Lecanemab: A Second in Class Therapy for the Management of Early Alzheimer's Disease

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Abstract

The Food and Drug Administration granted traditional approval of lecanemab for the treatment of Alzheimer's disease (AD). Lecanemab is a humanized anti-amyloid monoclonal antibody directed towards Aβ protofibrils. Lecanemab is the only drug that targets Aβ soluble protofibrils and has shown statistical differences in mild AD or mild cognitive impairment. In its landmark phase III trial, lecanemab was shown to slow the progression of clinical decline, and a reduction in amyloid protein accumulation. The difference in mean CDR-SOB score improvement between the treatment and placebo groups was -0.45, of which the clinical significance could be argued. Amyloid burden was also considerably reduced as well, but the true clinical consequence of this reduction remains to be seen. This beneficial impact on daily living is offset by rare but serious side effects including amyloid-related imaging abnormalities (ARIA) causing cerebral edema (ARIA-E) or cerebral microhemorrhages or hemosiderin deposits (ARIA-H). Benefits of therapy must be considered against the risk of cerebral microhemorrhages and edema. Affordability must also be taken into consideration. The current estimated yearly cost for twice monthly lecanemab infusion is $26,500. In addition to the significant cost challenges, the frequent infusions may pose concerns related to access. Additional agents within this class are in the pipelines with possibly increased efficacy or decreased adverse events.

Keywords: alzheimer's disease, monoclonal antibodies, lecanemab

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Introduction

Alzheimer's disease (AD) is one of the most common forms of dementia worldwide and affects an estimated 5.7 million patients in the United States alone.1 Healthcare costs in 2018 related to hospitalization, long term care and hospice services for AD was $277 billion (U.S. dollars). Due to the cost along the spectrum of AD progression, disease modifying agents are an attractive proposition to slow down this process. The incidence and prevalence of AD is expected to grow in the future and may lead to increased strain on caregivers and the healthcare system at large. In turn, the potential for increased financial burden on healthcare systems and caregivers cannot be understated. Therefore, it is important to weigh the therapeutic benefit of novel agents against true cost. Markov modeling is one method to assess the clinical and financial impact of a potential intervention along disease state severity.2 Specifically, Markov models used in the healthcare setting can be a tool to help with the decision-making process for formulary addition of disease modifying agents such as monoclonal antibodies targeting AD pathology.

AD is thought to be due to several genetic and/or environmental risk factors, with an estimated 70% of risk factors being associated with genetic or inherited risk.3 The highest recognized genetic risk factor is due to the apolipoprotein E gene (ApoE) and its associated polymorphisms ε2, ε3 and ε4. Apolipoproteins are responsible for transporting lipids and cholesterol in the periphery as well as in the central nervous system.4

Impaired cholesterol or lipid metabolism is thought to be one of the hallmark pathways for downstream neurodegenerative processes in AD. Carriers of ApoE (ε4 > ε3 > ε2) have a higher risk of amyloid deposition, increased Aβ production, and reduced Aβ clearance.5 The highest risk of development of AD is with ε4 homozygotes, with heterozygotes having a lower risk of AD development. The constellation of symptoms associated with presentation and progression of AD is related to accumulation of extracellular amyloid plaques and neurofibrillary tangles (NFT). The primary theory for AD pathology is the amyloid hypothesis and is associated with amyloid beta (Aβ) deposits and aggregation into plaques. Accumulation of NFTs and Aβ plaques lead to a pathological pattern of progressive neuronal cell death and loss of cognitive function.

Previously approved Food and Drug Administration (FDA) treatment options for AD are focused on symptom management.6 Traditionally, therapeutic agents for AD include drugs that are primarily from two classes of medications: acetylcholinesterase inhibitor (AChEI) and N-methyl-D-aspartate (NMDA) receptor antagonist (Table 1).7-16 AChEI medications such as donepezil, rivastigmine, and galantamine target loss of cholinergic activity in the brain and are clinically proven to reduce the symptoms of mild to moderate AD based on validated cognitive function tests such as the AD Composite Score (ADCOMS), Mini-Mental State Exam (MMSE) or Alzheimer's Disease Assessment Scale – cognitive subtype (ADAS-cog). Patients taking galantamine or rivastigmine may have more difficulty reaching target doses based on adverse

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drug effects than patients taking donepezil. Memantine is a NMDA receptor antagonist and modulates glutamate activity. Modulating glutamate activity reduces aberrant neuronal overexcitation seen in AD. Memantine shows initial benefit on cognitive function and symptoms but may have limited long-term benefit on symptoms.

