2] Ultimately, this rhetoric of revolution has often been brandished instead of rigor when discussing the clinical benefits of aducanumab and other anti-amyloid antibodies.[3]

On July 6. 2023, the FDA approved lecanemab (Leqembi®; Eisai, Tokyo, Japan), an anti-Aβ monoclonal antibody which reduced amyloid in the brain, did not slow cognitive decline in women, and enhanced the decline of study participants with 2 *APOE4* genes. The claim of 27% of slowing cognitive decline in 18 months with lecanemab over placebo is due to a misinterpretation of data and trivial miscalculation; the real number is 9.3%.[4]

On July 2, 2024, the FDA approved donanemab (Kisunla™; Eli Lilly and Company,[5] Indianapolis, USA), an anti-Aβ monoclonal antibody for people with early symptomatic AD. The claim of 36% of slowing cognitive decline in 18 months with donanemab over placebo is due to a misinterpretation of data and trivial miscalculation; the real number is 9.6%.[6] On July 26, 2024, the European Medicines Agency (EMA) did not approve lecanemab, saying that "the benefits of lecanemab did not counterbalance the risk of serious side effects, especially bleeding and swelling in the brain".[7] Lecanemab, now being approved in China, Israel, Japan, and the USA, but nowhere else, raises the obvious question: How is it possible the same clinical trial data can be interpreted so differently, as providing experimental evidence to argue both for and against the efficacy and safety of lecanemab in human use?

The debate around disease modification in Alzheimer's disease

Indeed, there is no consensus on what we mean by the benefit/risk measure of anti-amyloid immunotherapies. Planche and Villain recently summarized 3 kinds of arguments for and against disease modification, pathophysiology, biomarker evidence, and clinical trial data, and argued that "With currently available data, one can therefore argue that anti-amyloid immunotherapies are [disease-modifying therapies (DMTs)] and are not".[8] One's position on the "disease-modifying" debate naturally depends on how one defines both AD (i.e., disease) itself, and what kind of modification is considered to be important for regulatory decision-making. It is not accidental that the largely USA-based definition of AD[9] as brain amyloidosis separate from cognitive symptoms led to regulatory approval of anti-amyloid antibodies, whereas the more European definition of AD[10] requiring symptoms before diagnosis, also led to more skepticism about benefit for patients.[11]

Concerning Planche and Villain's 3 classes of arguments for disease modification,[8] we consider that the AD field in general has been over-reliant on theoretical criteria, i.e., the amyloid hypothesis and amyloid-centric biomarkers including PET scans, to evaluate treatments.[12] We argue that the field should go beyond theoretical criteria to consider empirical and statistical criteria that historically were at the heart of decision making at the FDA.[13] We think it is important to consider objective, clinical criteria for claims of disease modification. Importantly, none of the recently approved monoclonal antibodies for AD reach thresholds for minimal clinically important difference (MCID)[14] in various cognitive domains.[15] However, the clinical level is not reducible to the cognitive level. It is important to consider functional and neuropsychiatric symptoms of AD when discussing disease modification.[16] A positive disease-modifying treatment should not worsen neuropsychiatric[17] or functional symptoms. Even though AD is a complex disease with different pathways,[18] we argue that the worsening of non-cognitive symptoms would be an argument against modification of those underlying disease processes leading to abnormal functioning.

In the context of these considerations of clinical benefit, it should be noted that an acetylcholinesterase inhibitor, donepezil (Aricept; Eisai) provides comparable, if not better, benefit in cognition and behavior than the anti-Aβ antibodies as measured by CDR-SB.[19] However, because of the fame of the amyloid hypothesis of AD,[20] and since donepezil does not reduce amyloid in the brain,[21] it is by definition not considered to be a disease-modifying treatment. What is important for the disease modification debate is whether objective measures in cognition with anti-amyloid treatments are maintained or even increase over time as compared to donepezil.[22]

However, these data for anti-amyloid treatments are not yet available. Evidence suggests that long-term use of donepezil leads to reduced functional decline[23] and mortality[24] in AD patients and also in nursing home residents with mixed dementia.[25] Interestingly, a causal inference study using data from electronic health records suggests that combination use of donepezil and memantine (an NMDA receptor inhibitor) creates "a significant beneficial additive drug-drug interaction" leading to significantly improved (ST) in AD patients.[26] In American veterans, memantine was associated with increased ST compared to donepezil.[27]

