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The anti-amyloid monoclonal antibody Lecanemab: 16 cautionary notes

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Abstract

The recent CLARITY AD results for the monoclonal anti-amyloid antibody Lecanemab have been interpreted as promising, supporting the amyloid hypothesis of Alzheimer's disease and leading to consideration for approval by the Food and Drug Administration. Here we explain why the claimed benefits on cognition and activities of daily living are uncertain, why Lecanemab may yield net harm for some subsets of patients and why the data do not prove the amyloid hypothesis but support other important population covariates driving disease. We note potential biases in the cohort arising from inclusion bias, unblinding, and dropouts, among other issues, which may affect the veracity of the data. Together with substantial adverse effects and subgroup heterogeneity, we conclude that Lecanemab's efficacy is not clinically meaningful and may be insignificant when considering the study limitations and biases highlighted. The data are consistent with numerous analyses to date suggesting that Aβ and its derivatives are not the main causative agents of Alzheimer's dementia.

Keywords: Alzheimer's disease; beta-amyloid; antibody; Lecanemab; subgroup analysis

Introduction

With nearly 40 million Alzheimer's disease (AD) patients in the world and up to a million deaths per year[1–3], new treatments are urgently needed[2,4,5]. Monoclonal amyloid-β peptide (Aβ) antibodies have received enormous attention as treatments inspired by the amyloid cascade hypothesis[6–9]. However, many previous antibodies failed in clinical trials and produced adverse effects[10–13], with Donanemab, Aducanumab, and Lecanemab being possible exceptions by showing some benefits[14–16], although these are modest and highly debated[17–20]. The Food and Drug Administration (FDA) recently gave accelerated approval of Aducanumab, endorsing drug-induced changes in brain amyloid-levels measured by positron emission tomography (amyloid-PET) as a surrogate measurement of clinical efficacy[18,21]. This decision caused widespread controversy, with 10 out of 11 independent FDA advisors voting against approval, and three resigning in protest when approval was nevertheless granted against their recommendation[19,21–26]. More recently, another antibody Lecanemab became the latest in a long list of interventions lowering Aβ, with FDA approval being sought in early 2023[27–29].

The amyloid hypothesis

The current definition of AD is predicated on the presence of amyloid deposition of the Aβ peptide in the brain[2,30–32]. This disease nosology is based on the amyloid hypothesis stating that an increase in Aβ aggregation, in one or more *in vivo* molecular forms acting on some processes in the brain, is the primary cause of disease[6,7,9] and thus that therapies that reduce Aβ should have a strong beneficial impact[13]. However, dementia associated with AD is a complex disorder[5,33–43], with genome-wide association studies implicating risk genes unrelated to Aβ processing[44–48], as well as diverse metabolic[49,50], vascular[51–53] and other important risk factors[1,38,54]. Furthermore, familial AD (fAD) which results in genetically determined increase in Aβ deposition in the brain, represents only a very small percentage of total cases with the large majority occurring sporadically[55,56]. It is not yet clear that Aβ is the cause of dementia in fAD, or that fAD and sporadic AD (sAD) are the same disease, and that Aβ is a major risk factor for sAD, as amyloid load correlates only modestly with clinical presentation[57–60] (see also below). Many people have brain Aβ amyloid fulfilling diagnostic criteria for AD yet without symptoms[57,61–65],

and technical challenges limit the use of amyloid-PET as a surrogate[63,66–69], with the amyloid-PET-clinical relationship being uncertain and sometimes possibly based on misinterpreted data[70].