More recently, clinical trials for AD have utilized the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SOB) to assess global cognitive outcomes. This assessment tool is favored for its ability to track precise changes over time.17 The CDR-SOB assessment tool was validated by the Texas Alzheimer's Research Consortium Study. CDR-SOB scores for dementia staging may aid in delineating mild cognitive impairment (MCI) from very early AD. The CDR-SOB tool was developed by Washington University and is scaled from 0 to 18 points. Categories assessed include memory, orientation, judgement, and problem solving, community affairs, home and hobbies, and personal care. The severity of impairment is scored from 0, 0.5, 1, 2 and 3, with 3 indicating severe impairment. The sum of these categories correlates to the AD staging category. A score of 0.5 to 2.5 is staged as questionable impairment, 3.0-4.0 as very mild dementia, 4.5-9.0 as mild dementia, 9.5-15.5 as moderate dementia, and 16.0-18.0 as severe dementia.

Recognition and detection of incremental changes in cognitive function in patients suspected of, or diagnosed with, AD using cognitive scoring analyses reflects the downstream effects of neuropathological changes. Detection of Aβ serum or cerebral spinal fluid (CSF) levels with clinical correlation may offer an opportunity to treat the neurocognitive decline at an earlier stage.18 Furthermore, development of anti-amyloid monoclonal antibodies has led to the emergence of pharmacotherapeutic pathways to attempt to slow the trajectory of AD.19 In January 2023, the Food and Drug Administration (FDA) granted accelerated approval of lecanemab for the treatment of mild AD with full approval given five months later.20 The applicability and interpretation of clinical trials for lecanemab as it relates to clinical practice will be discussed here.

Methods

A literature search was conducted on PubMed using the search terms "BAN2401" and "lecanemab." Studies were limited to clinical trials with human subjects, and the search was conducted in November 2023 with a search period of ten years. Ten articles resulted as follows: phase I dose finding trial, three phase II trials, a statistical analysis of a phase II trial and another of a phase III trial, one major phase III trial, and finally one trial on a quality-of-life analysis based on phase III trial results. Two trials were excluded, one for being a review article and another due to lack of relevance to the study medication.

Results

Pharmacology and Pharmacokinetics

Lecanemab is a humanized anti-amyloid monoclonal antibody directed towards both soluble and insoluble forms of Aβ.21 Specifically, lecanemab has a high affinity for oligomers, protofibrils and fibrils, with a thousand-fold higher selectivity for protofilbrils than monomers. Protofibrils induce an inflammatory process through the initiation of toll-like receptors and microglial activation.22 Due to this pathology, protofibrils have been proposed as being the primary toxin in AD. Lecanemab is currently the only anti-amyloid that preferentially binds to protofibrils; thus blocking both the ongoing formation of Aβ plaque and reducing inflammation contributing towards AD.

Dosed at 10 mg/kg (total body weight) every two weeks intravenously (IV), lecanemab requires an infusion time of one hour through a 0.2-micron IV filter tubing. 21 Phase I clinical trial data for single ascending doses (SAD) and multiple ascending doses (MAD) of 10 mg/kg every two weeks showed first-order elimination kinetics. The 10 mg/kg MAD arm achieved steady state after the third dose. Serum levels of Aβ increased during treatment but subsequently declined after treatment was discontinued in the MAD arm. In the 10 mg/kg biweekly MAD arm, lecanemab had a mean half-life of 5.3 days after the final dose. Lecanemab is eliminated through proteolytic cleavage and does not rely on hepatic metabolism or renal elimination. During a study period of 18 months, anti-drug antibodies were observed in ~25% of patients. The clinical impact of these antibodies is not yet known.