Survival time in Alzeimer's disease

Alzheimer's disease is a slowly progressing irreversible disorder of the brain and mind, and ST, after diagnosis at age 65 and over, is 4–20 years. There is a general consensus that earlier age of AD onset leads to a more aggressive form of the disease with a shorter ST.[28] To our knowledge, there has been no discussion of ST as a criterion for disease modification in AD. This is perhaps related to the ambiguity about whether AD is fatal, since in most cases, patients with severe AD die of secondary complications resulting from inadequate personal care and immobility, including pneumonia.[29] We can nevertheless draw on literature from oncology that uses ST as an important measure of disease modification.[30] From a public health perspective, improving ST is of vital importance, since AD is cited as a leading "cause of death," at 7th place in the USA.[31]

If the anti-amyloid therapies are AD modifying treatments in slowing disease progression and cognitive decline, then we argue that they should increase ST more than supposedly "symptomatic" treatments such as acetylcholinesterase inhibitors (donepezil, rivastigmine and galantamine) and/or memantine. Survival time is likely to be the most solid estimate for clinically meaningful benefit of putative treatments for AD, including current and future anti-Aβ monoclonal antibodies, since it has high value to public health and a low chance of bias compared to current measures used to evaluate treatments for AD, which may be sensitive to unblinding and not translate into clinical benefit.[32]

We also consider that over-reliance on anti-Aβ treatments as sources of disease modification has led to under-use of acetylcholinesterase inhibitors and memantine in both clinical trials and care. For instance, a recent longitudinal study of over 25,000 French nursing home residents found that over 80% of residents had received no exposure to either acetylcholinesterase inhibitors or memantine.[25] The authors of this study concluded that "use of conventional anti-dementia drugs is associated with a lower mortality in nursing home residents with dementia and should be widely used in this population".[25] We agree with this conclusion and argue that there is a solid case to be made for this to be applied to the research context of clinical trials. In other words, acetylcholinesterase inhibitors and/or memantine should be used as the "standard of care" control instead of placebo in amyloid-lowering and other clinical trials in Alzheimer's patients (dependent on disease stage).[33] We consider that provision of such care should be an ethical duty of trial sponsors, the absence of which would amount to withholding treatment, which would require further ethical justification.[34] We also consider that over-reliance on the amyloid hypothesis to find a disease-modifying treatment may also have led to neglect for studying the possible positive long-term consequences of acetylcholinesterase inhibitors and/or memantine. We consider that it is not appropriate to reduce the effects of these treatments to the merely "symptomatic" such as when the National Institute of Aging claims that they are "FDA-approved medications to manage symptoms".[33]

We argue that following up current patients and analyzing historical data on ST for AD trials should be a priority to establish the value of anti-amyloid and other therapies in the treatment and prevention of AD. Following up cases of autosomal dominant early-onset AD (ADAD) would provide the highest evidence of disease modification.[35] Survival time analyses have been performed in ADAD, finding that age of symptom onset is a stronger predictor of ST than different mutant variants of APP or PS1 responsible for ADAD.[36] However, the few cases of ADAD and the limited trial data on treatments[37] reduce statistical power and limit the amount of evidence available. Thus, follow up of the ST of tens of thousands of individuals having volunteered in historical and ongoing prevention trials in cognitively normal subjects at risk of developing AD with lecanemab (AHEAD3 and AHEAD45 studies) and donanemab (TRAILBLAZER-ALZ 3 study) will provide crucial analyses of disease modification. Importantly, our long-term follow-up proposal overcomes the current problem of the trial, i.e. disease mismatch, since current 12–18 month trials are only a snapshot of the long AD process.[8]

