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Alzheimer's disease: Have we opened the Golden Gate to disease-modifying therapy?☆

The Clinical Trials in Alzheimer's Disease (CTAD) conference gathered from 29th November to 2nd December 2022 in San Francisco, home of the iconic Golden Gate Bridge, named after the turbulent strait that it traverses. Having sailed the increasingly choppy waters of AD therapy since 2008, this year's CTAD meeting was memorable for its juxtaposition of two contrasting landing points; Eisai's much-lauded CLARITY-AD trial of Lecanemab showing slowing of disease progression in prodromal and mild AD [1] and Roche's negative Graduate 1 and 2 trials of Gantenerumab in the same target population. However, beyond the vastly different mood music accompanying the topline data presentations, these two studies were remarkably similar both in their clinical outcomes and their contributions to our understanding of the neurobiology of AD.

Does the extent of amyloid clearance matter?

The Graduate studies did in fact show a trend towards a benefit of Gantenerumab on the primary outcome measure (CDR-SB); however the magnitude was well below that predicted and the studies were therefore underpowered to demonstrate statistical significance. A potential explanation for Gantenerumab's disappointing performance was that the reduction in amyloid burden on brain PET imaging (21–24 centiloids at 12 months, 47–58 centiloids at 27 months) was lower than anticipated from Roche's prior phase II studies [2] (100 centiloids is the difference in uptake between a true negative and a median amyloid positive AD patient for the amyloid ligand used in the study [3]).

Lecanemab, on the other hand, achieved rapid and robust reductions in brain amyloid (approximately 35 centiloids at six months; 55 centiloids at 18 months), with a lower rate of silent or symptomatic Amyloid Related Imaging Abnormalities (ARIA) (cerebral oedema and/or haemorrhage associated with anti-amyloid therapies) compared to Gantenerumab; a significant achievement.

An emerging hypothesis is that clinical benefit only accrues once a specific threshold for amyloid lowering is reached, leaving trials of slower-acting drugs underpowered to demonstrate benefit over 18 to 24 months. This might even compromise a four-year trial, justifying Roche's decision to terminate its nascent SKYLINE secondary prevention study of Gantenerumab in asymptomatic amyloid-positive individuals. However, meta-analysis of recent anti-amyloid monoclonal antibody trials with Aducanumab, Lecanemab and Donanemab suggests a small but significant class effect [4]; more data are required to confirm a correlation between the magnitude of amyloid reduction and clinical benefit. Results from Eli Lilly's phase III TRAILBLAZER-ALZ 2 trial of Donanemab are therefore hotly anticipated given that Donanemab may deliver even faster reductions; in the phase 2 TRAILBLAZER-ALZ study it achieved an impressive 70 centiloids at six months and 84 centiloids at 18 months [5].

Is the clinical benefit meaningful?

Amidst the celebrations of the first apparent disease-modifying effect ever to be shown in an AD trial, the limitations of CLARITY-AD were at times overlooked. Lacanemab was associated with a 27% reduction in decline on the CDR-SB. The absolute effect was small; 0.45 points on the CDR-SB, and 1.44 points on the ADAS-Cog14, considered below the generally accepted minimal clinically important difference for both measures [6–8]. Compared to Donepezil, Lecanemab is about 75% as effective by CDR-SB [9] and half as effective by ADAS-Cog [10]. It will be hard to convert this finding into a meaningful result in discussions with patients; it does not mean at the individual level that patients with AD will have preserved activities of daily living that otherwise would be lost. The most persuasive argument is that Lecanemab delays progression by about 6 months over an 18-month period.

Whether the magnitude of this benefit remains static, increases or decreases beyond 18 months remains unknown, and models claiming to predict the future should be interpreted with caution. Benefits of Lecanemab emerged within six months, and did not diverge greatly on most outcome measures between 12 and 18 months (indeed, the difference between drug and placebo on ADAS-Cog14 appeared to decline towards the end of the study); thus a partially symptomatic effect rather than a purely disease-modifying one can't be fully excluded. This would be consistent with several studies demonstrating acute effects of amyloid-beta on brain function [11,12].