Phase I Clinical Trial

The first clinical study of lecanemab was published in 2016 by Logovinsky and colleagues.23 This phase I study focused on the safety and tolerability of BAN2401 at multiple doses while also assessing the pharmacokinetic properties of study drug. The pharmacokinetic properties were discussed in the previous section and thus will not be summarized here.

A multicenter double-blind randomized placebo-controlled study was conducted in adults at least 50 years of age with mild to moderate AD (MMSE scores 16-28) and on stable treatment regimens for AD. This was a two-part trial in which subjects were enrolled into the SAD or MAD treatment groups. Eight patients were enrolled in the SAD group of which two patients were randomized into the placebo group and six into the treatment arm. Those in the SAD group received doses of 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, and 15 mg/kg with doses administered four weeks apart. The MAD group had the same number of subjects in the treatment and placebo arms as the SAD group. Those in the MAD group received doses of 0.3 mg/kg, 1 mg/kg, and 3 mg/kg administered four weeks apart then received 10 mg/kg biweekly for seven doses. The safety of BAN2401 was evaluated at three weeks post each dose with a non-contrast brain magnetic resonance imaging (MRI) to assess for amyloid-related imaging abnormalities (ARIA) causing cerebral edema (ARIA-E) or cerebral

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microhemorrhages or hemosiderin deposits (ARIA-H). Patients in the MAD group did not receive treatment until safety of that dose was confirmed within the SAD group.

The average age amongst those enrolled in all treatment groups was about 70 years old with half the subjects identified as females. At baseline, the mean MMSE score was 23.8 in the SAD arm and 23.3 in the MAD arm. Demographic and baseline characteristics between the SAD, MAD, and placebo groups were similar. With regards to the primary outcome of safety, ARIA-E did not occur in any subjects throughout the study. Asymptomatic ARIA-H was found in two patients within the SAD group, one each in the 0.3 mg/kg dose and 1 mg/kg dose. Within the MAD group, asymptomatic ARIA-H was found in both the placebo and treatment arms. One occurrence was detected at baseline in the placebo arm. During the 1mg/kg dosing segment, new ARIA-H was discovered in two patients within the placebo arm and one within the treatment group. Other notable side effects were dizziness, fatigue, orthostasis, and sinusitis with rates of sinusitis and orthostasis only occurring in those receiving the study drug. BAN2401 was generally well tolerated across the doses studied though a major limitation is the short duration of monitoring (6 months for the SAD arm and <9 months for the MAD arm). The results of this study were utilized to guide the doses for subsequent phase 2b trials.

Phase II Clinical Trials

Following positive results from the phase I study, Swanson and colleagues conducted Lecanemab 201, the first phase II prospective study to evaluate the safety and efficacy of lecanemab at various doses in patients with early AD.24 This 18-month, multi-center, double-blind, placebo-controlled clinical trial evaluated five different arms of study drug (2.5 mg/kg biweekly, 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg monthly, 10 mg/kg biweekly) and utilized a Bayesian adaptive design in order to randomize a greater number of patients to the treatment arm most likely to be the ED90 dose, defined as the simplest regimen that achieves greater than or equal to 90% of the predicted maximum treatment impact at specified interim analyses. The primary endpoint of this study was change in baseline ADCOMS at 12 months following treatment initiation. The primary outcome was met if the Bayesian analysis found at least 80% probability that the ED90 dose attained at least 25% less clinical deterioration on the ADCOMS scale versus placebo at the 12-month final analysis.

Between December 2012 and November 2017, 854 patients received treatment (lecanemab, 609; placebo, 245) across 117 sites in several countries. Baseline characteristics were similar among all groups, expect that there were a greater proportion of males randomized to lecanemab versus placebo (54% versus 42%). The adaptive randomization Bayesian method identified two treatment arms (10 mg/kg monthly, 10 mg/kg biweekly) as potential ED90 regimens and had the greatest number of subjects randomized to each; 253 and 161, respectively, accounting for 68% of all subjects. The 10 mg/kg biweekly treatment arm was identified as the ED90 dose at the 12-month analysis; however, did not meet the primary outcome, as it exhibited 64% probability of 25% less decline on ADCOMS, which was less than the prespecified threshold of 80%. Among secondary endpoints, lecanemab did illustrate a reduction in brain amyloid PET across the 18-month treatment duration, as well as a dose-dependent reduction in clinical decline versus placebo by multiple clinical measures. Lecanemab was well tolerated, exhibiting ARIA-E incidence of <10% in the general subject pool among the two highest doses, and 14.3% in ApoE ε4-postive subjects. Other adverse events, including infusion reactions, were not significantly different between subjects receiving lecanemab and placebo. Despite not meeting the primary endpoint, the beneficial impact on several key biomarkers following 18 months of treatment confirms efficacy of lecanemab.

