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Short Communication

The missing improvers: Tau pathology, neuroplasticity, and the case for tau-informed patient selection before amyloid immunotherapy

Eric Dinnerstein

Neurology department, The University of Texas Tyler School of Medicine, Tyler, TX, USA

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ABSTRACT

Amyloid immunotherapy with lecanemab and donanemab has been approved on the basis of statistically significant slowing of cognitive and functional decline in early Alzheimer's disease (1,2). Yet clinicians treating individual patients face the everyday challenge of estimating whether a given patient is declining at the rate that would be expected for them, and whether their trajectory reflects a response to treatment. I argue that this difficulty arises in large part because the field cannot yet routinely stratify patients by tau pathology before treatment, even though tau burden is among the strongest available predictors of both the rate of progression and the magnitude of response to amyloid-targeting therapy. Post-hoc and open-label analyses of the Clarity AD and TRAILBLAZER-ALZ 2 programmes suggest that patients with absent, low, or medium tau burden may constitute a biologically distinct group in whom amyloid clearance is most likely to permit clinical stabilization or measurable functional gain. These observations remain hypotheses, generated largely from subgroup, open-label, and biomarker data rather than from prospective trials designed to test them I propose that tau status should be given strong consideration in patient selection, that tau-guided selection should be evaluated prospectively, and that the access, reimbursement, and standardization barriers to tau positron emission tomography (PET) — together with the promise of scalable plasma tau biomarkers — be addressed deliberately as the field moves toward tau-informed treatment. One tau PET tracer is currently approved by the US Food and Drug Administration, and a regulatory decision on a second is anticipated in 2026.

1. Introduction

Two drugs are now available in clinical practice with the explicit promise of modifying the course of Alzheimer's disease: lecanemab (Leqembi; Eisai/Biogen) and donanemab (Kisunla; Eli Lilly). Their approvals by the US Food and Drug Administration were based on phase 3 randomised controlled trials demonstrating statistically significant slowing of cognitive and functional decline over 18 months [1,2]. The pivotal Clarity AD and TRAILBLAZER-ALZ 2 trials were rigorously conducted, and their primary outcomes were met.

Yet clinicians treating individual patients with mild Alzheimer's disease under these approvals face a genuine practical difficulty: judging whether a particular patient is declining at the rate that would be expected for them, and whether what they observe reflects the drug. Despite substantial evidence from clinical trials and natural history studies, the field still lacks validated statistical models that combine variables measured in an individual patient to project that patient's expected future trajectory. In the absence of such a benchmark, treatment effects that are real at the group level can be difficult to perceive at the bedside.

I argue that this difficulty reflects a set of intersecting problems: individual-level response data from the pivotal trials have not been published; the early-stage Alzheimer's disease population enrolled in those trials is biologically mixed; and patients are not stratified by tau pathology before treatment. I further argue that there are now sufficient data to support the identification of the patient phenotype most likely to benefit from these treatments — those with significant amyloid burden but absent, low, or medium tau pathology — but that this phenotype is not being reliably recognised in clinical practice, because the patients most likely to carry it are not being selected using the biomarker that would identify them. I advance this as a hypothesis to be tested prospectively rather than as an established conclusion.

1.1. What the trials showed: a critical reading

Donanemab's phase 3 trial made an important design choice that is rarely foregrounded in clinical discussions. Eligibility required evidence not only of amyloid but also of tau pathology on flortaucipir PET

E-mail address: Eric.Dinnerstein@uttyler.edu.

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imaging; participants were then stratified by tau burden into a low/medium tau group and a high tau group [2]. In the low/medium tau population (n = 1182), which served as the primary analysis population, donanemab slowed clinical decline by approximately 35% on the integrated Alzheimer's Disease Rating Scale (iADRS) and approximately 36% on the Clinical Dementia Rating sum of boxes (CDR-SB) over 18 months. In the combined population, which added the high tau group (n = 552; total n = 1736), the corresponding figures were approximately 22% and 29%. Patients with high tau analysed separately did not show significant slowing of decline on most outcomes — a pattern consistent with the hypothesis that advanced tauopathy may represent a threshold beyond which amyloid clearance is less able to rescue neuronal function [2]. This design was scientifically sound; it also means that, by enriching for earlier-stage disease, the trial concentrated benefit in the very patients most likely to respond.