Safety, funding and patient acceptability

Whatever its mechanism of action, were Lecanemab a low-cost oral medication with an established safety profile, like Donepezil or Memantine, there would likely be little opposition to its widespread uptake. The problem for Eisai is that patient selection, treatment (fortnightly intravenous infusions) and safety monitoring is highly complex and resource-intensive. It is not unreasonable for healthcare funders to ask whether the cost of the drug and its delivery is justified given the small scale of clinical benefit. This should not be interpreted as evidence that

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people with AD are being discriminated against compared to those with other life-limiting conditions such as cancer or spinomuscular atrophy. Quite the reverse; it means that Alzheimer's can now join the ranks of diseases that have clinically effective treatments but that these interventions must demonstrate cost effectiveness using the same rules that apply to everyone else.

Furthermore, it remains uncertain what proportion of patients, confronted with the significant and potentially lifelong medicalisation entailed in receiving Lecanemab, will opt for treatment and continue with it in the longer term. Manufacturers have a vested financial interest in patients taking their products indefinitely; however, anti-amyloid agents are more likely to demonstrate cost-effectiveness if treatment is time-limited. Given the inevitable progression in cognitive and social impairment rendering compliance increasingly challenging for individuals and families, establishing whether treatment can be temporarily ("drug holidays") or permanently suspended once a threshold of amyloid reduction has been reached is urgent. Indeed, continuing therapy beyond the point of clinical utility is unethical and financially unsustainable.

The slow rate of increase in amyloid burden in placebo subjects suggests that it might take years or even decades for the process to be completely recapitulated. Modelling of data from the phase 1b and 2 Donanemab trials suggests that in patients achieving reduction in amyloid PET levels to <11 centiloids after six months of treatment it would take approximately four years after ceasing treatment for levels to rise to a nominal threshold of positivity of 24 centiloids [13]. Furthermore, proof that amyloid therapies are indeed disease-modifying rather than symptomatic would be conclusively demonstrated by a trial of treatment cessation.

In addition, there are lingering concerns regarding both short and long-term safety of anti-amyloid drugs. Clinical use in patients with greater degrees of cerebrovascular disease than were allowed in the studies will inevitably carry higher risks of ARIA due to the association between imaging markers of cerebrovascular disease and underlying cerebral amyloid angiopathy. The CLARITY-AD authors should be commended for including people taking anticoagulants and the low rate of symptomatic haemorrhage overall. Nevertheless, the death from cerebral haemorrhage following tPA administration for acute stroke of a 65 year old female patient who was receiving Lecanemab as part of the open label extension needs to be reflected on, not assumed to be due to thrombolysis alone. Furthermore, Lecanemab joins the pantheon of anti-amyloid drugs that robustly cause overall brain shrinkage [14]; the effects of this beyond the current 18 to 24-month clinical trials are completely unknown.

What about non-amyloid pathways?

Conspicuous by its absence from the meeting was more than a passing curiosity about what drives the 77% of AD progression that to date remains unmitigated by amyloid-lowering therapy. Putting all our therapeutic eggs in the basket of tau pathology seems premature, given that Gantenerumab reduced CSF total tau and p-tau181 levels by 18% and 24% respectively without producing significant clinical benefit. Amyloid-lowering therapy is clearly insufficient to completely treat AD; the assumption that it is even necessary and should be included by default in any combination regimen needs to be tested in trials of drugs targeting other mechanisms, in which single and combination therapy arms will be needed.

Throughout the meeting, vascular contributions to cognitive impairment and dementia (VCID) seemed like prisoners on Alcatraz listening to the free citizens of neurodegeneration celebrate across the water. Yet only a minority of individuals living with dementia in their 80 s and 90 s, the largest and fastest growing cohort of those with the condition, have no cerebrovascular disease [15]. Furthermore, anti-amyloid studies typically impose upper age limits of 85 or 90 and have median participant ages in the low 70 s.

The exclusion of the oldest old and individuals with more than trivial cerebrovascular disease from all recent amyloid-lowering trials leaves a large group of patients, and potentially a majority of those aged over 80, with no safety (or efficacy) data on which to make an informed choice about treatment. Given the inevitable triggering of ARIA in a proportion of patients by amyloid mobilisation, therapies targeting non-amyloid pathways, such as PDE5 inhibitors or intensive blood pressure lowering, are urgently needed for this group. However, the drive to include biomarker confirmation of amyloid in all AD therapeutic trials, regardless of therapeutic target, is increasing research costs, reducing diversity (due to differential geographical access to amyloid diagnostics) and slowing down drug development. It also fails to reflect the pragmatic real-world environment in which anti-dementia drugs will be offered to the majority older population, in whom the specificity of CSF or PET amyloid is so low as to render these tools unusable [16]. In fact, screen failure rates in clinical trials due to participants with suspected AD having a negative amyloid biomarker are low; 22% of those meeting clinical diagnostic criteria for AD in the combined ENGAGE and EMERGE Aducanumab studies had a negative amyloid PET scan [17]. It would surely be more pragmatic and less expensive to increase study sample sizes by 25% to account for a minority of patients not having AD than to subject every participant to an amyloid PET or CSF examination.