Following publication of the aforementioned lecanemab phase IIb clinical trial 201, a follow-up study was published by Berry and colleagues to further explicate and defend the use of Bayesian adaptive design.25 Critique of utilization of the Bayesian adaptive randomization approach included that it allows authors to modify the study design. Rather, this design allows for a dynamic understanding of each treatment arm throughout the trial, specifically, at each interim analysis, and allows analysts to predict if the trial will reach its goal. In such a dose finding study, this approach allowed for greater efficiency, quickly revealing that the lower-dose treatment arms were ineffective, and as a result, assigned a greater number of patients to the higher-dose treatment regimens overall improving the treatment of participants. The use of Bayesian design also accounts for missing data. During lecanemab 201, a regulatory authority outside the United States mandated that subjects who were ApoE ε4 carriers be dropped from the 10 mg/kg biweekly treatment arm, decreasing both the number of patients in what was expected to be the ED90 dose as well as the overall power of the trial. Bayesian modeling allows for known observations to predict future observations to account for missing data, which undoubtedly is a limitation of the study. Moreover, concerns were raised regarding the lesser number of ApoE ε4 carrier subjects in receipt of the 10 mg/kg biweekly dose, possibly impacting conclusions about lecanemab and interactions with that specific patient population. Authors explain that the benefit of the 10 mg/kg biweekly dose increased between 12 and 18 months of treatment despite many patients stopping therapy per mandate. The impact of lecanemab persisted despite stopping treatment, as these particular patients continued to perform better on ADCOMS compared to placebo.

Another study published by McDade and colleagues built upon the original lecanemab 201 phase 2 study with an open label extension (OLE) study following the core data collection period

of 18 months.26 Following core data analysis, subjects could receive open label lecanemab 10 mg/kg biweekly for up to 24 months to evaluate long-term drug efficacy. A gap period existed between the end of core data collection and re-initiation of study drug where no drug was received, on average 24 months (range 9 – 59 months). Original treatment arm assignments remained blinded; however, statistical focus was placed on two groups: patients in receipt of placebo originally, and those who received 10 mg/kg biweekly from study start. Endpoints including CDR-SOB, ADCOMS, and ADAS-Cog14 were evaluated at OLE baseline and compared at treatment conclusion. A total of 180 patients from treatment core entered the OLE study. Of those patients, 45 received placebo originally and 38 received lecanemab 10 mg/kg biweekly during the core. At the 3 month follow up following treatment discontinuation, treatment differences seen in the lecanemab groups were maintained, but the treated subjects continued to exhibit clinical decline at the same rate as placebo, suggesting the need for continuation of therapy. During the OLE period, brain amyloid was statistically significantly decreased versus OLE baseline after 3 months of treatment in patients who were originally assigned placebo or lecanemab 10 mg/kg biweekly. In patients originally on placebo during the core study, during the OLE their amyloid status converted from positive to negative as early as 3 months following receipt of study drug, with greater than 80% of patients being amyloid negative by 12 – 18 months. Both groups of subjects (newly treated with lecanemab and re-treated with lecanemab 10 mg/kg biweekly) exhibited an increase in ADCOMS, CDR-SOB, and ADAS-Cog14. Decline in brain amyloid paralleled slowing of clinical decline across different clinical efficacy scores. Authors concluded results from the core study were reproduced in the OLE, and brain amyloid reduction by use of lecanemab is associated with slowing of clinical decline, clinical benefit, and may potentially act as a disease-modifying drug.