Neither pivotal trial was designed to detect, characterise, or report on the subset of patients who improve. Improvement — defined as movement from a worse to a better functional category, or as a positive change in CDR-SB from baseline — was not a primary or pre-specified secondary endpoint in either Clarity AD or TRAILBLAZER-ALZ 2. This is not a criticism of the investigators; it reflects the conventional framework of dementia therapeutics, in which any slowing of an otherwise relentless trajectory is counted as success. But it means that the patients who might constitute the most scientifically informative cohort in either trial — those whose function stabilised or improved after amyloid was cleared — were not systematically identified, characterised, or followed.

1.2. The clinical reality: where are the improvers?

A growing body of real-world evidence now describes outcomes with lecanemab and donanemab outside the trial setting, across several countries. A prospective single-centre cohort at a tertiary memory clinic in Tel Aviv reported that, among patients reaching six-month follow-up, Mini-Mental State Examination (MMSE) scores declined significantly over the period, with the decline significant in younger patients (under 75) but not in those aged 75 or older [3]. A prospective single-centre cohort in Eastern China (n = 76) found a manageable safety profile, with all observed amyloid-related imaging abnormalities (ARIA) asymptomatic and a significant reduction in amyloid PET signal after twelve months of treatment [4]. An Italian tertiary memory centre reported its first year of implementation of both agents under European safety-monitoring protocols, again with a focus on feasibility and safety rather than on detecting functional gain [5]. Preliminary data presented in abstract form extend this picture: an interim analysis of a retrospective multicentre US case series found that most patients remained at the same clinical stage over the observation period, with a minority improving and a minority progressing [6], and the first readout from the ALZ-NET national registry, also presented in abstract form, reported patients with mild cognitive impairment remaining broadly stable while those with mild dementia declined modestly over one year [7]. These conference findings are promising but preliminary and should be weighted accordingly.

Two features of this literature deserve emphasis. First, the real-world cohorts published to date are small, are typically followed for only six to twelve months, and were designed primarily to characterise safety and feasibility rather than to detect functional improvement. Differences between these observational cohorts and the pivotal trials — including treatment-selection bias, variable follow-up duration, adherence and infusion completion, heterogeneity of monitoring, and differences in baseline disease severity — may contribute to observed outcomes independently of tau burden, and caution against reading the absence of dramatic improvement as evidence of drug failure. Second, and most importantly for the present argument, none of these cohorts collected pre-treatment tau PET. It is therefore impossible to determine, from the existing real-world literature, what fraction of treated patients carried the absent-to-medium tau phenotype in whom benefit would be predicted to concentrate — and therefore whether the modest aggregate picture reflects the drugs' limits or the biological composition of who is being treated. This is precisely the evidentiary gap that tau-informed selection, and prospective study of it, would close.

A note of caution about "improvers" is warranted throughout. Apparent improvement on CDR-SB, MMSE, or ADAS-Cog over time may in part reflect measurement variability, regression to the mean, practice effects, or disease heterogeneity rather than true reversal of neurodegeneration, and open-label designs cannot exclude these explanations. The interpretation I advance below — that a subgroup experiences genuine functional stabilization or partial recovery — is a hypothesis that these caveats make all the more important to test under controlled, tau-stratified conditions.

The relative invisibility of improving patients in the case-report literature is also structurally explained. The publication ecosystem for individual patient reports rewards the unexpected: a catastrophic ARIA event, unusually rapid deterioration, a changed diagnosis. A patient who is mildly impaired and now slightly less so does not, by current conventions, constitute a publishable case report. The patients who may be most informative biologically are thus underrepresented in the literature by design.

