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PERSPECTIVE

Perspective: Minimally clinically important "symptomatic" benefit associated with disease modification resulting from anti-amyloid immunotherapy

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Abstract

Despite some skepticism regarding the amyloid hypothesis, there is growing evidence that clearing amyloid by targeting specific species of amyloid (plaque, oligomers, fibrils, and protofibrils) for removal has therapeutic benefits. Specifically, there is growing evidence that, in mild cognitive impairment and mild dementia due to Alzheimer's disease (AD), robust and aggressive removal of amyloid can slow cognitive decline as measured by global instruments, composite measures, and cognitive testing. Furthermore, clinical efficacy signals coupled with clear biomarker changes provide the first evidence of disease modification. This effect seems to be in addition to symptomatic treatments and opens speculation that the effect of anti-amyloid monoclonal antibodies might be clinically meaningful through symptomatic amelioration that is a result of disease modification.

KEYWORDS
Alzheimer disease, anti-amyloid treatments, donanemab, lecanemab, mild cognitive impairment, monoclonal antibodies

Highlights

- Clearance of brain amyloid plaques may lead to a clinical benefit in patients with early AD.
- Aggregated Aβ may play a role in both disease expression and progression.
- Anti-amyloid monoclonal antibodies might be clinically meaningful through symptomatic amelioration resulting from disease modification.

Recently reported phase 3 clinical trial results with the anti-amyloid antibodies lecanemab[1] and donanemab[2] convincingly demonstrate that clearance of brain amyloid plaques leads to a clinical benefit in patients with early Alzheimer's disease (AD), although it has been argued that differences in the rate of clinical progression for patients receiving drug therapy versus placebo do not exceed the criteria for minimally clinically important difference.[3,4] Although amyloid beta (Aβ)–directed therapy is inherently disease-modifying, close inspection of the results with these two specific agents, both of which target synaptotoxic forms of Aβ, suggests that the effects may not be solely due to a disease progression effect. A true disease progression effect is one on an irreversible component of the disease. In AD, which is

a chronic neurodegenerative disease, this effect would be slowing neuronal loss over time, most specifically neuronal loss in the hippocampus. The results with donanemab and lecanemab, interpreted in the context of current models of AD pathogenesis, suggest that, in addition to slowing disease progression defined in this manner, there is a substantial symptomatic effect (ie, a reversal of a functional deficit) associated with these two agents. Importantly, as assessed by the Clinical Dementia Rating Sum of Boxes (CDR-SB) score, the magnitude of the symptomatic effect in the early-stage population evaluated in the respective phase 3 trials is consistent with it being minimally clinically important.

Of note, Aβ neurotoxicity is not considered to be due to plaques but to soluble aggregates of Aβ,[5] concentrations of which are decreased with clearance of amyloid plaques. Furthermore, in animal models, aggregated Aβ first and foremost leads to reversible functional deficits (eg, impaired synaptic plasticity),[2] with neuronal loss being less prominent and occurring later. The primary targets of both lecanemab and donanemab are such synaptotoxic aggregated forms of Aβ: Aβ protofibrils in the case of lecanemab, and pyroglutamate Aβ oligomer in the case of donanemab. Preclinically, the murine parent of lecanemab rapidly reduces soluble Aβ protofibril levels, but not insoluble Aβ levels, in animals with preexisting plaques, and it prevents amyloid plaque deposition when administered before the appearance of amyloid plaques.[6] Similarly, a small-molecule inhibitor of pyroglutamate Aβ formation improves cognition in AD mouse models.[7] That is, the experimental evidence predicts that these anti-amyloid antibodies reduce levels of soluble aggregated synaptotoxic forms of Aβ, and such reduction through decreasing the suppressive effects of such aggregated Aβ on neuronal function would be expected to lead initially to a symptomatic effect, with a trailing effect on disease progression.

