Antiamyloid Antibody Therapy in Alzheimer Disease

The saga continues for development of antiamyloid monoclonal antibodies, aducanumab, lecanemab, donanemab, and gantenerumab for Alzheimer disease.

By Babak Tousi, MD

The aggregation of amyloid beta (Aβ) into insoluble plaques is a hallmark of Alzheimer disease (AD) pathology and the idea of amyloid accumulation triggering the cascade of neurodegenerative disease in AD, or the amyloid hypothesis, has dominated the field over the past 2 decades.[1] The proposed amyloid cascade begins with the breakdown of amyloid precursor protein (APP), releasing monomers that bind to each other to form oligomers that, in turn, aggregate into protofibrils and fibrils, which eventually buildup into amyloid plaques. Consequently, much research on disease-modifying therapies (DMTs) for AD has been focused on interrupting this cascade. Mechanisms of action for agents being studied in clinical trials range from interruption of Aβ production to removal of Aβ from the brain by passive immunotherapy with monoclonal antibodies (MAbs). The amyloid hypothesis gained some strength after initial positive results for the antiamyloid MAb aducanumab were seen in a phase 1b study after there had been a series of failed trials for other antiamyloid MAbs.

Aducanumab is 1 of 4 agents in the latest generation of antiamyloid MAbs and was approved by the Food and Drug Administration (FDA) via the Accelerated Approval Program. This approval—the first of a potential DMT for AD—was based on biomarker endpoint results rather than clinical outcomes.[2] The other 3, donanemab, lecanemab, and gantenerumab are being evaluated in phase 3 studies with results expected in late 2022 and early 2023. Gantenerumab was previously evaluated in a phase 3 trial at a lower dose of active medication. A biologic license application (BLA) has been submitted to the FDA requesting approval via the Accelerated Approval Program, although the phase 3 trial of lecanemab is not expected to be completed until late 2022.[3]

The approval of aducanumab via the Accelerated Approval Program triggered a heated discussion in the AD field regarding this class of medications. Questions were raised about the expected benefits, appropriate patient, logistics of implementing therapy, and risk-benefit ratio. A class of medications may work similarly to treat the same condition, but each has unique characteristics. New drugs in the same class are rarely compared with each other. If more antiamyloid MAbs are approved, there will be some parameters in common for making a rational choice among these drugs of the same class. This review covers 4 such areas, including pharmacodynamics, pharmacokinetics, tolerability, and costs. The strength and the quality of the evidence for effectiveness vary between drugs and are limited at this time.

Although all clinical trials of these 4 antiamyloid MAbs enrolled participants who were early in the course of AD (ie, with mild cognitive impairment [MCI] or mild AD), inclusion criteria were not the same. Participants in aducanumab and lecanemab trials had to have biomarker evidence of amyloid pathology, and the trial for donanemab required having biomarkers for both amyloid and tau pathology while excluding those with a high level of tau seen on positron emission tomography (PET) imaging with a tau marker.

Pharmacodynamic Properties

Target

All 4 of the antiamyloid MAbs discussed target aggregated forms of Aβ (Table). Lecanemab targets the soluble

TABLE. BINDING OF ANTIAMYLOID MONOCLONAL ANTIBODIES TO DIFFERENT SPECIES OF AMYLOID β

Antibody	Targets	Off-target binding
Aducanumab	Plaque	Fibrils, none to oligomer
Donanemab	Plaque	None
Gantenerumab	Plaque	Fibrils>protofibrils, monomers
Lecanemab	Protofibril	Protofibrils, oligomers>fibrils, monomers

protofibril,[4] and has been granted a breakthrough therapy designation by the FDA. The other 3 MAbs discussed all target amyloid plaques. Aducanumab is a human IgG1 MAb, targeting amino acids 3 through 7 of the Aβ peptide, and is specific for amyloid plaque.[5] Donanemab is directed at an *N*-terminal pyroglutamate Aβ epitope present only in established amyloid plaques and thus shows no off-target binding to other Aβ species.[6] Gantenerumab targets both the *N*-terminal and mid-domain Aβ epitopes on amyloid plaque and does not bind avidly to soluble Aβ.[7]