Overcoming limitations

However, there are limits to our position. Historical data on the first anti-amyloid therapy suggest that immunization with Aβ peptide as a treatment for AD provided "no evidence of improved survival".[38] However, historical data may be confounded by the fact that approx. 30% of people enrolled in amyloid-lowering trials were not amyloid positive and therefore, by definition, did not have AD before in vivo biomarkers became available.[39] Consequently, analyses of historical data should be limited to those where biomarker confirmation of AD was used. Second, older age leads to an exponential increase in all-cause mortality rates,[40,41] as well as less aggressive forms of dementia. Both of these factors could simultaneously lead to under- and

over-estimation of treatment effects on ST. Finally, there is evidence that age-standardized rates of dementia have been declining over the last few decades in higher-income countries,[42] perhaps due to a "compression" effect whereby people are increasingly developing dementia later in life and living with it for a shorter amount of time.[43]

Thus, when determining clinical meaningfulness by ST between treatment and non-treatment groups, there are several factors to take into count. These include age of symptom onset, age at the start of treatment, background demographics, and also longitudinal changes between cohorts. Nevertheless, if such factors can be controlled for and treatment groups can be shown to have increased ST, then we consider it both likely and meaningful that such treatments are modifying the disease process.

Conclusions

We consider that ST should be used to ground claims of disease modification in AD. We argue that, currently, the over-reliance on amyloid-lowering drugs has led to neglect of the long-term benefits of memantine and acetylcholinesterase inhibitors, which we do not consider to be merely symptomatic, since they demonstrate some long-term disease-modifying effects. We argue for increased use of acetylcholinesterase inhibitors in research (as a standard of care rather than placebo) and care settings (to reduce under-prescribing). Finally, we consider that if anti-amyloid treatments are truly disease-modifying as is claimed by the proponents and defenders of the amyloid hypothesis, then they should increase ST more than memantine or acetylcholinesterase inhibitors.

ORCID iDs

Markku Kurkinen https://orcid.org/0000-0001-5723-5298
Timothy Daly https://orcid.org/0000-0003-1650-242X

