VIEWPOINT

A Step Forward in the Fight Against Dementia—Are We There Yet?

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"Is there anything you can do to slow down the cognitive decline?" Each of us fields this question almost immediately after making a diagnosis of Alzheimer disease (AD). For many years, we have had to answer by gesturing toward future possibilities. This answer may soon change, thanks to results from Clarity AD, a phase 3 randomized clinical trial of lecanemab for patients with early AD.[1] While lecanemab was recently granted accelerated approval by the US Food and Drug Administration (FDA) based on earlier phase 2 data demonstrating significant amyloid plaque reduction by positron emission tomography (PET), consideration for full approval will follow later this year based on the clinical efficacy demonstrated by the phase 3 study, confirming the clinical signal observed in the phase 2 study.

Lecanemab is a humanized IgG1 monoclonal antibody that binds to amyloid-β (Aβ) soluble protofibrils. In Clarity AD, 1795 patients with mild cognitive impairment (MCI) or mild dementia due to AD were randomly assigned to receive 10-mg/kg biweekly intravenous infusions of lecanemab or placebo for 18 months. Primary and secondary outcomes, as well as multiple "downstream" biomarkers of AD pathophysiology, all favored lecanemab, demonstrating a clear-cut clinical benefit and possible modification of disease pathophysiology. The Clarity AD results converge with the phase 2 donanemab data (TRAILBLAZER-ALZ)[2] and 1 of 2 phase 3 aducanumab trials (EMERGE). Conversely, the ENGAGE trial (aducanumab) and phase 3 gantenerumab studies did not demonstrate clinical benefit. These discrepancies may be explained by differences within this antibody class, with donanemab and lecanemab appearing to be more potent in amyloid plaque reduction. In aggregate, these drugs robustly lowered amyloid plaques and resulted in modest slowing (22%-27%) of clinical decline.[3]

Lecanemab's clinical efficacy was demonstrated using well-established outcome measures. The primary outcome—the Clinical Dementia Rating–Sum of Boxes (CDR-SB; range, 0-18, with higher scores indicating greater impairment)—employs a structured interview with patient and care partner evaluating cognitive symptoms and daily function. Although the CDR-SB is an 18-point scale, its range in this population is narrow. In Clarity AD, patients' baseline CDR-SB score was approximately 3.2, and the placebo-group change was approximately 1.7 in 18 months. The lecanemab group's progression was slower by approximately 0.45 points. At this mild stage, small changes in the CDR-SB score may reflect substantial differences in people's lives (eg, 0.5 points may distinguish between "slight benign forgetfulness" vs "moderate memory loss" that "interferes with everyday activities"). Secondary clinical end points showed similar effects. The 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale, a cognitive test battery, favored lecanemab by 1.44 points (26%). Perhaps even more convincing was a 37% reduction (approximately 2 points) in decrease in score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment, a care-partner questionnaire assessing day-to-day function. A single point distinguishes between doing a task independently (eg, managing one's finances) and doing a task with assistance. Exploratory measures, including quality of life and caregiver burden, also favored lecanemab. Preliminary analyses suggested that the magnitude of drug-placebo clinical differences increased over this short-duration trial, which might magnify the benefit if extrapolated beyond 18 months. Long-term follow-up data via open-label extension (OLE) and emerging clinical patient registries are needed to confirm these findings.

Why are the clinical effects of lowering brain amyloid not greater? We would expect any drug targeting a single element of AD pathophysiology to have modest clinical effects. For patients with autopsy-proven AD, plaque-and-tangle pathology likely accounts for less than 50% of cognitive impairment, with most remaining variance explained by other pathologies (eg, cerebrovascular disease, TDP-43, and α-synuclein).[4,5] Post hoc analyses of Clarity AD suggest that benefit may also differ based on age, sex, and apolipoprotein E (*APOE*) genotype, although these observations should be interpreted with caution because they represent nonrandomized groups and were largely not statistically significant. We also hypothesize, based on TRAILBLAZER data, that individual responses to amyloid lowering may differ based on baseline tau PET staging.[2] As lecanemab enters clinical practice, we need to examine the characteristics of more and less robust responders, thus propelling the field toward a precision-medicine approach.

Any enthusiasm for the potential therapeutic benefits of lecanemab should be tempered by the risks. Amyloid-related imaging abnormalities (ARIAs) were twice as common in the lecanemab group than in the placebo group (21.5% vs 9.5%). Most ARIAs were asymptomatic (78%) and detected on magnetic resonance imaging (MRI) scans, but 2.8% and 0.7% of participants in the lecanemab group had symptomatic ARIAs with edema and ARIAs with hemorrhage, respectively, whereas 0% and 0.2% of participants in the placebo group had symptomatic ARIAs with edema and ARIAs with hemorrhage, respectively. As with similar drugs, risk is related to *APOE*, with ε4 homozygotes at highest risk. While death rates did not differ in the 18-month

study (0.7% vs 0.8%), to date 3 deaths have occurred among patients who received anticoagulants or who received thrombolytics for acute stroke.[6] Independent of antibody treatment, cerebral bleeding is not rare in patients with AD due to the high prevalence of cerebral amyloid angiopathy, which gives many clinicians pause in treating these patients with medicines that reduce hemostasis.[7] This will be even more important with lecanemab, and appropriate use guidelines will need to carefully address this risk.

Notwithstanding lecanemab's actual risks, there has been a tendency to lump all ARIAs into adverse effects of brain swelling and bleeding. To a neurologist, swelling connotes mass effect that is emergent. However, in most lecanemab-treated cases, swelling is asymptomatic with subtle signal changes detected on surveillance fluid-attenuated inversion recovery MRI, consistent with extracellular fluid without obvious mass effect. Similarly, bleeding (ie, ARIAs with hemorrhage) typically consists of asymptomatic microbleeds and rarely involves macrohemorrhages. Nevertheless, fatalities during OLE raise the question of whether anticoagulants and related medications should be considered contraindications to lecanemab; the current FDA label contains clear information about this but stops short of considering it a frank contraindication. While the small number of cases with serious consequences raise important concerns, we need to agree on reasonable language to communicate these more common adverse effects. It is not unusual for cerebral edema to be associated with aggressive treatment for other neurologic diseases, such as focal radiation therapy or chemotherapy. Many patients, families, and clinicians would argue that AD is a devastating illness like other serious medical illnesses where we accept risks for potential benefits of therapy.

As clinicians who take care of many patients with AD who fit Clarity AD study criteria, we feel these patients and families should have access to this drug. Accessible treatment requires full approval by the FDA and other regulatory agencies, as well as payer coverage, including the US Centers for Medicare & Medicaid Services (CMS). In 2022, the CMS rendered a National Coverage Decision for the class of anti-Aβ monoclonal antibodies, limiting reimbursement to patients in CMS-approved studies. This decision needs to be revisited. Coverage decisions should not be made for the entire class but should evaluate each drug on its own merit given clear differences between antibodies in biological effects and clinical efficacy.

Reflecting on our own experiences as clinician-scientists in the AD field for 2 decades, we marvel at the tremendous progress in developing in vivo biomarkers of AD pathology and biologically potent therapeutics. Progress has not been linear, and treatment trials have been fraught with setbacks. Yet with Clarity AD, we believe the tide is turning, and a new era of AD care is surfacing—an era in which an accurate clinical diagnosis will be made with high confidence at an early stage with the support of biomarkers, opening the door to molecular-specific therapies. Although much work remains, lecanemab's success represents a major milestone for the field, and a moment of great hope for patients and families living with this devastating disease.

ARTICLE INFORMATION

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