Very weak binding to different Aβ species has been observed for lecanemab, aducanumab, and gantenerumab.[8] Aducanumab showed no binding to oligomers. Gantenerumab and lecanemab, in contrast, displayed binding to oligomers and protofibrils with higher relative binding strength to protofibrils. Gantenerumab had higher affinity for fibrils vs monomers and protofibrils. Lecanemab bound to fibrils, but much less than it bound to protofibrils.[8]

Efficacy in Clinical Trials

Results for the efficacy of the MAbs discussed come mainly from phase 1b and 2 studies. Although clinical efficacy should be interpreted cautiously, all 4 antiamyloid MAbs have demonstrated the ability to clear amyloid plaques when measured in Centiloid units (CL).[9] There has been considerable variability in the quantitative outcomes of tracer retention in amyloid PET data across different studies. The Centiloid scale converts standardized uptake value ratio (SUVR) data from different PET ligands into a common, 100-point scale. Using the Centiloid scale, 0 represents the mean amyloid PET signal from adults, mean age 31.5± 6.3 (range 22-43), without cognitive impairment, and 100 represents the mean signal from people with AD.[9] Depending on the ligand used to measure amyloid load, 19 to 24 CL has been reported as an appropriate cutoff level for amyloid positivity/negativity based on comparing antemortem PET imaging levels with postmortem histopathologic assessment of amyloid plaques.[10-12]

Aducanumab. A dose-dependent reduction in amyloid plaques occurred with doses up to 10 mg/kg aducanumab every 4 weeks This dose removed 44 CL by 26 weeks and 57 CL by 54 weeks, resulting in a level of 27 CL.[13] In 2 parallel phase 3 trials of aducanumab, the Clinical Dementia Rating (CDR) scale was used as the primary outcome measure for participants who had early AD. Both studies were terminated earlier due to futility after 50% of participants had been enrolled for 78 weeks. Further data collection and analysis after the trials were terminated, however, showed that, in 1 of the trials, there had been a statistically significant benefit on CDR-Sum of Boxes (CDR-SB) with 10 mg/kg every 4 weeks dosage of aducanumab. At 78 weeks, in the trial that had shown benefit on CDR-SB, amyloid was reduced from a baseline mean of 64 to 21 CL when a 10 mg/kg every 4 weeks dose was administered. In the trial that showed no benefit on CDR-SB, at 78 weeks, less amyloid was removed, and amyloid load was reduced to only 37 CL.[14]

Gantenerumab. Initial phase 3 trials of gantenerumab used a much lower dose (maximum 225 mg every 4 weeks) than is currently being evaluated. The 2 trials were terminated owing to futility, although 1 was converted to a higher-dose open-label study.[14,15] In this open-label study, gantenerumab dose was titrated from 225 mg to 450 mg, 900 mg, or 1,200 mg for participants carrying the apolipoprotein E (ApoE) ε4 allele. For noncarriers of ApoE ε4, dose titration was 300 mg, 600 mg, or 1,200 mg. After 2 years of treatment with titration to higher doses, 51% of participants had Aβ plaque levels below 24 CL, the Aβ positivity threshold.[15]

Lecanemab. A phase 2 study of lecanemab in participants with early AD (MCI or mild dementia) used an adaptive Bayesian design that allowed for rapid decision about the most effective dose after 12 months of treatment with lecanemab or placebo, with an open-label extension in which participants received higher doses of lecanemab for 18 months. This trial design allowed all participants to reach at least 90% of the most effective dose, with most eventually receiving 10 mg/kg monthly or biweekly.[15] During the trial, some adjustments were made for safety (ie, avoiding amyloid-related imaging abnormalities [ARIA]) at the request of European regulatory agencies. These adjustments were to stop including participants who were homozygous for ApoE ε4 and to exclude people who were heterozygous for ApoE ε4 from treatment at the higher dose of lecanemab. These adjustments created an imbalance of people who were ApoE ε4 carriers in the group of participants receiving 10 mg/kg biweekly, which had been identified as the most effective dose.