References

1. Planche V, Villain N. US Food and Drug Administration approval of aducanumab: Is amyloid load a valid surrogate end point for Alzheimer disease clinical trials? *JAMA Neurol*. 2021;78(11):1307. doi:10.1001/jamaneurol.2021.3126
2. Biogen. Biogen to Realign Resources for Alzheimer's Disease Franchise. Cambridge, USA: Biogen; 2024. https://investors.biogen.com/node/27501/pdf. Accessed August 12, 2024.
3. Daly T, Kurkinen M. Measuring our language about anti-amyloid antibodies in Alzheimer's disease: Technical, theoretical, and lay language considerations. *Clin Neurol Neurosurg*. 2024;241:108314. doi:10.1016/j.clineuro.2024.108314
4. Kurkinen MT. Lecanemab (Leqembi) is not the right drug for patients with Alzheimer's disease. *Adv Clin Exp Med*. 2023;32(9):943–947. doi:10.17219/acem/171379
5. Eli Lilly and Company. Lilly's KisunlaTM (donanemab-azbt) Approved by the FDA for the Treatment of Early Symptomatic Alzheimer's Disease. Indianapolis, USA: Eli Lilly and Company; 2024. https://investor.lilly.com/node/51026/pdf. Accessed August 12, 2024.
6. Kurkinen MT. Donanemab: Not two without a third. *Adv Clin Exp Med*. 2023;32(10):1085–1087. doi:10.17219/acem/172673
7. Walsh F. EU regulator rejects Alzheimer's drug lecanemab. *BBC*. 24 July, 2024. https://www.bbc.com/news/articles/crgm0v1ne08o. Accessed August 12, 2024.
8. Planche V, Villain N. Advocating for demonstration of disease modification: Have we been approaching clinical trials in early Alzheimer disease incorrectly? *JAMA Neurol*. 2023;80(7):659. doi:10.1001/jamaneurol.2023.0815
9. Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement (N Y)*. 2024;20(8):5143–5169. doi:10.1002/alz.13859
10. Dubois B, Villain N, Frisoni GB, et al. Clinical diagnosis of Alzheimer's disease: Recommendations of the International Working Group. *Lancet Neurol*. 2021;20(6):484–496. doi:10.1016/S1474-4422(21)00066-1
11. Daly T, Keuck L. Alzheimer's disease: Engaging with an unstable category. In: Schramme T, Walker M, eds. *Handbook of the Philosophy of Medicine*. Dordrecht, the Netherlands: Springer Netherlands; 2024:1–24. doi:10.1007/978-94-017-8706-2_113-1
12. Høilund-Carlsen PF, Revheim ME, Alavi A, Satyamurthy N, Barrio JR. Amyloid PET: A questionable single primary surrogate efficacy measure on Alzheimer immunotherapy trials. *J Alzheimers Dis*. 2022;90(4):1395–1399. doi:10.3233/JAD-220841
13. Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs, Board on Population Health and Public Health Practice, Institute of Medicine. *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*. Washington, D.C., USA: National Academies Press; 2012:13219. doi:10.17226/13219
14. Ebell MH, Barry HC, Baduni K, Grasso G. Clinically important benefits and harms of monoclonal antibodies targeting amyloid for the treatment of Alzheimer disease: A systematic review and meta-analysis. *Ann Fam Med*. 2024;22(1):50–62. doi:10.1370/afm.3050
15. Walsh S, Merrick R, Milne R, Nurock S, Richard E, Brayne C. Considering challenges for the new Alzheimer's drugs: Clinical, population, and health system perspectives. *Alzheimers Dement (N Y)*. 2024;20(9):6639–6646. doi:10.1002/alz.14108
16. McLaughlin J, Scotton WJ, Hardy JA, Shoai M. Assessing clinical progression measures in Alzheimer's disease trials: A systematic review and meta-analysis. Preprint posted online August 29, 2023. medRxiv. doi:10.1101/2023.08.29.23294771
17. Panza F, Lozupone M, Bellomo A, Imbimbo BP. Do anti-amyloid-β drugs affect neuropsychiatric status in Alzheimer's disease patients? *Ageing Res Rev*. 2019;55:100948. doi:10.1016/j.arr.2019.100948
18. Rollo J, Crawford J, Hardy J. A dynamical systems approach for multiscale synthesis of Alzheimer's pathogenesis. *Neuron*. 2023;111(14):2126–2139. doi:10.1016/j.neuron.2023.04.018
19. Kurkinen M. Anti-amyloid therapies do not slow Alzheimer's disease progression. *Dement Neuropsychol*. 2023;17:e20230099. doi:10.1590/1980-5764-dn-2023-0099
20. Daly T. A philosophy of science approach to the amyloid hypothesis of Alzheimer's disease. *Eur J Neurosci*. 2024;60(5):4707–4722. doi:10.1111/ejn.16500
21. Ishibashi K, Miura Y, Wagatsuma K, Ishiwata K, Ishii K. Changes in brain amyloid-β accumulation after donepezil administration. *J Clin Neurosci*. 2017;45:328–329. doi:10.1016/j.jocn.2017.08.025
22. Daly T, Kepp KP, Imbimbo BP. Are lecanemab and donanemab disease-modifying therapies? *Alzheimers Dement (N Y)*. 2024;20(9):6659–6661. doi:10.1002/alz.14114
23. Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2012;366(10):893–903. doi:10.1056/NEJMoa1106668
24. Xu H, Garcia-Ptacek S, Jönsson L, Wimo A, Nordström P, Eriksdotter M. Long-term effects of cholinesterase inhibitors on cognitive decline and mortality. *Neurology*. 2021;96(17):e2220–e2230. doi:10.1212/WNL.0000000000011832
25. Havreng-Théry C, Oquendo B, Zolnowski-Kolp V, et al. Cholinesterase inhibitors and memantine are associated with a reduced mortality in nursing home residents with dementia: A longitudinal observational study. *Alzheimers Res Ther*. 2024;16(1):117. doi:10.1186/s13195-024-01481-0
26. Yaghmaei E, Lu H, Ehwerhemuepha L, et al. Combined use of Donepezil and Memantine increases the probability of five-year survival of Alzheimer's disease patients. *Commun Med*. 2024;4(1):99. doi:10.1038/s43856-024-00527-6
27. Lazzeroni LC, Halbauer JD, Ashford JW, et al. Memantine is associated with longer survival than donepezil in a Veterans Affairs Prescription Database, 1997 to 2008. *J Alzheimers Dis*. 2013;36(4):791–798. doi:10.3233/JAD-130662