Finally, Dhadda and colleagues reevaluated results from the lecanemab 201 study to provide confirmation of efficacy.27 Authors conducted sensitivity analyses using different statistical methods on three key secondary clinical endpoints including change in baseline in ADCOMS, CDR-SOB, and ADAS-Cog14. Statistical models utilized were disease progression model, natural cubic spline model, quadratic mixed model, and two types of mixed model for repeat measures (MMRM) including aMMRM1 and aMMRM2. Across all five additional statistical models, authors confirmed the robustness of original conclusions from the lecanemab 201 study and further confirm the drug's clinical efficacy.

Phase III Clinical Trial

The efficacy of lecanemab was evaluated in the major phase III trial, Clarity AD, whose results led to FDA approval.28 Clarity AD was an 18-month long, multicenter, double blind, placebo-controlled trial in patients with mild AD. Patients qualified for enrollment if they were 50 to 90 years old and were diagnosed with MCI due to AD or mild AD on the National Institute of Aging-Alzheimer's Association criteria. Additionally, patients had to have evidence of amyloids either through positron emission tomography (PET) scan or cerebrospinal fluid testing via lumbar puncture. The primary end point was the change in the CDR-SOB. Notable secondary outcomes include amyloid burden on PET scan and rates of ARIA-E and ARIA-H. Over 1,700 patients were enrolled with 898 receiving the study medication and 897 in the placebo arm. The average age between the two groups was 71 years with approximately half being female. At baseline, the mean CDR-SOB score in the lecanemab group was 3.17 vs 3.22 in the placebo group. In a modified intention to treat analysis the mean change in CDR-SOB score at 18-months was 1.21 vs 1.66 in the lecanemab group (n=859) and placebo group (n=875), respectively ($p<0.001$). The least squares mean change of -0.45, was found to be statistically significant as well (95% CI –0.67 to –0.23, $p<0.001$). A considerable change was found with regards to amyloid burden in the treatment group. The mean change in amyloid burden in the lecanemab group was –55.48 centiloids vs 3.64 centiloids in the placebo group ($p<0.001$). Other notable outcomes, particularly related to ARIA, were reported as well. The safety analysis including all patients enrolled in the trial. Rates of ARIA-H were as high as 17.3% in the treatment group and 9.0% in the placebo group, resulting in a number needed to harm of 12. ARIA-E occurred in 12.6% of the lecanemab group vs 1.7% in the placebo group. The most common reported adverse effect was infusion related reactions with higher rates in the lecanemab group.

The efficacy data was further analyzed through the employment of the Bayesian method by Costa and colleagues.29 The re-analysis failed to confirm the statistical significance of the primary outcome from the Clarity AD trial. In fact, the results of this analysis suggested the placebo arm performed better than the treatment arm, disputing the results Clarity AD.

Results from the Clarity AD trial were further analyzed to assess the effects of lecanemab on quality-of-life, specifically looking at the EQ-5D-5L and QOL-AD scores.30 Designed by the EuroQol Group, the EQ-5D-5L is a validated tool which measures the following parameters, mobility, self-care, daily activities, pain and anxiety or depression.31 Each parameter has five levels of severity, 1 being no problem to 5 being extreme problems. The result of this survey is represented by a 5-digit number which is used in a scoring algorithm corresponding to an index score, ranging from -0.59 to 1 (1 being best health state). Additionally, a visual analog scale (VAS) of 0 (worse health state) to 100 (best health state) is used for the patient to identify their current state of health. The QOL-AD is an interviewer led scoring tool evaluating various physical, social, emotional and financial aspects of daily life.32 A score of 1 meaning poor state and score of 4 being excellent state. The sum of all scores is the total score with a maximum possible score of 52.

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At baseline, the placebo group had an EQ-5D-5L (VAS) and a QOL-AD score of 81.4 and 39.1, respectively. Those in the lecanemab group had a baseline score of 82.2 for EQ-5D-5L (VAS) and 39 for the QOL-AD score. At the end of 18 months, the adjusted mean change in EQ-5D-5L was 2.07 (p=0.00383) between the two groups, favoring lecanemab. This correlated to a slower functional decline by 49% with treatment. When broken down into the five parameters, the difference was primarily led by an improvement in anxiety or depression and in usual activities. Similar results were seen with the QOL-AD scores with an adjusted mean treatment difference of 0.657 (p=0.00231) and a slower decline in function by 55.6% with lecanemab.