1.3. The tau hypothesis: a biological rationale for selective response

The amyloid cascade hypothesis, in its classical formulation, posits that beta-amyloid accumulation is an early event in Alzheimer's pathology, with tau hyperphosphorylation, neurofibrillary tangle formation, synaptic dysfunction, and neuronal death as downstream sequelae [8]. The temporal dissociation between amyloid accumulation, which may precede symptoms by decades, and the onset of cognitive impairment is attributed to the lag between amyloid burden and tau propagation: neurons may continue to function in the presence of significant amyloid until tau pathology reaches a threshold of disruption [8].

This temporal structure has a corollary that motivates the present hypothesis. In patients who are amyloid-positive but carry little or no tau pathology — those who have crossed the amyloid threshold but not yet the tau threshold — the dominant insult may be synaptic dysfunction mediated by soluble amyloid species rather than irreversible neuronal loss mediated by neurofibrillary tangles [9]. Synaptic dysfunction is, in principle, more reversible than neuronal death [10]. On this model, neurons that are functionally suppressed by chronic amyloid exposure, but not yet committed to degeneration, might retain the capacity for partial synaptic recovery if the toxic burden is removed. I emphasise that this remains a mechanistic hypothesis rather than an established account.

Evidence consistent with this mechanism has emerged from biomarker analyses within the lecanemab programme. In Clarity AD, treatment was associated with normalisation of cerebrospinal fluid neurogranin, a marker of synaptic integrity, while neurofilament light chain, a marker of neurodegeneration, did not differ significantly from placebo [1]. This dissociation is what a model of synaptic rescue without reversal of established neurodegeneration would predict: synaptic markers improve, while markers of neuronal loss do not. It is consistent with — though it does not prove — the proposition that the locus of benefit of amyloid immunotherapy, in those patients in whom it acts, is the synapse rather than the lost neuron.

The clinical correlate of this model appears in the open-label extension of Clarity AD. In the peer-reviewed three-year (36-month) extension analysis, a majority of the no/low tau PET subgroup remained stable or improved: on CDR-SB, 59% showed no decline and 51% showed improvement from baseline; comparable patterns were seen on ADAS-Cog14 (63% no decline, 61% improvement) and on the ADCS MCI-ADL functional scale (63% no decline, 59% improvement) [11]. These figures describe more than a slowing of decline in this biologically defined subgroup; they describe a majority remaining stable or gaining

measurable function over three years of treatment, in contrast with the overall trial population, in whom improvement is a minority outcome. Preliminary 48-month data from the same extension, presented in abstract form, suggest this pattern strengthens further with longer treatment (no decline 69%, improvement 56% on CDR-SB) [12]; these later data are promising but await full peer-reviewed publication and should be regarded as preliminary. Together these analyses generate, rather than confirm, the hypothesis that benefit concentrates in the lower-tau phenotype.

Support of a different kind comes from TRAILBLAZER-ALZ 2, where the prospectively greater benefit in the low/medium tau population than in the combined or high-tau analyses provides trial-level, tau-stratified evidence that aligns with the same biological logic [2]. The mechanism in this context can be framed as arresting amyloid accumulation early enough that the patient's own compensatory capacity can operate in an environment no longer dominated by amyloid-mediated synaptic toxicity — again, a hypothesis that prospective, tau-stratified study would be required to confirm.

1.4. The policy argument: toward tau-informed patient selection

Current clinical practice for amyloid immunotherapy requires confirmation of amyloid positivity by PET or cerebrospinal fluid assay, and structural MRI to evaluate contraindications and monitor for ARIA [13,14]. Tau PET is not required, is not consistently recommended for treatment selection, and is not routinely covered by insurance as a pre-treatment evaluation. The evidence summarised above suggests that this warrants reconsideration, and I set out the case for moving deliberately toward tau-informed selection.

Three observations support giving tau status strong consideration in selection. First, the probability of benefit from amyloid immunotherapy does not appear uniform across the amyloid-positive population: subgroup and open-label data suggest it is higher in patients with absent, low, or medium tau pathology and lower in patients with high tau burden [2,11]. Second, the principal harms of amyloid immunotherapy are not strongly modified by tau status: ARIA risk is chiefly a function of amyloid load, apolipoprotein E genotype, and treatment schedule, so patients with high tau may carry comparable harm risk with diminished probability of benefit [15]. Third, tau PET provides information about molecular staging that cannot be reliably inferred from cognitive testing, amyloid PET alone, or structural MRI [16].