Lecanemab

The monoclonal antibody Lecanemab was designed to target the N-terminal region of Aβ protofibrils deriving from the Arctic APP mutant, which favors protofibril formation[28]. The new data for Lecanemab from the phase 3 Clarity AD trial showed a modest but statistically significant clinical effect of slowing cognitive decline during the 18-month study period in a subset of patients[29]. The primary endpoint was the change in score on the 18-point Clinical Dementia Rating–Sum of Boxes (CDR-SB), but there were also significant effects on secondary endpoints, such as −1.44 on the 90-point Alzheimer's Disease Assessment Scale (ADAS-Cog14)[29]. For the primary endpoint, the mean change vs. the baseline (3.2) was approximately −0.45 difference vs. placebo (1.21 with Lecanemab and 1.66 with placebo), whereas for ADAS-Cog14 the effect was −1.44. This is claimed as a 27% reduced cognitive decline vs. placebo[29]. It was also claimed, based on an interpretation of the primary endpoint curve, that Lecanemab slows disease progression relative to placebo by about half a year[29]. These effects were associated with a clear reduction of amyloid-PET signal, as designed, but also with increased levels of CSF $A\beta_{42}$. However, upon analyzing these data, we propose that there are many uncertainties that should be considered in relation to Lecanemab.

Cautionary notes regarding Lecanemab's efficacy

Several points regarding both the efficiency and risk-benefit balance are noteworthy:

(1) Lecanemab use was associated with a 27% slowing of decline in the CDR-SB measure of cognition, relative to the placebo group. However, the absolute reduction relative to placebo is 0.45 on an 18-point scale. The authors stated that "A definition of clinically meaningful effects in the primary end point of the CDR-SB score has not been established" but recent literature estimates this to be equal to 1[71,72]. That is, an effect below 1 cannot be expected to be perceived by patients. Furthermore, the 0.45 points reduction in decline seen in the Lecanemab group is a maximal effect achieved after careful patient selection (59.6% of initially screened individuals at many sites did not meet inclusion criteria or fulfilled exclusion criteria) and may be subject to

uncertainties and potential biases (see below). The problem will be compounded in real life use, where many patients have numerous co-morbidities, plausibly reducing further the impact of the drug. It is also unknown whether the "maximal benefits" seen in this trial will persist over longer exposure, or after drug is ceased, even in this highly selected cohort[29].

(2) Bias from unblinding of patients due to protocols related to ARIA and infusion reactions could reduce the effect further[73]. Although the authors performed sensitivity analysis to address this[29], a quarter of the treatment arm had such effects and the risk of functional unblinding from ARIA cannot be overcome by blinded raters when patients learned they are on treatment by virtue of side effects. Such unblinding biases responses on subjective scales such as CDR-SB, ADCOMS & ADCS-ADL-MCI.

(3) The endpoint measurements are based on a reduced cohort due to faster dropout in the treatment group. Although relatively small as judged from the total dropout rates (many of which are non-problematic) there were more than double the dropout rates in the treatment group due to severe adverse events (6.9% vs. 2.9%), and the analysis was done with the reduced cohort, not the final cohort at 18 months. Thus, the particularly worse outcomes in the treatment group continuously dropped out at more than double the rate of the placebo group. For the survival analysis in Figure S6 of the paper[29] ("time to worsening of global CDR score", rate of progression to "next stage") the dropout was very large. Such drop out differences are a well-known source of bias[74] and could explain some of the difference between the primary and secondary endpoints. It is unclear whether this large dropout rate influenced the data. Thus, the trial data need to be analyzed with standard methods to at least show how large an impact this bias has on the endpoint curves[75].

(4) The effect was extremely heterogenous in the subgroup analysis. For example, all endpoints showed 100−300% more effect in men. For the primary endpoint the effect in women was only 12%, vs. 43% for men, an enormous 3.5-fold difference in impact (Figure S1B). This need to be understood either biologically, as an artefact relating to the biases discussed above, or at least, as a point of note for the label regarding the lesser effect and therefore lower benefit-risk ratio in women (who are more at risk of AD) if eventually approved.

