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Anti-amyloid drugs and the mystery of treatment-associated brain shrinkage

By Madhav ThambisettyNov. 28, 2022

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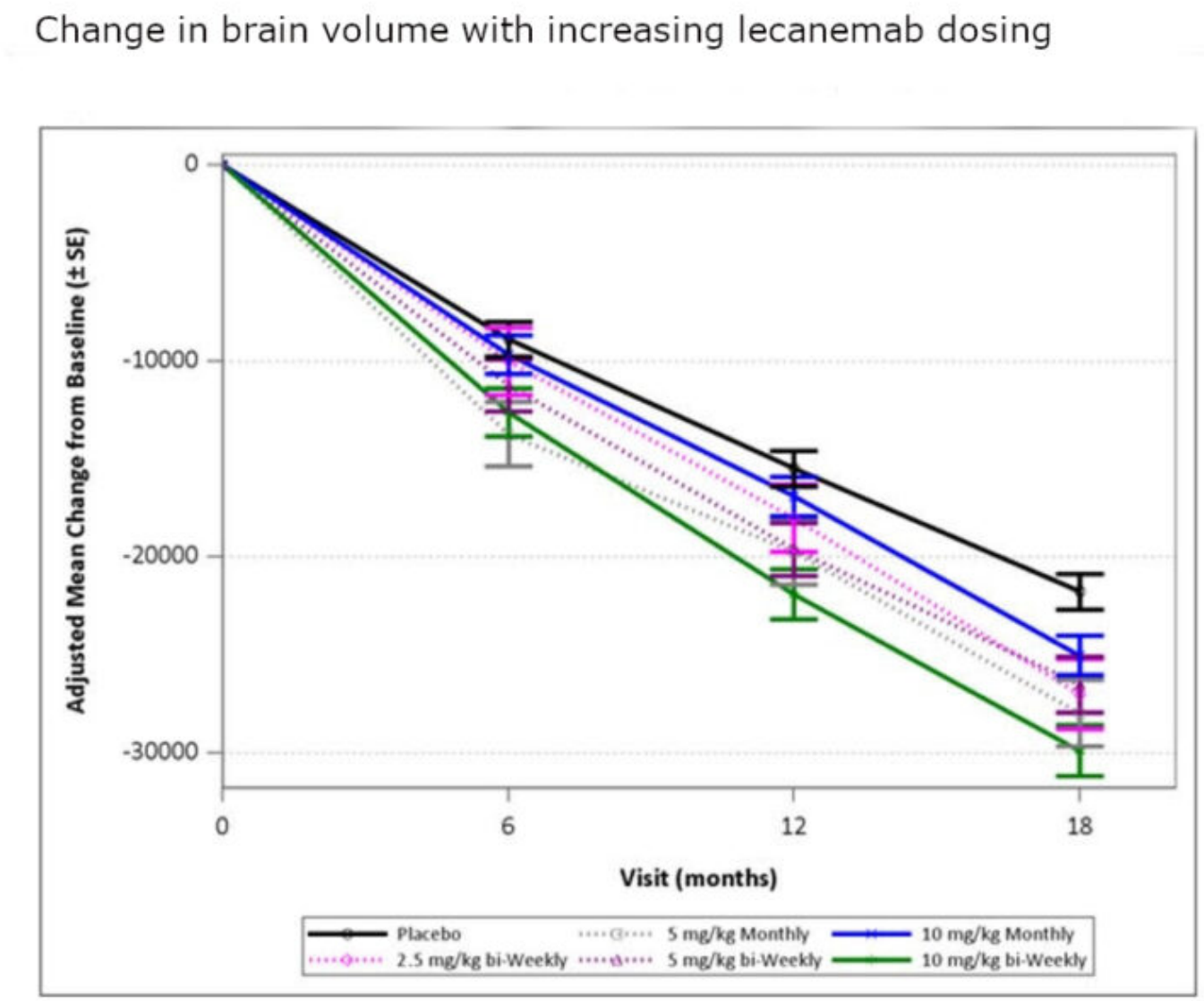
Eisai's announcement[2] that lecanemab, its antibody drug for Alzheimer's disease that targets the buildup of amyloid protein in the brain, modestly slowed cognitive decline in a Phase 3 trial offers hope to people with

Alzheimer's disease. But what I'll be looking for in the final data — which have not yet been presented or published — is whether the brain shrinkage[3] seen in the Phase 2 trial remains.



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This graph shows a reduction in whole brain volume in participants treated with lecanemab compared to placebo in the Phase 2 trial of this anti-amyloid therapy. Chart used under a Creative Commons license[5] from Supplemental figure S4B in Swanson CJ et al, Alzheimers Res Ther 2021 Apr 17;13(1):80[6].

