Advocating for Demonstration of Disease Modification-Have We Been Approaching Clinical Trials in Early Alzheimer Disease Incorrectly?

Vincent Planche, Nicolas Villain

Advocating for Demonstration of Disease Modification - Have We Been Approaching Clinical Trials in Early Alzheimer Disease Incorrectly?

Vincent Planche[1,2], MD, PhD and Nicolas Villain[3,4,*], MD, PhD.

1. Univ. Bordeaux, CNRS, IMN, UMR 5293, F-33000 Bordeaux, France.

2. Centre Mémoire Ressources Recherches, Pôle de Neurosciences Cliniques, CHU de Bordeaux, F-33000 Bordeaux, France

3. AP-HP Sorbonne Université, Hôpital Pitié-Salpêtrière, Department of Neurology, Institute of Memory and Alzheimer's Disease, Paris, France

4. Sorbonne Université, INSERM U1127, CNRS 7225, Institut du Cerveau - ICM, Paris, France

* Corresponding author: Dr. Nicolas Villain, MD, PhD

Institut de la Mémoire et de la Maladie d'Alzheimer
Département de Neurologie
Groupe Hospitalier Pitié-Salpêtrière
47-83 boulevard de l'Hôpital
75651 PARIS Cedex 13, France
nicolas.villain@aphp.fr
tel: 33 1 42 16 75 31

The Alzheimer's Disease (AD) community was unanimous in welcoming the positive results of Clarity-AD[1], an 18-month methodologically sound phase 3 trial of lecanemab in early AD. For the first time, an anti-amyloid immunotherapy demonstrated an indisputable clinical effect. Eventually, lecanemab received an FDA accelerated approval.

However, time to severe AD dementia is, on average, 7-17 years in this early AD population[2], and 18-month clinical trials in early AD can only provide limited insight into the drug's effectiveness in relation to the overall disease-course and its long-term impact. In this context, the 18-month therapeutic index of lecanemab was questioned: the effect size on the primary endpoint (0.45 points on an 18-point hybrid functional/cognitive scale of dementia severity) being balanced with significant side effects and uncharacterized long-term efficacy[1]. Cost-effectiveness was also debated, relying on assumptions on the long-term impact of the drug.

These debates illustrate the complexity of translating these early AD clinical trials results into the real-world, and highlight the importance of estimating the long-term effects of lecanemab. Long-term trials with pragmatic outcomes (such as institutionalization rates) could settle these uncertainties. Still, they are not a realistic option, considering their duration, costs, methodological biases (attrition rates), and ethical issues (delay before drug availability). Therefore, it is of utmost importance to assess the level of evidence for disease-course modification, which implies an enduring change in the disease's clinical progression[3]. Enduring changes ensure that treatment discontinuation will only partially impact the benefits and that benefits may increase over time if the treatment is effective all along the disease continuum. Disease-course modification can be demonstrated using and combining various data types: *(i)* effect on mechanisms central to the proposed pathophysiology of AD, *(ii)* biomarker measures, and *(iii)* clinical trial designs[3].

Concerning the first of these, under the assumption of the amyloid cascade hypothesis, anti-amyloid drugs could be disease-modifying therapies (DMTs) since removing amyloid should stop or alleviate the progression of tauopathy, neurodegeneration, and clinical symptoms. However, a pure "symptomatic" effect of anti-amyloid immunotherapies is also biologically conceivable. One can assume that the restoration of synaptic function might be at the root of the clinical effect of amyloid-β (Aβ) clearance through the toxicity reduction of different Aβ species on synaptic transmission ("Aβ stress")[4]. Still, Aβ clearance might be transiently clinically effective without interfering with tauopathy and processes leading to cell death.