(5) The *APOE* ε4 genotype was associated with a consistent reduction of the clinical benefit of Lecanemab (non-carriers most benefit, heterozygotes less benefit, and homozygotes even less

benefit). *APOE* ε4 is a known risk factor for AD and has been thought to enhance Aβ pathology[38,76,77]. Quite apart from clinical implications, the fact that people at higher AD risk due to *APOE* ε4 showed less benefit with Lecanemab is hard to reconcile with the amyloid-based disease hypothesis (i.e., if patients are at increased risk, they should have responded better to a treatment targeting the primary cause). Together with the influence of population covariates on outcome in the subgroups, the result in practice suggests involvement of important *non-amyloid* etiologies.

(6) Europeans had only 41% of the benefit of the drug measured on the primary endpoint compared to Americans ((CDR-SB; 14 vs. 34%, Figure S1A). Given the very large confidence intervals, some of this could be real population covariates or mostly low sampling certainty, invoking the need for further data. This is particularly true since in the current trial data, population health covariates influence the claimed efficiency by the same magnitude as the effects observed, which suggests that the trial may have identified previously unidentified covariates of AD risk and progression.

(7) The subgroup analysis for the ADAS-Cog14 score also shows a concerning tendency that the use of symptomatic medicine at baseline dominates as a covariate of the endpoint efficacy, with almost double efficacy of Lecanemab if the patient is already on a symptomatic medicine (Figure S2 of the paper[29]). This is not expected from a causal disease-modifying treatment.

(8) Further supporting this concern are previous trials giving remarkably similar effect curve shapes for non-causal (symptomatic) drugs such as donepezil[78,79]. If Lecanemab had been disease modifying one would expect a larger effect. Furthermore, the similarity for the two drugs suggests that Lecanemab does not work by disease modification but by some other non-specific effect or a common bias in the trial, such as drop-out, unblinding or cohort selection bias discussed above.

(9) For both the primary endpoint CDR-SB and for ADAS-Cog14, age was a major covariate of efficacy, with the drug having essentially no effect on the primary endpoint for patients < 65 years (6% vs. 23−40% in the higher ages, large confidence interval, Figure S1B) and half effect by ADAS-Cog (14% vs. 29−30% for older ages, Figure S2B). Notably this 6% CDR-SB effect for combined sex <65 years includes women with less than 1/3 benefit as judged from the sex-stratified estimate for all ages (12% women, 43% men, Figure S1B in the paper[29]).

(10) The combined subgroup results suggest that effects could in fact be negative in some patient groups, such as *APOE* ε4 allele carriers, Europeans below 65 years, women, and especially combinations of these. These effects probably reflect demographic risk factors and show the importance of other covariates determining disease outcome than Aβ amyloid alone. However, subgroup stratification of adverse effects as well as clinical effects of composite groups are missing for those in whom administration could plausibly be net harmful (e.g., female *APOE* ε4 carriers under 65y).

Points of caution regarding adverse effects as red flags

(11) One of the advantages of Lecanemab is its development based on the Arctic APP mutation (E22G) that presumably forms protofibrils quickly, making the antibody attack N-terminal epitopes of protofibrils[28] and supposedly producing fewer amyloid-related imaging abnormalities (ARIA), the most prevailing adverse effect seen for these types of antibodies[27]. Yet, the adverse effects in Table 3 of the trial paper were very substantial and included 12.6% ARIA[29].

(12) The twice as high drop-out rate in the treatment group due to serious adverse effects (6.9 vs. 2.9%)[29] not only risks biasing the efficacy estimates in the endpoint curves, but is also by itself a red flag on overall risk-benefit: An overall good drug in balance of benefits and adverse effects would not be expected to give so many more adverse effects in the treatment group. Long-term follow up of all patients, including those who left the trial, is essential before drawing conclusions about the safety of the drug.

(13) Another separate major concern is the evidence for brain atrophy in both the Phases 2 and 3 of Lecanemab[27]. Brain volume changes are also seen with other antibodies[80]. Just as amyloid accumulation does not cause brain swelling, amyloid clearance is not very likely to explain the brain atrophy, as postmortem studies in preclinical models and patients indicate that the overall volume of amyloid deposition accounts for less that 1% of the neocortex[81,82], i.e., this could be a red flag of neuronal damage. The lack of rigorous data ruling out brain volume changes due to treatment related tissue damage is of utmost concern for clinicians and patients.