Discussion

The study of medications targeting Aβ proteins has been on-going for years with few trials ever culminating into phase III studies with significant positive outcomes. Lecanemab is the only drug that targets Aβ soluble protofibrils and has shown statistical differences in mild AD or MCI. In its landmark phase III trial, lecanemab was shown to slow the progression of clinical decline, evaluated using CDR-SOB scores, and a reduction in amyloid protein accumulation. While protein burden does not correlate to severity of the disease, statistical significance was found in the change in CDR-SOB score. The difference in mean CDR-SOB score improvement between the treatment and placebo groups was -0.45. On a scoring scale of 0 to 18, the difference of –0.45 may be the difference between memory loss that interferes with daily activities versus benign forgetfulness. The clinical significance of this could be challenging to quantify, especially with the Bayesian re-analysis refuting the statistical significance.29 To better assess these benefits, the manufacturer performed a simulation model using data from Clarity AD.33 This model predicted that in mild AD or mild MCI, lecanemab in addition to standard of care could result in a mean delay in progression to AD dementia of 2.95 years.

This impact on daily living is offset by a rare but serious side effect of ARIA-E and ARIA-H. Amyloid plaques along the cerebral vessel wall contribute to vascular dysfunction and vascular wall weakness.34 Mechanistically, reduction of amyloid burden would expose weakened vascular walls and contribute towards blood vessel rupture. The Clarity AD trial showed lecanemab was able to decrease large burdens of amyloid which may explain rates of microhemorrhages. A case report was published after the release of the Clarity AD trial results of a patient with multiple cerebral hemorrhages after receiving intravenous tissue plasminogen activator (t-PA). While this patient was homozygous for the ApoE e4 allele, the risk of hemorrhagic stroke should be considered by vascular neurologists in all patients receiving lecanemab.35 Rates of ARIA-H were higher in patients concurrently taking antiplatelet or anticoagulants, thus lecanemab should be avoided or used cautiously in patients on those agents.36

Amyloid proteins can also trigger cellular apoptosis and an inflammatory response and subsequent cerebral edema. Significantly higher rates of ARIA-E and ARIA-H mandates the need for routine imaging, ideally through MRI, which can be cost prohibitive. Evaluation of amyloid burden was performed using PET. Access to such technology outside of the clinical trial setting is uncommon, questioning the feasibility of routine monitoring for amyloid burden and if there is any clinical significance in such monitoring.

The most comparable medication on the market is aducanumab, which was granted accelerated approval by the FDA in 2021.37 Aducanumab, a monoclonal antibody, is highly selective for aggregate forms of Aβ.38 In the EMERGE trial, aducanumab resulted in a mean change from baseline in CDR-SOB score of –0.39 (95% CI, -0.69 to –0.09), favoring aducanumab. Like lecanemab, aducanumab significantly reduced Aβ burden.39 These benefits were offset by high rates of ARIA-E and ARIA-H. ARIA-E occurred in >30% of patients receiving aducanumab compared to 2% in the placebo group. Rates were higher in subjects identified as ApoE ε4 carriers. The primary outcome was not significant in the ENGAGE trial, which was published concurrently with EMERGE. Both studies were halted early due to a futility analysis.

While these lecanemab and aducanumab have not been compared in a head-to-head trial, lecanemab was associated with lower rates of ARIA-E in the ClarityAD (12.6% lecanemab vs 1.7% placebo) trial versus aducamumab in both the EMERGE (35% high dose aducanemab vs 2% placebo) and ENGAGE (36% high dose aducanumab vs 3% placebo) trials.28, 39 This difference may be explained by their primary Aβ protein targets. Unlike lecanemab, aducanumab removes existing amyloid plaques while the primary mechanism of lecanemab is to prevent the formation of such plaque. As mentioned previously, vessels walls can become less stable with removal of existing Aβ plaque, potentially explaining the higher rates of ARIA with aducanumab. Higher affinity for the Aβ precursor, protofibrils, may also explain the statistical significance in the mean change in CDR-SOB found with lecanemab but not found with aducanumab.