Second, recent anti-amyloid immunotherapies demonstrated a solid ability to clear amyloid plaques. They also induced changes in "downstream" biomarkers, supporting the amyloid cascade hypothesis and disease-course modification[1]. Despite using small subsamples, aducanumab,

donanemab, and lecanemab significantly and consistently demonstrated regional effects on tau-PET. Effects on fluid biomarkers such as plasma and CSF p-tau should be interpreted cautiously since amyloid pathology could directly influence their measure. Effects on markers of neurodegeneration remained unclear. On the one hand, a significant decrease in CSF total-tau and neurogranin and a slower rate of hippocampal atrophy were reported in Clarity-AD. On the other hand, no anti-amyloid immunotherapies (except high-dose gantenerumab) showed a significant effect on CSF or plasma NfL. More disturbingly, global atrophy and ventricular enlargement acceleration were reported in almost all phase 2 and 3 anti-amyloid trials[5]. To clarify these conflicting results, future studies with pre-specified mediation analyses are necessary to assess the relationships between biomarkers and the primary outcome: for example, between amyloid PET load clearance, tau PET load dynamics, rate of medial temporal lobe atrophy, and CDR-SB (based on the "quantitative-ATN" model hypothesis).

Third, in parallel-groups clinical trials, the clinical evolution of patients treated with anti-amyloid immunotherapies *vs.* placebo can also provide indirect evidence of disease-course modification. In case of DMT, the difference between the two groups should gradually increase. Eli Lilly disclosed the figures of the absolute difference between placebo and treated groups on the primary endpoint (iADRS) at each timepoint in the donanemab phase 2 trial. These figures showed a plateauing difference after 52 weeks[6]. Likewise, the observation of CDR-sb slopes in the Clarity-AD trial showed an initial divergence and then a parallelization during the rest of the trial[1], which is not consistent with disease-course modification but rather with a symptomatic effect. However, slope analysis has some limits: lack of divergence does not exclude disease-course modification in case of non-linear and latent effects.

With currently available data, one can therefore argue that anti-amyloid immunotherapies are DMTs and are not (table 1). New trials with delayed-start designs could provide a higher level of evidence for disease-course modification. In these double-blind trials, patients are randomized to receive either a placebo or active treatment during the first stage of the trial. During the second stage of the trial, all patients receive active treatment. In case of DMT, the delayed-start group will never catch up to the early-start group, consistent with an enduring change in the clinical course. These trials differ from the current parallel-groups trials and their open-label extensions since there is *i)* no variability in the wash-out period before delayed-start, *ii)* no randomization bias related to the optional nature of open-label extensions, *iii)* continued blinding during the two stages of the trial and *iv)* a pre-specified analysis of the primary endpoint at the end of each trial's stage. The lecanemab Clarity-AD trial was powerful enough to evidence a significant difference

between the two parallel groups at ~6 months. Besides, the anti-amyloid effect seems to plateau after ~12 months. Hence, the total duration of a delayed-start trial testing anti-amyloid immunotherapies in early AD could be 18-24 months: as long as the current parallel-groups trials. However, isolated delayed-start trials have limitations and can be flawed, leading to an erroneous interpretation of disease-course modification. For instance, differential dropout between the placebo and the treated groups during the first trial's stage could bias the results, especially if treatments have both symptomatic and disease-modifying properties[7]. Still, lessons were learned, and such designs were used recently to test anti-synuclein immunotherapies in early Parkinson's disease. It demonstrates the ethical, methodological, and financial feasibility of delayed-start trials when testing immunotherapies at the early stages of neurodegenerative diseases.

In conclusion, a positive clinical trial with a delayed-start design combined with a pre-specified mediation analysis of "downstream" biomarkers as a co-primary endpoint will highly increase the level of evidence for disease-course modification. This will be of utmost importance for physicians to provide appropriate information to patients and caregivers in the shared decision-making process regarding the putative long-term effects of anti-amyloid immunotherapies. It will also help payors and regulators worldwide to confirm an acceptable long-term risk/benefit ratio and cost-effectiveness of anti-amyloid immunotherapies in early AD.

Acknowledgments

During the past three years, VP was a local unpaid investigator or sub-investigator for the following trials: Evoke and Evoke+ (NCT04777396, NCT04777409, NovoNordisk), Tango and Embark (NCT03352527, NCT04241068, Biogen), Lucidity (NCT03446001, TauRx Pharmaceuticals), Autonomy (NCT04619420, Janssen), Green Memory (NCT04520412, Green Valley Pharmaceuticals) and INFRONT-3 (NCT04374136, Alector). He received research grants from Fondation Bettencourt Schueller (CCA-Inserm-Bettencourt) and Fondation PSP-France.