(14) Another important red flag is the reports of three deaths during the trial, several associated with ARIA[83–85], although anticoagulants may have contributed to the observed brain swelling and haemorrhage.[83,84] The trial authors stated that there were no deaths associated with

ARIA[29]. However, independent assessments suggest Lecanemab contributed to death in at least two subsequent cases[84,85], which urgently requires analysis before FDA moves to approval, as fatal outcomes due to ARIA (with a prevalence of 12.6%) could change the risk-benefit balance considerably, especially given lack of long-term follow-up information.

(15) That ARIA increases with *APOE* ε4 genotype, as also seen for Gantenerumab[86] and Bapineuzumab[12], strongly argues for caution of use in these patients[87] and illustrates the importance of having both adverse effects and clinical benefits stratified better on population subgroups, in order to first do no harm.

(16) Importantly, especially in context with the above-described heterogeneity and uncertainty, the trial was short, and we do not know the long-term effects of treatment; it is possible that there is an unexpected long-term impact (e.g., of ARIA) that change the risk-benefit substantially. In addition to the many concerns, we must prepare for the eventuality that the real-world effects of Lecanemab may be much smaller than reported in the trial, due to the biases and heterogeneity discussed above. We note that patients often have comorbidities that make them more vulnerable to side effect risks and less likely to respond to treatment.

In sum, the data point to limited if any benefit on cognition and potential net detrimental effects at very least for particular patient subgroups (e.g., women, Europeans, people under 65, and APOE ε4 carriers). Taken as a whole, the data do not provide compelling evidence for benefits of Lecanemab on cognition, while the risks remain poorly understood.

Discussion: CLARITY AD in context

There was strong evidence before Lecanemab of a limited impact of reducing Aβ in AD patients[13]. The amyloid hypothesis, the theoretical basis for the Aβ reduction strategy, has been criticized for its simplicity and inconsistencies[31,33,88–96]. Many fAD mutations associate with reduced Aβ production[31,97–105] but increase the $A\beta_{42}/A\beta_{40}$ ratio[106–108]. Aβ toxicity conclusions were drawn from Aβ applied to cells at 1000-fold physiological Aβ concentrations[33,97]. The absence of fAD mutations in the α- and β-secretase that prevent or start production of Aβ[109] or in non-PS1 subunits of γ-secretase important for enzyme[110,111] production of Aβ also suggests against Aβ processing as a major single cause of AD. Along similar lines, no known mutations yield fAD risk in the key metalloproteases degrading Aβ, such as insulin degrading enzyme[112–114] and

neprilysin[115–117], expected if Aβ overload really caused disease[96]. Such anomalies among many others[31,33,91,96,97,109,118,119] illustrate that lowering of Aβ by itself cannot have a major impact.

These expectations have been confirmed in clinical trials, including now Lecanemab: We disagree that disease modification was demonstrated, since biomarker changes were not correlated directly to same subgroup clinical outcomes or studied for causal relationships. There was no evidence of dose-response effect as this was a single-dose trial. ARIA is known to be dose-dependent from previous antibody trials[120], and we expect at least the same level of dose-response benefit as adverse effects if a drug is disease-modifying.

The claimed beneficial effects with Lecanemab in some subgroups (but not clearly in all, see above)[29], if indeed they were to hold up, are not understood and could be due to clearance of toxic Aβ, precursors of this Aβ, or reconstitution of beneficial Aβ monomers[121]. While the association between brain amyloid and cognitive impairment is poor, reaching 5:1 ratio by age 85[122,123], the correlation between low soluble $A\beta_{42}$ and dementia is high: Most individuals with AD have CSF $A\beta_{42}$ below 800 pg/ml[124]. Soluble $A\beta_{42}$ increased substantially due to Lecanemab treatment (Figure S5 in[29]), which has been associated with a net positive clinical effect by itself[124,125].