These considerations must, however, be weighed against real practical limitations, and I do not argue for an immediate mandate. Tau PET remains unevenly accessible and inconsistently reimbursed; tracers and interpretation methods vary; and validated, standardized cutoffs for treatment decisions are not yet established. A hard requirement imposed before these issues are resolved would risk creating inequities, particularly for patients seen in community and rural settings where tau PET is least available. Plasma biomarkers, notably p-tau217, may in time provide much of the relevant stratification at far lower cost and far greater scale, either as a complement to tau PET or, eventually, as a partial substitute; their maturation may reshape what tau-informed selection looks like in practice. For these reasons, the appropriate posture at present is strong consideration of tau status in selection and rigorous prospective evaluation of whether tau-guided selection improves clinical outcomes and cost-effectiveness, rather than an immediate categorical requirement.

The updated Appropriate Use Criteria for amyloid and tau PET, issued jointly by the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging, already identify tau PET as appropriate when evaluating eligibility for anti-amyloid therapies, while stopping short of requiring it [16]. The direction of this guidance is consistent with the argument advanced here; what is needed is the prospective evidence that would justify strengthening it.

The reimbursement question is closely linked. Medicare now covers amyloid PET for multiple scans across a patient's treatment course, having retired its single-scan restriction in recognition of the role of imaging in the era of disease-modifying therapy [17]. Against the substantial annual cost of therapy and of the MRI monitoring and ARIA management it entails, the cost of a single pre-treatment tau PET scan is modest, and would be readily justified if tau-guided selection were shown to identify patients unlikely to benefit and to spare them treatment-related risk [18]. Establishing that benefit prospectively is the necessary next step, and coverage policy should be prepared to follow the evidence.

Finally, the failure to identify and systematically study the subgroup of patients who improve represents a real opportunity cost. A prospective registry enrolling amyloid-positive patients with absent, low, or medium tau, treated with lecanemab or donanemab and followed with serial tau PET, synaptic and neurodegeneration biomarkers, plasma tau measures, and detailed neuropsychological assessment, would characterise the responders directly and would generate mechanistic data on the relationship between amyloid clearance, tau dynamics, synaptic function, and cognitive reserve. Such a study would be among the more informative the field could mount in the current decade.

2. Conclusions

The approved amyloid immunotherapies are real drugs with real biological effects, and the efficacy signal in the phase 3 trials is genuine. But the group-average framing of their results obscures the heterogeneity of individual response, and the absence of tau stratification before treatment means that the patients most likely to benefit are not being reliably identified, while patients less likely to benefit may be exposed to comparable risk. The available subgroup and open-label data suggest that the lower-tau responders are not rare — in the right biological substrate they may be the majority — but they remain a hypothesis-defined population that current clinical pathways are not designed to find.

I therefore call for three things, framed to match the current state of the evidence. First, that tau status be given strong consideration in patient selection for amyloid immunotherapy, and incorporated into clinical guidance in a phased way as access and standardization improve. Second, that tau-guided selection, and reimbursement to support it, be evaluated prospectively rather than assumed, with plasma tau biomarkers studied in parallel as a scalable complement. Third, that a prospective registry of amyloid-positive patients with absent, low, or medium tau, treated with amyloid immunotherapy and followed with serial tau and synaptic biomarkers, be established with the explicit goal of characterising the responders who remain the most underexplored population in contemporary Alzheimer's therapeutics.

Ethical statement

This is a Perspective article based entirely on previously published and publicly presented data. No original studies on human participants or animals were conducted by the author. Accordingly, informed consent, ethics committee approval, and trial registration are not applicable.

Declaration of generative AI and AI-assisted technologies

During the preparation of this work, the author used Claude AI in order to optimize readability and language and assist with editing.

After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the publication's content.

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Declaration of competing interest

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