Independent of this work, NV received research support from Fondation Bettencourt-Schueller, Fondation Servier, Union Nationale pour les Intérêts de la Médecine (UNIM), Fondation Claude Pompidou, Fondation Alzheimer and Fondation pour la Recherche sur l'Alzheimer; travel grant from the Movement Disorders Society, Merz-Pharma, UCB Pharma, and GE Healthcare SAS; is an unpaid local principal investigator or sub-investigator in NCT04241068 and NCT05310071 (aducanumab, Biogen), NCT04437511 (donanemab, Eli-Lilly), NCT05463731 (remternetug, Eli-Lilly), NCT04592341 (gantenerumab, Roche), NCT03887455 (lecanemab, Eisai), NCT03352557 (gosuranemab, Biogen), NCT03828747 and NCT03289143 (semorinemab, Roche), NCT04619420 (JNJ-63733657, Janssen – Johnson & Johnson), NCT04374136 (AL001, Alector), NCT04592874 (AL002, Alector), NCT04867616 (bepranemab, UCB Pharma), NCT04777396 and NCT04777409 (semaglutide, Novo Nordisk), is an unpaid national coordinator for NCT05564169 (masitinib, ABScience); and has given unpaid lectures in symposia organized by Eisai and the Servier Foundation.

References

1. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med*. Published online November 29, 2022. doi:10.1056/NEJMoa2212948
2. Vermunt L, Sikkes SAM, van den Hout A, et al. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. *Alzheimers Dement J Alzheimers Assoc*. 2019;15(7):888-898. doi:10.1016/j.jalz.2019.04.001
3. Cummings J, Fox N. Defining Disease Modifying Therapy for Alzheimer's Disease. *J Prev Alzheimers Dis*. 2017;4(2):109-115. doi:10.14283/jpad.2017.12
4. De Strooper B, Karran E. The Cellular Phase of Alzheimer's Disease. *Cell*. 2016;164(4):603-615. doi:10.1016/j.cell.2015.12.056
5. Ayton S. Brain volume loss due to donanemab. *Eur J Neurol*. 2021;28(9):e67-e68. doi:10.1111/ene.15007
6. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in Early Alzheimer's Disease. *N Engl J Med*. 2021;384(18):1691-1704. doi:10.1056/NEJMoa2100708
7. Olanow CW, Rascol O, Hauser R, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med*. 2009;361(13):1268-1278. doi:10.1056/NEJMoa0809335

Table 1. Are anti-amyloid immunotherapies disease-modifying therapies (DMTs)? Summary of currently available evidence. * as reported by Eisai at the 2022 CTAD conference (https://www.bioarctic.se/sv/wp-content/uploads/sites/4/2022/11/clarity-ctad-presentation.pdf)

	Pros	***Cons***
Non-clinical observations - Biological plausibility	Anti-amyloid immunotherapies could be DMTs by blocking the trigger of the amyloid cascade	Anti-amyloid immunotherapies could have symptomatic properties by alleviating the direct synaptic toxicity of amyloid Aß fibrils/oligomers
Biomarker measures	- Consistent "downstream" regional effects on tau-PET - Effects on some neurodegenerative biomarkers (CSF total-tau, CSF neurogranin, hippocampal volume)	- Accelerated global brain atrophy and ventricular enlargement - No consistent effect on CSF/plasma NfL - No mediation analyses to assess the individual relationships between biomarkers and clinical outcomes
Trial designs – Clinical outcomes	Linear modelization of the Clarity-AD trial shows an increasing separation over time between lecanemab and placebo groups (rate of change over time [mean slope] based on CDR-SB change from baseline analyzed using a linear mixed effects model*)	- Use of parallel groups designs - Raw data observations of donanemab and lecanemab trials shows that the gap between lecanemab and placebo groups stops increasing after ~12 months