28. Barnes J, Bartlett JW, Wolk DA, Van Der Flier WM, Frost C. Disease course varies according to age and symptom length in Alzheimer's disease. *J Alzheimers Dis*. 2018;64(2):631–642. doi:10.3233/JAD-170841
29. Kukull WA, Brenner DE, Speck CE, et al. Causes of death associated with Alzheimer disease: Variation by level of cognitive impairment before death. *J Am Geriatr Soc*. 1994;42(7):723–726. doi:10.1111/j.1532-5415.1994.tb06531.x
30. Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis part I: Basic concepts and first analyses. *Br J Cancer*. 2003;89(2):232–238. doi:10.1038/sj.bjc.6601118
31. National Institute on Aging. Alzheimer's Disease Fact Sheet. Bethesda, USA: National Institutes of Health (NIH); 2023. https://www.nia.nih.gov/health/alzheimers-and-dementia/alzheimers-disease-fact-sheet. Accessed August 12, 2024.
32. Espay AJ, Herrup K, Imbimbo BP, Kepp KP, Daly T. Recalibrating the risk-benefit profiles of lecanemab and donanemab: Scales, immunoreactivity, and changes in amyloid-β42. *J Alzheimers Dis*. 2024;99(3):877–881. doi:10.3233/JAD-240171
33. National Institute on Aging. How Is Alzheimer's Disease Treated? Bethesda, USA: National Institutes of Health (NIH); 2023. https://www.nia.nih.gov/health/alzheimers-treatment/how-alzheimers-disease-treated. Accessed August 12, 2024.
34. Millum J, Grady C. The ethics of placebo-controlled trials: Methodological justifications. *Contemp Clin Trials*. 2013;36(2):510–514. doi:10.1016/j.cct.2013.09.003
35. Levin J, Vöglein J, Quiroz YT, et al. Testing the amyloid cascade hypothesis: Prevention trials in autosomal dominant Alzheimer disease. *Alzheimers Dement (N Y)*. 2022;18(12):2687–2698. doi:10.1002/alz.12624
36. Pavisic IM, Nicholas JM, O'Connor A, et al. Disease duration in autosomal dominant familial Alzheimer disease: A survival analysis. *Neurol Genet*. 2020;6(5):e507. doi:10.1212/NXG.0000000000000507
37. Salloway S, Farlow M, McDade E, et al. A trial of gantenerumab or solanezumab in dominantly inherited Alzheimer's disease. *Nat Med*. 2021;27(7):1187–1196. doi:10.1038/s41591-021-01369-8
38. Holmes C, Boche D, Wilkinson D, et al. Long-term effects of Aβ42 immunisation in Alzheimer's disease: Follow-up of a randomised, placebo-controlled phase I trial. *Lancet*. 2008;372(9634):216–223. doi:10.1016/S0140-6736(08)61075-2
39. Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med*. 2014;370(4):311–321. doi:10.1056/NEJMoa1312889
40. Brookmeyer R, Evans DA, Hebert L, et al. National estimates of the prevalence of Alzheimer's disease in the United States. *Alzheimers Dement (N Y)*. 2011;7(1):61–73. doi:10.1016/j.jalz.2010.11.007
41. Jack CR, Therneau TM, Lundt ES, et al. Long-term associations between amyloid positron emission tomography, sex, apolipoprotein E and incident dementia and mortality among individuals without dementia: Hazard ratios and absolute risk. *Brain Commun*. 2022;4(2):fcac017. doi:10.1093/braincomms/fcac017
42. Knopman DS. The enigma of decreasing dementia incidence. *JAMA Netw Open*. 2020;3(7):e2011199. doi:10.1001/jamanetworkopen.2020.11199
43. Dufouil C, Beiser A, Chêne G, Seshadri S. Are trends in dementia incidence associated with compression in morbidity? Evidence from the Framingham Heart Study. *J Gerontol B Psychol Sci Soc Sci*. 2018;73(Suppl 1):S65–S72. doi:10.1093/geronb/gby001