Cost and Accessibility

In March 2023, the Veterans Health Administration released notification that it will provide coverage of lecanemab for veterans meeting criteria.40 The Centers for Medicare and Medicaid Services have announced their agreement to cover treatment for qualified participants once the FDA grants full approval of lecanemab through the traditional pathway.41 In July 2023, the FDA granted full traditional approval for lecanemab for adults with AD.42 The makers of lecanemab have also announced a subcutaneous version of lecanemab to be in the pipelines which may aid in the accessibility of treatment for patients with transportation or geographic

obstacles. The current estimated yearly cost for the twice monthly lecanemab infusion is $26,500.43 This does not include neuroimaging, biomarkers/analysis, infusion center costs, or any additional costs to the patient.

Estimating the overall utility of agents on a cost-efficacy basis relies on several subjective and objective outcomes. Predictive models for cost efficacy are one method that has been suggested to assist with the decision-making process.44 By accepting the use of assumed values, modeling cannot completely account for all the potential "real-world" scenarios of patients across the spectrum of disease progression. Recently, The Institute for Clinical and Economic Review (ICER) used Markov modeling to assess cost-effectiveness of formulary addition of lecanemab.45 ICER's expert panel suggested that current evidence was not sufficient to balance the potential cost of lecanemab against standard of care. The estimated total cost of lecanemab against standard of care was significantly higher. Recent publications used similar modeling of a hypothetical APOE gene therapy to assess maximal cost-effectiveness against quality-adjusted life-years (QALY). This strategy has been criticized as potentially problematic due to its methodology. Therefore, it may be more prudent to adopt institutional best-use strategies on an individualized approach to different therapeutics to help with cost-containment, while using cost-efficacy modeling as a tool for assistance in the larger decision-making process, rather than the sole determining factor.

Future therapies

Multiple therapeutic mechanisms of action for reduction in AD burden have been evaluated in clinical trials. Previously or currently investigated therapeutic targets include BACE-1 inhibitors, γ-secretase inhibitors, passive immunotherapy agents, anti-tau protein antibodies, and anti-amyloid agents like lecanemab. Selected disease-modifying biologics of interest include remternetug, gantenerumab, and donanemab.46

Remternetug is a monoclonal antibody that targets Aβ plaques.47 Remternetug can be administered as either a subcutaneous injection or intravenous infusion.48 This agent is currently being evaluated in a placebo-controlled, phase III study, TRAILRUNNER-ALZ1, with a primary outcome of amyloid plaque clearance. Investigators have an anticipated primary completion date of October 2023. Interim trial data from an ongoing phase I trial showed positive results in the reduction of amyloid positivity in a dose-related fashion.49

Gantenerumab is an anti-amyloid antibody with high affinity to Aβ fibrils investigated in clinical trials for reduction of cognitive decline, reduction of amyloid plaques, and prevention of cognitive decline.50 Use of gantenerumab in clinical trials was suspended by the manufacturer due in part to a pre-planned analysis of the GRADUATE I and II trials showing futility.51, 52 The entirety of the GRADUATE I & II phase III trials were published on November 16th, 2023.53 Administered as a subcutaneous injection, this agent could reduce barriers regarding accessibility. Unfortunately, as expected, no difference was found in the primary outcome of the mean difference in CDR-SOB scores from baseline to the end of the study period in GRADUATE I (-0.31, p=0.1) and GRADUATE II (-0.19, p=0.3). Of interest, these trials excluded patients on anticoagulation but had overall ARIA-H rates of 22.9% in the treatment group versus 12.3% in the placebo group. Surprisingly, these rates were slightly higher than that of Clarity AD (17% treatment group vs 9% placebo). It is unknown if rates of ARIA-H would have been significantly higher in those on anticoagulation and gantenerumab or if the use of such agents would have made minimal difference in ARIA-H rates. Due to the futility of the GRADUATE I and II trials, the manufacturer has reformulated gantenerumab in combination with their brain shuttle technology to increase transport across the blood-brain barrier.54 This reformulated agent, RG6102, is currently in phase I and II trials.