The Bayesian model had defined success as an 80% likelihood of a 25% difference in cognitive decline between people treated with lecanemab vs placebo in the first 12 months of the study. The cognitive outcome measure used was the AD Composite Score, which combines 4 AD Assessment Scale–cognitive subscale (ADAS-cog) items, 2 Mini-Mental State Examination (MMSE) items, and all 6 CDR-SB items. Although differences were observed in those treated with lecanemab vs placebo, these did not reach statistical significance as defined by the Bayesian model.[16]

Brain amyloid levels were reduced below 24 CL, the cutoff for amyloid positivity, in 81% of participants. Differences in Aβ plaque levels were maintained for approximately 2 years in the long-term extension study. In all participants, Aβ plaque reduction was observed at 3 months in the open-label extension without a need for dose titration. An increase in $A\beta_{42/40}$ ratio during treatment correlated with PET amyloid levels and clinical outcomes during the treatment phase in both the first

12 months and the open-label period. In contrast, during the gap between the first 12-month study and the open-label period, when lecanemab was not administered, plasma $A\beta_{42/40}$ ratios began decreasing, which is an early indicator of Aβ plaque accumulation. This correlated with clinical decline observed after treatment discontinuation, suggesting that continued treatment in early AD may be beneficial.[17]

Additionally, the clinical treatment difference in participants with early AD was maintained after discontinued dosing over the 24-month gap period, suggesting potential disease-modifying effects. Clinical decline, however, does continue over the gap period and biomarker data show disease progression and buildup of amyloid plaque will continue.

The phase 3 CLARITY trial[a] of 10 mg/kg lecanemab biweekly is ongoing with a primary outcome measure of change on the CDR-SB.

Donanemab. Participants in a phase 2 study of donanemab had early AD with positive findings on PET for both amyloid and tau. Donanemab was given 10 mg/kg every 4 weeks for 3 months, and then 20 mg/kg monthly for 15 months. At 24 weeks, 40% of participants were amyloid negative (<24 CL), and at 76 weeks, 67.8% were amyloid-negative.[18] At week 76, treatment with donanemab vs placebo resulted in a 24% decrease vs a 6% increase from baseline in the biomarker plasma p-tau217, which is thought to correlate with AD progression.[19] On the primary outcome measure, the integrated Alzheimer Disease Rating Scale (iADRS), there was a 32% slowing of AD progression, meeting the prespecified primary outcome.[20] The iADRS measure both cognition and function.

Pharmacokinetics

Route and Frequency of Administration

Aducanumab, donanemab, and lecanemab were all administered intravenously in clinical trials; gantenerumab was administered subcutaneously. A subcutaneous formulation of lecanemab has been developed and is planned to be offered to participants in open-label extensions of the ongoing phase 3 trial. The development of a subcutaneous formulation of aducanumab has been suspended.

Different formulations have different cost-benefit profiles, and individuals may have preferences for different routes of administration. Subcutaneous formulations can be self-administered or given by caregivers, which can decrease dependency on health care providers, reduce patients' stress, and reduce costs. The route of administration should be considered in shared decision-making if the ability to choose amongst these treatments comes to fruition.

With lecanemab, the goal is to have comparable efficacy with an average subcutaneous dose equivalent to 10 mg/ kg biweekly given intravenously and lower predicted incidence of ARIA-edema (ARIA-E) due to a lower C_{max} with a subcutaneous formulation.

Aducanumab and donanemab are given monthly and gantenerumab and lecanemab are administered every 2 weeks. Lecanemab is the only antiamyloid MAb discussed that does not require titration.

Safety and Tolerability

ARIA describes imaging abnormalities associated with antiAβ MAb treatment and is the critical adverse event of Aβ-lowering therapies that needs to be monitored and managed. There are 2 types of ARIA: 1) ARIA-E represents parenchymal or pial edema and 2) ARIA-hemorrhage (ARIA-H) hemosiderin deposition in the form of superficial siderosis or hemorrhage.[21] The rate of amyloid removal does not necessarily correlate to the incidence of ARIA-E.