Is 2022 the Alzheimer's disease community's 1987 moment?

San Francisco is rightly famous for playing a key role in the discovery of HIV and the development of effective and humane treatment for people with HIV/AIDS. Despite all the aforementioned caveats, the AD community might be correct in believing that we find ourselves in a similar position to our HIV counterparts in 1987, when AZT was shown to reduce mortality and opportunistic infection and increase CD4 count, despite ultimately proving insufficient to control the disease on its own. That the biology of AD remains substantially less well understood than HIV, and that dementia has multiple causes in addition to AD should not deter us from continuing the search for effective treatments. We must also remember that, as in HIV, prevention is preferable to cure. Policymakers need to act on the existing evidence that up to 40% of dementia is preventable [18] and that secondary prevention in dementia is as much about properly resourced social care (which has few if any adverse effects) as it is about drugs. Nevertheless, the spirit of optimism that characterised CTAD wasn't entirely misplaced; perhaps we truly have unlocked the Golden Gate to a cure for AD, with the prospect of forcing it open completely appearing less daunting than it did even a year ago.

References

[1] van Dyck C.H., Swanson C.J., Aisen P., Bateman R.J., Chen C., Gee M., Kanekiyo M., Li D., Reyderman L., Cohen S., Froelich L., Katayama S., Sabbagh M., Vellas B., Watson D., Dhadda S., Irizarry M., Kramer L.D., Iwatsubo T. Lecanemab in early Alzheimer's disease. N. Engl. J. Med. 2022 Nov 29. doi: 10.1056/NEJMoa2212948.

[2] G. Klein, P. Delmar, N. Voyle, S. Rehal, C. Hofmann, D. Abi-Saab, M. Andjelkovic, S. Ristic, G. Wang, R. Bateman, G.A. Kerchner, M. Baudler, P. Fontoura, R. Doody, Gantenerumab reduces amyloid-β plaques in patients with prodromal to moderate Alzheimer's disease: a PET substudy interim analysis, Alzheimers Res. Ther. 11 (1) (2019 Dec 12) 101, https://doi.org/10.1186/s13195-019-0559-z.

[3] W.E. Klunk, R.A. Koeppe, J.C. Price, T.L. Benzinger, Devous MD Sr, W.J. Jagust, K. A. Johnson, C.A. Mathis, D. Minhas, M.J. Pontecorvo, C.C. Rowe, D.M. Skovronsky, M.A Mintun, The Centiloid project: standardizing quantitative amyloid plaque estimation by PET, Alzheimers Dement. 11 (1) (2015 Jan) 1–15, https://doi.org/10.1016/j.jalz.2014.07.003, e1-4.

[4] N. Villain, V. Planche, R. Levy, High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 1: meta-analysis and review of efficacy and safety data, and medico-economical aspects, Rev. Neurol. (Paris) (2022 Sep 29), https://doi.org/10.1016/j.neurol.2022.06.012. S0035-3787(22)00738-X.

[5] M.A. Mintun, A.C. Lo, C. Duggan Evans, A.M. Wessels, P.A. Ardayfio, S. W. Andersen, S. Shcherbinin, J. Sparks, J.R. Sims, M. Brys, L.G. Apostolova, S. P. Salloway, D.M Skovronsky, Donanemab in early Alzheimer's disease, N. Engl. J. Med. 384 (18) (2021 May 6) 1691–1704, https://doi.org/10.1056/NEJMoa2100708.

[6] A. Schrag, J.M. Schott, Alzheimer's disease neuroimaging initiative. What is the clinically relevant change on the ADAS-Cog? J. Neurol. Neurosurg. Psychiatry 83 (2) (2012 Feb) 171–173, https://doi.org/10.1136/jnnp-2011-300881.