Donanemab is an anti-amyloid antibody poised to be the third agent in this drug class to come on the market. In the phase II trial, TRAILBLAZER-ALZ, patients with early AD showed significant reductions in functional and cognitive decline.55 Those in the treatment group, however, had a larger sample of patients affected with ARIA-H compared to placebo (40 [n=131] vs 9 [n=125]) as well as a higher dropout rate (37.4% v 27.2%). Comparatively these adverse event rates were higher with donanemab than with lecanemab. Donanemab was rejected by the FDA for accelerated approval in January 2023 due to the lack of safety data.56 The manufacturer plans to resubmit accelerated approval pending the results of TRAILBLAZER-ALZ2, an anticipated confirmatory phase III trial.

Conclusion

In the Clarity AD trial, all patients experienced a clinical decline based on CDR-SOB scores, however the decline was less severe in the lecanemab group. Although amyloid burden was also considerably reduced in those treated with lecanemab, amyloid burden does not always correlate with severity, so the true clinical consequence of this reduction remains to be seen. While lecanemab had a more favorable safety profile than aducanumab due to lower rates of ARIA, the benefit of therapy compared with its risks warrants careful consideration and further study. Ultimately, the magnitude of clinical benefit of lecanemab noted in the Clarity AD trial when analyzed against its potential true cost is not unassailable. In a simulation study seeking to estimate long-term healthcare outcomes, lecanemab potentially can increase time spent in the community, rather than in institutional care settings.57 Further open-label extension analyses from the manufacturer noted a continued 6-month response with lecanemab beyond the initial 18-month trial period.58 Despite this, adding medications like lecanemab to formularies is not without need for continual reevaluation of use and cost/benefit. If healthcare systems are

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to add novel monoclonal antibodies targeting AD pathology, it should be done so carefully with cost-containment restrictions in place (outpatient use only, select physician groups, follow-up medication use evaluations to assess true system cost) and with enhanced safety measures, including restricting use to select patients without high-risk comorbidities or medications.

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Table 1. Medications for Alzheimer's Disease

Medication (dosage forms available)	Dose Range (Target or Maximum)	Recommended Titration	Common Side Effects (>5%)
Donepezil (IR, transdermal patch)[8,9]	IR: 5 mg once daily (10 mg target, maximum of 23 mg) Transdermal: 5 mg/24 hour (10 mg)	IR: 10 mg daily after 4-6 weeks of 5 mg dose Transdermal: 10 mg/24 hour after 4-6 if 5 mg/24 hour tolerated	Nausea, vomiting, diarrhea, insomnia, muscle cramps, fatigue, anorexia
Rivastigmine (IR, transdermal patch)[10,11]	IR: 1.5 mg twice daily (6 mg twice daily) Transdermal: 4.6 mg/24 hours, once daily (13.3 mg/24 hours)	IR: Increase by 1.5 mg twice daily every two weeks until maximum tolerated dose Transdermal: After a minimum of 4 weeks, titrate to 9.5 mg/24 hours. If tolerated after 4 weeks, may increase to 13.3 mg/24 hours	Nausea, vomiting, diarrhea
Galantamine (IR, ER)[12]	IR: 4 mg twice daily (8-12 mg twice daily) ER: 8 mg once daily (16-24 mg)	IR: if starting dose tolerated, increase to 8 mg twice daily for ≥4 weeks, and if tolerated, increase to 12 mg twice daily ER: if starting dose tolerated for 4 weeks, increase to 16 mg once daily for ≥ 4 weeks; if tolerated, increase to 24 mg once daily	Nausea, vomiting, diarrhea, dizziness, headache, suppressed appetite, weight loss
Namenda (IR, XR)[13,14]	IR: 5 – 20 mg daily (20 mg) ER: 7 mg daily (28 mg)	IR: Increase by 5 mg weekly until maximum dose tolerated ER: increase daily dose weekly by 7 mg until maximum dose tolerated	Dizziness, headache, confusion, constipation

ER, extended release; IR, immediate release; XR, extended release

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