Of note, with a disease-modifying approach, any symptomatic effects would likely present clinically in a different way than would be the case with symptomatic therapies, such as the acetylcholinesterase inhibitors, which have direct and acute pharmacological activity. For donanemab and lecanemab, the effect on amyloid plaque as measured by positron emission tomography (PET) scan (ie, the disease-modifying effect) is progressive over 6 to 12 months; therefore, any symptomatic effects would be expected to emerge gradually over that period, during which there is continued disease progression (which was not seen in the time frame and patient population used in evaluating the cholinesterase inhibitors). Accordingly, any symptomatic effects would be mixed in with clinical progression and, rather than producing a clear improvement, would reveal themselves as a shallower slope of the curves of the clinical endpoints (ie, a lower rate of decline) during the time period in which the symptomatic effect emerges, with a higher rate of decline once the maximum symptomatic effect has taken hold.

Regarding donanemab, one of the study inclusion criteria in phase 3 was the presence of tau pathology assessed by 18F-flortaucipir PET. Furthermore, the tau PET scans were categorized as low/medium or high tau, and the efficacy analyses were stratified by this grouping. Because the maximal treatment effect in donanemab phase 2b was in the low/medium tau population, the sample size was based on the low/medium tau population, and 80% of the alpha was spent against the analysis in this population.[2] It is in this low/medium tau population that a symptomatic effect for donanemab is most evident. Specifically, for the primary endpoint in the phase 3 study, the integrated Alzheimer Disease Rating Scale, the curve of the change from baseline through week 36 (the timeframe during which plaque is cleared) is nearly flat for donanemab and less so for placebo (although the curve for placebo in the initial 36 weeks is less than thereafter, the difference is less for placebo), consistent with a symptomatic effect. The results for CDR-SB, although showing more decline in the donanemab arm than for the primary endpoint, do show a greater divergence in the slopes during the initial 36 weeks than thereafter, leading to a donanemab-placebo CDR-SB difference of 0.5 at week 36.[2] Later, both donanemab and placebo showed a decline, and the curves were either parallel (most endpoints) or further diverged (CDR-SB, by an additional 0.08 points in the last 24 weeks). Because donanemab treatment in the study was discontinued after amyloid plaque clearance had been demonstrated on PET scans, an alternative explanation for the decrease in activity after 36 weeks is that it was the result of the treatment discontinuation. However, the effect on amyloid plaque effect persisted.

Intriguingly, the initial flattening of the curve for donanemab is not seen in high tau participants (eFigure 10 in Sims et al.[2]), who would be expected to have more fixed and fewer reversible deficits. We believe that these findings, the lack of early effect in the high tau group and an early effect in the low/medium population that would be expected to have greater capacity for symptomatic effect, are further evidence of such an effect. Moreover, the 16.5% slowing in CDR-SB change (6% slowing on the primary endpoint, integrated Alzheimer Disease Rating Scale) in that population may represent the magnitude of the pure disease progression effect, consistent with the 10% to 15% slowing in hippocampal volume loss by magnetic resonance imaging that the authors report (eFigure 6 in Sims et al.[2]).

For lecanemab, the symptomatic effect is most evident in the phase 2b clinical study, particularly on the 14-item Alzheimer Disease Assessment Scale, Cognitive Subscale (ADAS-Cog14). There was a clear improvement (decrease in score from baseline) on this measure at the highest dose level (ie, the dose taken into phase) at week 12, whereas there was a worsening in the placebo arm; thereafter, the curves declined in parallel fashion. This improvement on ADAS-Cog14 was not replicated in phase 3; however, there was evidence of symptomatic effect by this measure, with a difference in ADAS-Cog14 of 1.0 point at month 6, with curves declining in parallel through the remainder of the study. On the primary endpoint, CDR-SB, the curves diverged most prominently at early timepoints in the lecanemab phase 3 trial, with a difference of 0.5 points at 9 months and 12 months, with a parallel decline in placebo and active treatment curves thereafter.[1] The most prominent symptomatic effect on the primary endpoint was seen in an unpublished exploratory analysis in which there was an improvement (decrease) of 0.4 points in the CDR-SB score in the lecanemab-treated participants after 18 months of treatment, whereas there was a mean 0.1-point worsening (increase) in placebo recipients in the 40% of the study participants who had no or low tau PET signal at baseline.[8] Furthermore, at the end of 18 months of label extension treatment, the CDR-SB score in the original placebo recipients approximated that