We also note that the Clarity AD trial confirms previous data in suggesting that Aβ by itself is not a major cause of AD[97]. Lecanemab offers yet further evidence that anti-amyloid therapies are unlikely to produce clinically meaningful benefits in broader patient groups.

Real-world clinical use of Lecanemab

It could be claimed that a modest decline of cognition in a relatively healthy patient cohort over the 18 months of the CLARITY AD trial would make positive effects harder to identify, such that even minimal effect seen on cognition should be a cause of optimism. However, uncertainty of effect is not an argument for treatment with so many red flags. The 59.6% non-inclusion suggests that the cohort is far from representative of real-world settings, where desperate patients and busy clinicians meet. Under the pressures of intense clinical practice with broader patient groups, the drug is unlikely to work as well as in the ideal settings monitored by Clarity AD *even* if biases and subgroup heterogeneity discussed above had been small. In other words, the uncertainty of benefit is very much to the direction of smaller, if any, effect.

While it is thus unclear whether the short 18-month trial documents meaningful benefits, the long-term risks are also unclear. We have pointed above to our concerns about the high drop-out rate, red flags relating to mortality, and uncertain long-term adverse effects, including but not limited to AD patients with comorbidities excluded from the trial, and concerns about brain-volume loss that have been inadequately addressed, among other issues. Stringent monitoring of side effects will be much more difficult in real-world settings where many comorbidities are the rule, not the exception. Accordingly, the long-term risk-benefit balance of the drug is very unclear, with some patient groups (e.g., women under 65y or *APOE* ε4 carriers) potentially at even greater risk of net harm from administration. The data in the study are insufficient to allow us to estimate this issue, which again suggests against therapeutic use to patient groups in real-world settings without a much better understanding of the risk-benefit balance.

Finally, the issue of financial sustainability should be addressed, as these costly and marginally effective therapies may deplete funding on public and private health budgets.

Conclusions

Analysis of the available data from CLARITY-AD suggests that Lecanemab's efficacy is below that accepted as clinically meaningful. There are potential biases in the cohort from inclusion bias, unblinding, and dropouts, among other issues, which may affect the veracity of the data. Substantial adverse effects and subgroup heterogeneity is clearly present. Thus, the translation of the clinical trial data into real world effects is very uncertain. All these issues are consistent with a large body of previous data suggesting that Aβ overall plays a minor role in etiology despite its clear role in pathology.

The present discussion is urgent for everyone – patients and clinicians, but also researchers. There is reason for concern based on an objective assessment of the available data. To end the scourge of AD on our families and our society, we must ensure scientific and medical rigor focused on developing other etiology-based treatments for this devastating disease.

Conflicts of interest

Dr. Sensi has received grant support from the Alzheimer's Association, The Italian Ministry of Health and the Italian Ministry of Research. He is a scientific advisory board member without compensation for SINDEM the Italian Neurological Society for the Study of Dementia. He serves on the editorial boards of the Journal of Alzheimer's Disease, PLOS ONE, Frontiers in Aging, Frontiers in Neuroscience, and Frontiers in Psychiatry.

Dr. Perry is a consultant for Synaptogenix and Nervgen and is acting Editor-in-Chief of the Journal of Alzheimer's Disease.

Dr. Espay has received consultant fees from Neuroderm, Amneal, Acadia, Acorda, Bexion, Kyowa Kirin, Sunovion, Supernus (formerly, USWorldMeds), Avion Pharmaceuticals, and Herantis Pharma; honoraria for speakership for Avion; and publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer. He cofounded REGAIN Therapeutics and is co-owner of a patent on synthetic soluble nonaggregating peptide analogues. He serves on the editorial boards of the Journal of Parkinson's Disease, Journal of Alzheimer's Disease, European Journal of Neurology, Movement Disorders Clinical Practice, and JAMA Neurology.

Other authors did not report any conflicts of interest related to this work.

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