In the phase 1b trial, 47% of people treated with 10 mg/ kg aducanumab every 4 weeks had ARIA-E compared with 5% of those who received placebo. During phase 3 trials, 35% of people treated with 10 mg/kg aducanumab every 4 weeks had ARIA-E, and a 6-month titration period was used to reduce the incidence of ARIA-E.[14]

In clinical trials, treatment with donanemab also resulted in a high incidence of ARIA-E (27%), and one-fifth of those who developed ARIA-E had clinical symptoms of this adverse event. Approximately 90% of participants in this study were found to have developed antibodies to donanemab.[18]

With lecanemab, the rate of ARIA was lower, at approximately 10% overall, and 60% of ARIA-E occurred during the first 3 months of treatment.

In the initial phase 3 studies of gantenerumab, the incidence of ARIA-E varied from 24% to 39%, with ApoE ε4 carriers having a higher incidence than non-carriers.

The ARIA-E rate in the lecanemab trial was modest, at about 10% overall, with 60% occurring within the first 3 months of treatment and most MRI findings of ARIA-E resolving within 4 to 16 weeks. It must be considered, however, that most carriers of the ApoE ε4 allele, which increases the risk of ARIA-E, did not receive the maximum dose of 10 mg/kg every 2 weeks. Exposure-response modeling suggests that incidence of ARIA-E is primarily driven by maximal concentration of the treatment and higher exposure correlates with greater amyloid reduction and clinical effects.[22,23] All participants entering in the open-label study of lecanemab, including the 69.4% who were ApoE ε4 carriers, received the higher dose, however, and pooled data showed that incidence of ARIA-E was 42.9% in people who were homozygous for ApoE ε4, 7.6% for heterozygous ApoE ε4 carriers, and 7.1% for ApoE ε4 noncarriers, with a 13.1% overall incidence. The overall ARIA-E rate was 9.7% (20/206) among participants treated with lecanemab 10 mg/kg biweekly.[23]

[a] A Study to Confirm Safety and Efficacy of Lecanemab in Participants With Early Alzheimer's Disease (Clarity AD) (NCT 03887455).

Cost

After months of concern raised by the community and advocacy groups, the list price of aducanumab was lowered to $28,200 for the annual maintenance dose (10 mg/kg) for individuals of average weight (74 kg).[24] The actual cost of administering intravenous medication, however, goes beyond the cost of the drug and includes infusion-related administration costs and nursing time. MRI monitoring for ARIA-E and increased monitoring, if it is detected, will also increase costs.

The list price for the other discussed MAbs will not be announced unless and until these are approved by the FDA. Both gantenerumab and lecanemab have subcutaneous formulations that can reduce related costs and may be more convenient and tolerable for many patients and care partners. There is a concern that subcutaneous administration may cause higher immunogenicity risk, although that may not be universally valid for all medications.[25-27]

Risk-Benefit Analysis

True risk-benefit analysis will not be achievable until clinical benefit is proven for any of the treatments in this drug class. At that point, the debate will shift to the magnitude of benefit vs risks and the identification of the patients most likely to benefit from treatment. The appropriate patient for treatment is at an early stage of AD (ie, MCI or early dementia), similar to the recruited participants in phase 2 and 3 clinical trials of the discussed antiamyloid MAbs, and with positive findings for brain Aβ with PET or Aβ measurement in cerebrospinal fluid (CSF). Previously obtained PET scans that are positive for Aβ from previous studies should be accepted rather than requiring a new positive scan. ApoE genotyping can be done for those with unknown ApoE ε4 status, which can be helpful when discussing the risk and expected benefits because ApoE ε4 carriers, especially those who are homozygous for ε4, have a higher incidence of ARIA than noncarriers.

There will be barriers to conducting testing for Aβ confirmation, including insurance coverage of amyloid PET scan or even evaluation of CSF or plasma for AD biomarkers. Recent evidence of plasma AD biomarkers (eg, p-tau217 and p-tau181) is gaining momentum as a potential surrogate marker of AD.[28]

In recent years, new information has emerged suggesting that many other age-related mechanisms also contribute to neurodegeneration, which affects people differently. Thus, it is unlikely that any of the antiamyloid MAbs will cure AD. The next phase of research should focus on finding a promising drug or combination therapy that targets multiple contributing pathologies. ■

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Disclosures

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