in the original lecanemab recipients, arguing that the symptomatic effect accounted for the majority of the treatment effect during the placebo-controlled period. This demonstration of a symptomatic effect in the patients with low levels of neurodegeneration, seen in both the donanemab and lecanemab phase 3 trials, is consistent with the concept of targeting the synaptic dysfunction stage of neurodegenerative disorders,[9] a stage in which clinical disease expression is driven by a functional deficit rather than frank neuronal loss. A potential reason that these two antibodies were able to demonstrate a symptomatic effect in this phase of the disease is that they are able to reverse the effects of aggregated Aβ on synaptic function.

Additional context is provided by the results of the A4 study in preclinical AD,[10] in which the participants would be expected to have low levels of neurodegeneration and be firmly in the synaptic dysfunction phase of the neurodegenerative disease process. In A4, there was no significant difference between solanezumab, which targets monomeric Aβ, and placebo with respect to the primary endpoint, which was change in the Preclinical Alzheimer Cognitive Composite score over a period of 240 weeks. Of note, solanezumab did slow, relative to placebo, the increase in amyloid PET signal over the course of the study, but it did not reduce the signal relative to baseline, as was seen with lecanemab and donanemab. We believe this difference in the effects on "amyloid clearance" as determined by PET is consistent with solanezumab because it targets only monomeric Aβ, not clearing aggregated Aβ. In contrast, lecanemab and donanemab do clear these toxic forms of Aβ, resulting in the clinical effect that we have discussed. The specificity of the symptomatic effects seen with lecanemab and donanemab is also supported by the phase 3 results with aducanumab[11] and gantenerumab,[12] both of which do not target specific forms of Aβ. In both cases, although there are significant effects on amyloid plaque load as measured by PET, which, in the case of aducanumab, are similar to those of lecanemab and donanemab, there is limited to no separation from placebo in the curves of worsening on the CDR-SB during the initial 12 months of treatments.

By aligning with the finer mechanistic details of the amyloid hypothesis, our interpretation provides stronger validation of that hypothesis, including a role for aggregated Aβ in both disease expression and progression. From a drug development standpoint, the clinical trial results point to the benefit of a symptomatic effect toward demonstrating a treatment effect, particularly within the initial 6 to 12 months of treatment. Moreover, for patients, a clinically meaningful improvement in the short term that persists (the data indicate that it persists to 18 months), along with a long-term disease progression effect, might be more meaningful than a pure disease progression effect. With respect to the clinical meaningfulness of the symptomatic benefit in the early AD population, a difference of 0.5 points in the CDR-SB is inherently minimally clinically important because the CDR-SB in the lower range is scored in 0.5-point increments. That is, a 0.5-point reduction in the CDR-SB in the lower ranges implies that there is improvement in one functional domain from either moderate to slight impairment or slight to no impairment, either of which is a minimally clinically important difference as defined by the CDR-SB.[13,14] At the same time, a disease progression effect that is approximately half of the overall effect has important implications for long-term outcomes (eg, time to dependency). To uncover additional effects on disease progression, researchers could investigate either upstream of amyloid plaques and target cholinergic degeneration in the basal forebrain[15] or downstream and target tau and neuroinflammation.[16]

AUTHOR CONTRIBUTIONS

John Alam drafted the manuscript, and Marwan N. Sabbagh provided critical review and edits to the manuscript.

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CONFLICT OF INTEREST STATEMENT

John Alam is the founder and CEO of CervoMed. Marwan N. Sabbagh discloses ownership interest (stock or stock options) in uMETHOD Health, Lighthouse Pharmaceuticals, and Alzheon; consults for Roche-Genentech, Eisai, Lilly, Synaptogenix, NeuroTherapia, Signiant Health, Novo Nordisk, Prothena, Anavex, Cognito Therapeutics, GSK, and AbbVie; and is on the board of directors for CervoMed. Author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no datasets were generated or analyzed during the current study.

ETHICS STATEMENT

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CONSENT STATEMENT

Patient consent was not required for this perspective article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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