[7] J.S. Andrews, U. Desai, N.Y. Kirson, M.L. Zichlin, D.E. Ball, B.R. Matthews, Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials, Alzheimers Dement. (N Y) 5 (2019 Aug 2) 354–363, https://doi.org/10.1016/j.trci.2019.06.005.P.
[8] C.J. Lansdall, F. McDougall, L.M. Butler, P. Delmar, N. Pross, S. Qin, L. McLeod, X. Zhou, G.A. Kerchner, R.S. Doody, Establishing clinically meaningful change on outcome assessments frequently used in trials of mild cognitive impairment due to Alzheimer's disease, J. Prev. Alzheimers Dis. (2022), doi:10.14283/jpad.2022.102.
[9] S.L. Rogers, M.R. Farlow, R.S. Doody, R. Mohs, L.T Friedhoff, A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil study group, Neurology 50 (1) (1998 Jan) 136–145, https://doi.org/10.1212/wnl.50.1.136.
[10] J.S. Birks, R.J. Harvey, Donepezil for dementia due to Alzheimer's disease, Cochrane Database Syst. Rev. 6 (6) (2018 Jun 18), CD001190, https://doi.org/10.1002/14651858.CD001190.pub3.
[11] S. Epelbaum, I. Youssef, P.N. Lacor, P. Chaurand, E. Duplus, B. Brugg, C. Duyckaerts, B. Delatour, Acute amnestic encephalopathy in amyloid-β oligomer-injected mice is due to their widespread diffusion in vivo, Neurobiol. Aging 36 (6) (2015 Jun) 2043–2052, https://doi.org/10.1016/j.neurobiolaging.2015.03.005.
[12] J.H.Y. Yeung, T.H. Palpagama, W.P. Tate, K. Peppercorn, H.J. Waldvogel, R.L. M. Faull, A. Kwakowsky, The Acute Effects of Amyloid-Beta1-42 on Glutamatergic Receptor and Transporter Expression in the Mouse Hippocampus, Front Neurosci 13 (2020 Jan 17) 1427, https://doi.org/10.3389/fnins.2019.01427.
[13] S. Shcherbinin, C.D. Evans, M. Lu, S.W. Andersen, M.J. Pontecorvo, B.A. Willis, I. Gueorguieva, P.M. Hauck, D.A. Brooks, M.A. Mintun, J.R. Sims, Association of Amyloid Reduction After Donanemab Treatment With Tau Pathology and Clinical Outcomes: the TRAILBLAZER-ALZ Randomized Clinical Trial, JAMA Neurol. 79 (10) (2022 Oct 1) 1015–1024, https://doi.org/10.1001/jamaneurol.2022.2793.
[14] S. Ayton, Brain volume loss due to donanemab, Eur. J. Neurol. 28 (9) (2021 Sep) e67–e68, https://doi.org/10.1111/ene.15007.
[15] S. Agrawal, J.A. Schneider, Vascular pathology and pathogenesis of cognitive impairment and dementia in older adults, Cereb. Circ. Cogn. Behav. 30 (2022 Jun 30) 100148, doi: 10.1016/j.cccb.2022.100148.
[16] J.D. Isaacs, M. Boenink, Biomarkers for dementia: too soon for routine clinical use, Lancet Neurol. 19 (11) (2020 Nov) 884–885, https://doi.org/10.1016/S1474-4422(20)30365-3.
[17] S. Budd Haeberlein, P.S. Aisen, F. Barkhof, S. Chalkias, T. Chen, S. Cohen, G. Dent, O. Hansson, K. Harrison, C. von Hehn, T. Iwatsubo, C. Mallinckrodt, C. J. Mummery, K.K. Muralidharan, I. Nestorov, L. Nisenbaum, R. Rajagovindan, L. Skordos, Y. Tian, C.H. van Dyck, B. Vellas, S. Wu, Y. Zhu, A. Sandrock, Two randomized phase 3 studies of aducanumab in early Alzheimer's disease, J. Prev. Alzheimers Dis. 9 (2) (2022) 197–210, https://doi.org/10.14283/jpad.2022.30.
[18] G. Livingston, J. Huntley, A. Sommerlad, D. Ames, C. Ballard, S. Banerjee, C. Brayne, A. Burns, J. Cohen-Mansfield, C. Cooper, S.G. Costafreda, A. Dias, N. Fox, L.N. Gitlin, R. Howard, H.C. Kales, M. Kivimäki, E.B. Larson, A. Ogunniyi, V. Orgeta, K. Ritchie, K. Rockwood, E.L. Sampson, Q. Samus, L.S. Schneider, G. Selbæk, L. Teri, N. Mukadam, Dementia prevention, intervention, and care: 2020 report of the lancet commission, Lancet. 396 (10248) (2020 Aug 8) 413–446, https://doi.org/10.1016/S0140-6736(20)30367-6.

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