As the investigators in that trial concluded, "The long-term implications of these findings are unknown and may be assessed in longer-term follow-up and in the phase 3 study (Clarity-AD)."

The acceleration of brain shrinkage — also known as atrophy or reduction in brain volume — has been described in clinical trials of other anti-amyloid antibodies, including aducanumab (now FDA-approved as Aduhelm) and donanemab. It's important to fully understand this phenomenon and its long-term implications, because in people with Alzheimer's disease, brain shrinkage, typically measured on MRI scans as a reduction in brain volume or an increase in the volume of the brain's fluid-filled spaces (known as ventricles), has been consistently associated with *progression* of the disease[7] rather than slowing of symptoms. Brain shrinkage also correlates with severity of pathological changes[8] in the brain due to Alzheimer's assessed at autopsy.

The observation that antibody-induced amyloid clearance results in faster brain shrinkage is worrisome because, in the absence of compelling evidence to the contrary, it suggests a potential worsening of degenerative changes in the brains of people with Alzheimer's disease.

Since the first report[10] of ventricular expansion after exposure to an anti-amyloid antibody in 2016, the most commonly advanced rationale for this phenomenon is that the loss of brain volume represents space that was previously occupied by plaques that have been cleared by the amyloid-targeting antibodies. Yet there are few empirical data to support this hypothesis. On the contrary, simple calculations[11] based on the estimated amount of space occupied by beta amyloid in the brain performed by Scott Ayton, a neurodegeneration researcher at the Florey Institute in Melbourne, Australia, suggest that the clearance of amyloid plaque is too small to be detected on MRI scans and hence does not represent a plausible explanation for brain volume loss.

To assess the importance of brain volume loss after exposure to this latest generation of Alzheimer's treatments, I propose four questions that should be pursued in the clinical trial data about lecanemab[12] and other amyloid-targeting antibodies. These are:

- Does the loss of brain volume track with worsening cognitive performance or other side effects such as headache, confusion, and dizziness?
- Is there a relationship between brain volume loss and frequently observed amyloid-related imaging abnormalities (ARIA) that cause brain swelling or microbleeds in patients treated with these drugs?
- Is loss of brain volume related to higher levels of biomarkers of neurodegeneration?
- Are patients who show brain volume loss on MRI scans more likely to develop long-term worsening of cognitive decline?

Most current clinical trials of Alzheimer's disease collect blood samples from participants for analyses of various proteins that may provide clues about the efficacy or side effects of these drugs. One such protein is called neurofilament light (NfL), a biomarker of neurodegeneration that also appears to correlate with the number of neurofibrillary tangles in the brain, a key pathological hallmark of Alzheimer's. In an earlier phase-2 trial of donanemab, being developed by Eli Lilly, investigators observed[13] a statistically significant relationship between an increase in levels of NfL in the blood and a decrease in whole brain volume. This observation is concerning because it suggests that loss of brain volume in people treated with donanemab, and possibly other anti-amyloid antibodies, may indicate that the drugs are worsening neurodegeneration.

Lack of attention toward better understanding the consequences of brain volume loss are especially evident in the analyses of data submitted to the Food and Drug Administration from the two Phase 3 trials of aducanumab. Although the clinical and statistical analyses of these results both by the FDA and Biogen run into hundreds of pages, are forensically detailed and publicly[15] available[15], I could find no assessment of the relationship, if any, between brain shrinkage and severity of cognitive impairment.

The FDA's clinical review of aducanumab trial data also includes reports of nine deaths in people treated with the drug. Did their brain MRI scans show accelerated loss of brain volume? Could these changes be used to predict serious adverse events in people treated with anti-amyloid drugs? We do not know the answers to these questions because it is not evident that they were addressed in the FDA's analyses.

Similarly, results from the EMBARK study[16], an open-label extension trial of aducanumab, have not been published and little information is currently available on the long-term consequences of these changes in individuals treated with the drug.

With data from the aducanumab trials already available with the FDA, these analyses must be pursued with urgency and made publicly available at the earliest. In the absence of clear and compelling evidence that brain atrophy and ventricular expansion after exposure to anti-amyloid antibodies do not represent adverse treatment effects, existing data suggest cause for concern and uncertainty about the long-term effects of these changes.

As a physician who cares for people with Alzheimer's and other dementias, I hope that these emerging anti-amyloid antibody therapies represent a significant advance in our ability to treat this devastating disease. But it is incumbent on drug developers and researchers to examine all the available data dispassionately and make rational, evidence-based decisions about the safety of these drugs.

Madhav Thambisetty is a neurologist and an adjunct professor of neurology at Johns Hopkins University School of Medicine. The views expressed here are his alone and do not necessarily reflect those of his employer or Johns Hopkins.

About the Author

Madhav Thambisetty

@MadhavThambiset[18]
linkedin.com/in/madhav-thambisetty-599a9776/[19]

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